PROMETHAZINE ORALLY DISINTEGRATING TABLET

Except where reference is made to the work of others, the work described in this dissertation is my own or was done in collaboration with my advisory committee. This dissertation does not include proprietary or classified information.

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PROMETHAZINE ORALLY DISINTEGRATING TABLET

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PROMETHAZINE ORALLY DISINTEGRATING TABLET

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VITA

Roger Dale Graben, son of Joseph Olen and Nealene (England) Graben was born in Talladega, Alabama on September 15, 1962. He attended public schools in Clay County, AL and graduated from Lineville High School in 1980. He received the Bachelor of Science (Honors) in Pharmacy and the Masters of Science in Pharmaceutics from Auburn University in 1985 and 1987, respectively. He obtained his pharmacy license in 1985 and has practiced pharmacy in hospital, retail, and clinical settings. Between 1987 and 1995, he worked as a Research Scientist with Solvay Pharmaceuticals and as a Manager of Pharmaceutical Technology and Director of Quality Assurance/ Quality Control with Chelsea Laboratories, a Rugby Generics/Marion Merrill-Dow company. He was self employed from 1996 until 2004, owning Young's Drug Store in Lineville, AL and Graben Pharma, Inc. in Anniston, AL. In 2004, he returned to Auburn University as a Research Associate. He is married to Pamela Chandler Graben and they have four children..

DISSERTATION ABSTRACT

PROMETHAZINE ORALLY DISINTEGRATING TABLET

Roger Dale Graben

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(M.S., Auburn University, 1987)
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Orally Disintegrating Tablets (ODTs) which disintegrate rapidly (< one minute) in the mouth and do not require water for administration have become a very popular dosage form. Current methods of manufacturing ODTs are complex and require multiple processes. The specific aim of this study was to develop a simple, inexpensive method of manufacturing ODTs. Promethazine HCL, a highly soluble drug with an extremely bitter taste and an unpleasant anesthetic effect in the oral cavity, was chosen as a model drug.

Simple low shear blending followed by direct compression was the preferred manufacturing method and was first examined. Taste-masking studies were conducted by directly mixing Promethazine with a number of substances. Taste-masking was assessed by dissolution studies and informal taste testing.

A 1:1 Magnesium Stearate: Promethazine mixture V-blended for one hour was effective in masking the bitter taste of this drug. The next step was to formulate an ODT which would rapidly disintegrate with this large amount of Magnesium Stearate. Magnesium Stearate is commonly known to increase both tablet friability and disintegration time, both of which are undesirable in an ODT dosage form.

After initial failures with Mannitol, Dextrates, NF was the primary diluent utilized in this system. Tablets were produced with various combinations of disintegrants with various mechanisms of action. Tablets were also manufactured with a variety of materials with potential for producing a less friable tablet with a lower compression force. Flavor and sweetener trials were also conducted.

A combination of Promethazine, Magnesium Stearate, Dextrates, and disintegrants was found to yield robust tablets (Friability < 1.0% with 0 broken at 25 rpm, for 4 minutes) with rapid disintegration (*in vitro* < 21 seconds, *in vivo* < one minute). Although the bitter taste was masked, the unpleasant anesthetic effect was not completely eliminated. The addition of 3.0% Menthol with sublimation post-tableting resulted in a visibly more porous tablet with shorter *in vitro* and *in vivo* disintegration times. These tablets yielded a pleasant taste without numbing. These tablets met compendial Dissolution and Content Uniformity requirements for conventional Promethazine tablets.

These trials indicate an acceptable ODT can be produced using conventional excipients and simple blending followed by direct compression. In the case of Promethazine, the addition of Menthol followed by post-tableting sublimation was required to overcome the unpleasant numbing effect. While the sublimation of Menthol is an additional step, it only required a common laboratory oven and 48 hours.

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Style manual used AAPS PharmSciTech.

Computer software used Microsoft Office Word 2003 and Microsoft Office Excel 2003.

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1. INTRODUCTION

Tablet dosage forms which rapidly (< one minute) disintegrate in the mouth and can be taken without water have become extremely popular in recent years[1]. These products offer the convenience of a tablet with the ease of swallowing a liquid[2]. These dosage forms are of particular advantage in certain patient groups such as children, elderly, and psychiatric patients[2-4]. Certain medical conditions such as pain, migraine, nausea, panic attack, allergic conditions, cough/cold, and Alzheimer's may benefit from these dosage forms[2, 4]. Product life cycle management has led pharmaceutical companies to be very interested in using these dosage forms to extend brand name use after the initial dosage forms become available generically[3].

Although the official name for this dosage form is Orally Disintegrating Tablets (ODTs)[5], many other names have been utilized. These include, but are not limited to, "fast-dissolve", "fast-melt", " rapidly disintegrating", "quick-melt", "quick-dissolve", "crunch-melt", "bite-dispersible", "mouth-dissolve", and orodispersible[2, 4, 6-8].

One common misconception with this dosage form regards their time of onset of action[3]. Although assumed to be faster onset than conventional tablets, in some cases this difference may be more perception than reality. This is of special interest for drugs taken to relieve acute symptoms of conditions such as pain, migraine, nausea, panic attack, and so forth. This is best understood by looking at the individual steps which

must be completed to achieve onset of action. For systemically acting drugs taken for relief of acute symptoms, these steps include:

1. appearance of symptom(s);
2. drug administration;
3. dissolution and absorption;
4. distribution and onset of action[3].

For Orally Disintegrating Tablets, the step most often affected is the time between symptom appearance and drug administration. The portability and ease of administration of ODTs may significantly reduce this step. In most cases, the rapid disintegration in the mouth does not result in sublingual absorption or substantially faster gastric absorption. In fact, taste coating may actually result in a decreased rate of dissolution[3]. This topic is discussed below after the discussion regarding taste.

Market research has shown taste to be an important factor in patient acceptance of an ODT dosage form[9]. Biologically, taste may be defined as a chemical reaction derived from sensory responses from taste perceptions. The four main taste perceptions are salt, sour, bitter, and sweet. Other perceptions include umami (fullness) and trigeminal (burning)[9]. Smell contributes greatly to taste in that the brain interprets combined nasal and taste bud responses into one taste response. Consistency and mouthfeel also greatly contribute to taste[9]. People perceive flavors in different ways and these perceptions are affected by factors such as age and ethnicity[9].

If used in an ODT formulation, most drugs require taste-masking[9]. Methods used typically either prevent dissolution of the drug within the oral cavity or otherwise minimize the presented surface area of the drug[9]. Processes commonly used for ODTs

include wet granulation, roller compaction, spray-drying, and coating. Taste-coating may be based upon time or pH dependent dissolution of a coating polymer. Other taste-masking methods include the use of cyclodextrins, encapsulation using coacervation, electrochemical coating, and the use of supercritical fluids[9].

Following oral administration of a solid dosage form, the bioavailability is rate limited by either drug dissolution or absorption[10]. Dissolution rate is directly related to solubility[10]. For an ODT dosage form, the dissolution rate is also affected by the taste-coating. Ideally, any taste-coating method for an ODT should completely prevent dissolution for a short time, such as 2-5 minutes, and then subsequently not delay dissolution. How rapid this subsequent dissolution occurs depends upon the solubility of the drug itself. A rapid rate of dissolution is desired if the drug is to be used for acute symptom relief. Some ODTs are used to deliver enteric-coated or sustained-release products[1, 3]. In this case, delayed or slow dissolution is sought.

The effect of any small delay in dissolution upon the rate of absorption will depend upon whether the particular drug in question is bioavailability rate limited by dissolution or absorption. Promethazine HCl was chosen as a model drug for these studies (Why chosen is discussed further below). This drug is very water soluble (500 mg/ml)[11]. The bioavailability of highly soluble drugs is typically not dissolution limited[10]. One pharmacokinetic study showed no significant difference in the area under the plasma concentration time curves ($AUC_{0-\infty}$) for an oral solution, a generic tablet, and the innovator tablet of Promethazine[12]. Although no precise mathematical relationship was established, this same study concluded the compendial *in vitro* dissolution test assures satisfactory bioavailability[12].

An ODT dosage form should possess certain ideal properties. These include no water required for administration, disintegration within seconds, pleasant taste and mouthfeel, porous, bioequivalent if a line-extension, sufficient strength to withstand manufacturing/packaging/shipping/environmental factors, adaptable to standard manufacturing and packaging equipment and materials, allow high drug-loading, and be cost effective (directly compressible, royalty-free, etc.) [4, 8]. Fast disintegration and the ability to take without water are required for this dosage form to offer broad advantages over conventional tablets. Pleasant taste and mouthfeel are required for patient acceptance. Porosity is required for water wicking and rapid disintegration. From a regulatory standpoint, bioequivalence to the reference product is required for rapid approval. Even an improvement in bioavailability results in additional regulatory requirements since a larger dose would be delivered in this case. Rapid disintegration must be carefully balanced with sufficient strength to withstand manufacturing, packaging, shipping, dispensing, patient handling, and exposure to moisture and other environmental factors. A friable and/or moisture sensitive product may disintegrate rapidly. However, this product would be of limited value if it could not be packaged, shipped, dispensed, taken by the patient, and have a suitable shelf-life. The ability to adapt to standard manufacturing and packaging equipment and to be produced in a cost effective manner are attributes sought for any new product. Otherwise, the benefit to cost ratio must be exceedingly high. Unless high drug-loading is achievable, the dosage form is limited to low dose drugs.

No current ODT product or manufacturing method meets all of the above described ideal properties. Manufacturing methods such as freeze-drying and molding

result in rapidly (2-15 seconds) disintegrating yet friable dosage forms[1, 2, 13]. These manufacturing methods are expensive and may be patent protected. Products made using a conventional tablet press are more robust but high porosity and rapid disintegration are more difficult to achieve[1, 2, 13]. Current ODT tableting methods are complex and require pre-tableting treatments such as wet granulation, dry granulation, melt granulation, spray-drying, or flash-heating; or require post-tableting treatments such as sublimation, effervescence, sintering, or humidity treatment[1]. Although direct compression methods using superdisintegrants and/or other excipients exist, a separate taste-coating process is required[1, 2, 9, 13]. Methods to date rely upon complex and/or multiple processes to accomplish both taste-masking and rapid disintegration[1, 2, 9, 13].

The specific aim of this study is to develop a simple method of manufacturing Orally Disintegrating Tablets that better meet the ideal properties listed above. It is hypothesized that a method of manufacturing ODTs which preferably utilizes only simple blending followed by direct compression can be developed (More discussion on the broad hypothesis and secondary hypotheses appears later in this section.). This is the simplest, most economical process of manufacturing any tablet, conventional or rapidly disintegrating[1, 10, 14]. This method should utilize conventional, routinely available manufacturing equipment as well as simple and economical processing methods. This is of special concern for the generic market where manufacturing costs may be more critical. Materials used should be those with a history of safe use in the pharmaceutical industry. Compendial status is preferred for all materials to be utilized. Tablets produced by this method should be rugged enough to be packaged using conventional packaging materials (bottle or blister) and conventional packaging equipment. Tablets should meet

friability requirements for conventional tablets and compendial dissolution requirements for the drug. Complicated shipping, dispensing, and patient handling procedures should not be required.

Promethazine HCL was chosen as a model drug for these studies. Promethazine is a phenothiazine derivative with antihistamine (H1 receptor blocker) and anti-cholinergic properties[15, 16]. Clinically useful effects include anti-emetic, antihistamine, and sedative effects[15, 16]. Promethazine HCl's offensive taste and anesthetic effect coupled with its high water solubility (500 mg/ml)[11, 17] enable it to be an excellent model for testing an ODT formulation platform and manufacturing method. Any method which succeeds in taste-masking this highly water soluble and bitter tasting drug should be adaptable to masking the taste of less soluble or less offensive tasting drugs.

Not only do taste and solubility characteristics make Promethazine HCl an excellent model, the development of an ODT dosage form of this drug meets an existing clinical need. Alternative dosage forms of Promethazine are needed to overcome the limitations of current dosage forms, especially in the outpatient setting. Conventional tablets generally require fluid intake which may worsen acute nausea and vomiting[15]. In addition, this fluid intake may lead to vomiting and expulsion of the drug delivered via a conventional tablet. This may result in under-dosing whereas repeating the dose may result in over-dosing. Currently available syrups not only share these problems, but also are limited due to their availability only in a single pediatric strength[16, 18]. In addition, syrups lack the portability of an Orally Disintegrating Tablet. Although suppositories overcome some of the above described limitations, they are an undesirable dosage for the majority of the patient population. In addition, Phenergan suppositories require

refrigeration[16, 18] which limits portability. An Orally Disintegrating Tablet could overcome many of the above described limitations. The ability to take anytime, anywhere, without fluid, offers numerous advantages in the treatment of nausea and vomiting. Its portability and ease of administration also enable an ODT to be very helpful in the treatment of motion sickness or allergic conditions. A directly compressible formulation for the 25 mg dose could be compressed at lower weights to achieve lower doses for use in children. ODTs are currently used in pain/fever, cold/cough, and other children's products[1, 2].

The broad hypothesis for this study is that a simple manufacturing method for ODTs can be developed. Preferably, this method should require only simple blending followed by direct compression. In that case, the first component of the broad hypothesis is that a material or combination of materials exists which when simply blended with Promethazine HCL, will result in an acceptable degree of taste-coating. The research was limited to this approach due to the availability of only a V-blender and an open, kitchen-type, planetary mixer. Neither of these pieces of equipment generates a notable amount of heat or shear, both of which can aid in particle coating. No high shear mixer/granulator or fluid bed coater was available. Both of these technologies have been used successfully in producing taste-coatings[1, 9].

The materials to be considered for taste coating primarily consist of tablet lubricants. Lubricants function to prevent sticking of the tablet to the punch faces and to reduce die wall friction during compression and ejection[10]. Boundary lubricants attach to the metal oxide film on the punch and die surfaces[10]. These lubricants include, but are not limited to, Magnesium Stearate, Calcium Stearate, Zinc Stearate, and Stearic Acid.

Among these, Magnesium Stearate is the most effective tablet lubricant, probably due to its smaller particle size[10, 14]. These hydrophobic, waxy materials may retard disintegration and dissolution due to the ability of these small particles to physically adhere to and coat the active ingredient and other excipients. Since longer mixing results in greater coating of the drug and excipients, this delay in disintegration and dissolution as well as the compression problems (discussed in next paragraph) caused by these materials increase as mixing time increases. For this reason, these lubricants are added to the final blending stage and blending time is kept at a minimum[10, 14].

These lubricants may also adversely affect compression. To understand how this occurs, we must first understand the physics of tablet compression. Powders (or granules) are subjected to applied mechanical loads to form a tablet via compaction[10]. The behavior of these powders under these applied loads is a major factor in determining the success or failure of the formulation and process.

Tableting may be defined as compaction of powders or granules in a die, between two punches, by application of a significant mechanical force[10]. The compaction process itself may be defined as the compression and consolidation of a two-phase (particulate solid/air) system due to applied forces[10]. Compression is the decrease in bulk volume resulting from air displacement. Consolidation is an increase in mechanical strength of the powder mass resulting from particle-particle interactions[10].

During compression, the bulk volume may be decreased by the plastic, elastic, or brittle fracture mechanisms of deformation. In many pharmaceutical systems, the applied force exceeds the elastic limit of the material and subsequent compression is due to visco-elastic or plastic deformation, and/or brittle fracture[10]. Certain materials are ductile or

easily deformed whereas some materials are brittle and fracture. Cellulose derivatives are a good example of a ductile material whereas sugars are a good example of a brittle material. A material may exhibit both properties but one property may predominate.

Consolidation, an increase in mechanical strength, is due mainly to particle surfaces closely approaching one another and facilitating intermolecular bonding via van der Waals forces[10]. In addition, pressures developed at particle-particle point contacts may lead to localized melting followed by bridging[10]. The boundary lubricants such as Magnesium Stearate may cause a decrease in tablet tensile strength and an increase in friability by adversely affecting particle-particle bonding and bridging[10]. The ability of these lubricants to coat other particles leads to this effect. Brittle materials may be less impacted by this phenomenon since the breaking into multiple particles will expose new surfaces not coated by lubricant and thus available for bonding[10].

Due to these potential problems with boundary lubricants, another type of lubricants will be investigated first for their ability to taste-mask. These lubricants form a finite film on punch and die surfaces and are referred to as fluid lubricants[10]. These have a larger particle size and require a longer blending time. These lubricants include hydrogenated vegetable oil and newer partial glycerides of vegetable origin[10, 19, 20]. The newer glyceride lubricants have been successfully used for taste-masking, but thus far only with the use of heat or high shear[19, 20]. These trials will evaluate whether extended simple blending can accomplish taste coating with these materials. If these larger, spherical particles are ineffective, trials with the boundary lubricants or other hydrophobic or gel forming materials will be undertaken.

The V-blender and planetary blender will be used for most trials. Some materials may be preliminarily screened by mixing in a mortar and pestle. The effectiveness of taste coating will be evaluated primarily by dissolution testing. As discussed above, ideally, the dissolution profile would consist of no drug dissolved at the initial time-point followed by subsequent rapid dissolution. Although this type of profile is attainable with true coating processes such as fluid bed coating, a more gradual increase in dissolution rate may be realized with a simple physical mixture. The acceptance criteria will be an initial decrease in dissolution rate as compared to Promethazine HCl powder alone followed by subsequently meeting compendial dissolution requirements for Promethazine HCl tablets. The compendial dissolution method for conventional Promethazine HCl tablets will be utilized. This procedure will be adapted to incorporate modifications recommended for ODT dosage forms. As discussed above, one pharmacokinetic study concluded this compendial method to be acceptable in assessing bioavailability[12]. Although this requirement for subsequent dissolution rate is quantitative, the assessment of dissolution at the initial time point will be a mixture of qualitative and quantitative assessment. Although a numerical value will be obtained, an absolute limit has not been pre-established.

So as not to rely solely on dissolution data, taste screening will also be performed by taste testing by two researchers, one of which will be blinded. A small amount of powder will be tasted then expectorated. This qualitative testing is limited due to the limited number (2) of tasters and possible bias. As noted earlier, people perceive taste differently and taste varies with age, ethnicity, and other factors[9]. Therefore, a large sample size of blinded, independent subjects would be required to fully evaluate taste.

However, it should be noted that no decisions will be based upon the lack of bitter taste alone without supporting dissolution data.

Upon successful development of a simple and inexpensive Promethazine powder taste-coating method, the next step will be to insure the taste-coating will withstand the final blending with other tablet excipients and tablet compression process. At this stage the next hypothesis will be that a taste coated blend prepared by simple blending will withstand further blending and compression. The taste-coating will be evaluated by dissolution and taste as described above. For these purposes, the blend will be mixed with Pharmaburst and compressed. Pharmaburst is an off-the-shelf co-processed mixture of compressible sugars, disintegrants, and other excipients used in producing ODTs[21].

If the hypothesis that the taste-coating process will withstand final blending and compression is accepted, formulation trials will begin. The second hypothesis at this point is that Promethazine HCl taste-coated by the above method can be formulated into a directly compressible, non-offensive tasting, rapidly disintegrating (less than one minute *in vivo*) tablet which meets compendial Dissolution and Content Uniformity requirements. Content Uniformity assessment is required to demonstrate uniform distribution of active ingredient in individual tablets throughout the entire batch of finished product.

Tablets will be primarily assessed by weight, hardness, thickness, friability, and *in vitro* disintegration testing. Weight variation is accurate, quantitative, and reproducible. However, weight control is not anticipated to be a key factor in this research. Hardness is a term routinely used in the pharmaceutical industry to assess tablet strength[10, 14]. This is not an accurate use of the term hardness. The test is also referred to as crushing strength,

which is also a misnomer[10]. The most correct name for this test is breaking force[10]. Tablets are caused to fail by applying a load across the tablet diameter via means of a moving plunger while the tablet rests against a fixed anvil. While newer testers which apply force via an electronic load cell can detect and record the initial break in the tablet, older testers like the one employed in this work may completely demolish the tablet and actually record a demolition force[10]. Older testers like the one employed are also subject to greater user and mechanical variation. Although a numerical result is obtained, there is no strictly defined target value. This value is useful primarily in qualitative comparison to patterns in friability and disintegration time. A very high number typically correlates with a prolonged disintegration time whereas a very low number typically correlates with a friable product.

Tablet thickness is quantitative and can be accurately determined. Although at first glance it may appear to be of limited use in evaluating formulations, a more thorough examination reveals otherwise, and especially so in ODT formulations. A formulation capable of forming a stable compact at a lower compression force will be more porous[10]. This tablet will likely be thicker than it would have been if subjected to a higher compression force. As noted previously, porosity is very important in achieving rapid disintegration[4]. Qualitative patterns between hardness, thickness, friability and disintegration will be evaluated.

Balancing friability and disintegration is a key driver in developing an ODT formulation. An ODT must be non-friable and rapidly disintegrating. Friability is quantitative in the sense that no broken tablets and less than one percent weight loss (limit recommended by USP for conventional tablets)[22] is acceptable. However,

comparisons of values below 1.0% are somewhat qualitative in nature. Disintegration is quantitative and reproducible. However, the overall formulation decisions are based upon qualitative comparisons of these above described physical parameters. No exact value requirements are pre-established and patterns are sought. This approach does not lend itself to statistical analysis and therefore has inherent weaknesses.

Taste testing will also be performed by two researchers who will place the tablet in the mouth and leave undisturbed until complete disintegration occurs. All particles will be expectorated followed by rinsing the oral cavity with water. The approximate *in vivo* disintegration time will be noted. This taste testing is qualitative and subject to the limitations previously noted. However, it should be noted that formulation decisions are not made based upon acceptable taste results alone.

The problems encountered from this point onward are dependent upon the material selected as a taste-coating agent. In this case, Magnesium Stearate in a 1:1 ratio with Promethazine HCl was eventually determined to accomplish taste-coating via simple V-blending. This taste-coating was maintained after final blending and compression. As discussed above, Magnesium Stearate both retards disintegration and increases friability, both of which are problematic in an ODT dosage form.

At this point the third hypothesis is that certain classes of excipients will overcome the anticipated compression and disintegration problems of Promethazine HCl Orally Disintegrating Tablets. Preliminary trials will be undertaken to evaluate various combinations of diluents, binders, and superdisintegrants (Superdisintegrant is a term used within the pharmaceutical industry to describe newer disintegrants which are typically chemically modified or cross-linked versions of starches or celluloses

previously used as disintegrants. These are referred to as superdisintegrants because as compared to older disintegrants, they produce much faster disintegration at much lower use levels[10].). These trials will be preliminary in nature. The goal of these trials is to determine a basic diluent or diluent/binder system to be studied further. The need for a glidant to aid flow will also be assessed. Preliminary assessment of superdisintegrants will also be undertaken. Excipients to be utilized will be selected based upon properties relevant to requirements for an ODT in general as well as properties important in this system containing a large amount of Magnesium Stearate. For example, spray-dried mannitol will be evaluated as a diluent based upon its fast rate of dissolution as compared to other sugars commonly utilized in ODTs[23]. Dextrates, NF will be evaluated as a diluent because these large crystallized particles[24] are expected to undergo brittle fracture[10] and thus be more likely to overcome lubricant sensitivity problems. Dextrates spherical particle shape[24] is expected to yield good flow properties and this material also dissolves rapidly[23]. A qualitative comparison of physical test results will be utilized to determine what basic diluent or diluent binder system to utilize in subsequent trials. At this point, an acceptable formulation is one which can be compressed and yield a non-friable tablet.

The formulation chosen from preliminary trials will then be used in disintegrant trials. Various superdisintegrants with different mechanisms of action (wicking, swelling, wicking and swelling, etc.) will be evaluated. Non-traditional disintegrants will also be investigated. The use of Soy Polysaccharides as a disintegrant in ODT formulations will also be examined. The supplier of this material states this material has not been previously used in this manner. The initial goal prior to beginning this work

was to evaluate two disintegrants at a time utilizing the 3^2 randomized full factorial design as utilized by Gohel and coworkers.[25] In our case, the two factors to be investigated are the individual disintegrants at low, medium, and high use levels, based upon use levels routinely used for each specific disintegrant studied. The amount of each individual disintegrant is the independent variable with disintegration time and friability selected as dependent variables. This selection is based upon the balancing of disintegration time and friability being critical to development of an ODT. The statistical model as used allows for the evaluation of the average result from changing one disintegrant at a time from its low to high values and allows for evaluation of the response changes when two factors are simultaneously changed. Terms to investigate non-linearity are also included. This type of design allows for robust results which can be readily generalized. Unfortunately, in our case, the basic formulation was too sensitive to allow for multiple changes at multiple levels. In our trial, only one variable at a time was changed. This resulted in more batches required and data which are less robust. The physical test data were compared with decisions being made primarily based upon a qualitative comparison of disintegration time and friability. Taste was also examined.

Beyond this point, this same basic approach was utilized for different types of ingredients. These materials were evaluated stepwise in attempts to further improve factors such as disintegration time, friability, and taste. These materials included:

- Materials which promote binding therefore enabling a lower compression force to be utilized;
- Materials which increase the overall hydrophilic or hydrophobic nature of the tablet;

- Surfactants;
- Flavors/Sweeteners.

As before, qualitative comparison of friability and dissolution data were utilized to make formulation decisions. Also as before, taste was a secondary qualitative parameter. In addition to examining different types of materials as described above, the technique of incorporating a volatile substance followed by post-tableting sublimation to increase tablet porosity was examined.

A large amount of data will be collected for these studies. Although some limitations in equipment and methods exist, valuable information is expected from these trials. These include:

- Can taste-coating be accomplished via simple blending alone and, if so, what drugs are candidates for this technology;
- Can this taste-coating accomplished by this simple method withstand further blending and compression;
- Can a very high Magnesium Stearate content formulation be combined with other materials to result in a non-friable, rapidly disintegrating tablet;
- Can Soy Polysaccharides be useful as a disintegrant in ODT formulations;
- Can sublimation be combined with this methodology to further improve its usefulness as a method to produce ODT tablets?

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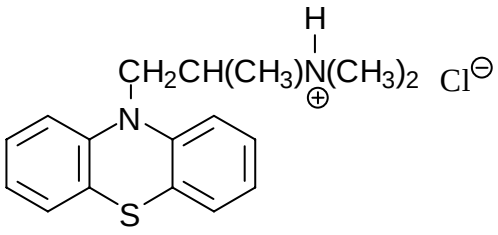
2. REVIEW OF LITERATURE

2.1 Promethazine HCl

Promethazine is a phenothiazine derivative (Figure 2.1)[1, 2] with antihistamine (H1 receptor blocker) and anti-cholinergic properties[3, 4]. Clinically useful effects include anti-emetic, antihistamine, and sedative effects[3, 4]. Promethazine differs structurally from antipsychotic phenothiazines by the presence of a branched side chain and no ring substitution[3]. This is believed to be responsible for Promethazine's lack of dopamine antagonist properties[3].



Molecular Weight 320.88
Melting Point 220° C
pka 9.1

Solvent	Solubility (mg/ml @ Room Temperature)
Water	500
Chloroform	335
Methanol	320
Ethanol USP	150
Ethanol, absolute	85
Isopropanol	9
Ethyl Acetate	1

Figure 2.1. Promethazine HCl: Structure and Properties

As shown in Figure 2.1, the hydrochloride salt is very soluble in water and non-polar solvents[1-3]. With a pka of 9.1[1], Promethazine is essentially completely ionized at all physiological pH ranges.

Promethazine is a safe and effective treatment for simple nausea and is among the most prescribed agents for this condition[4]. Essentially every person suffers from nausea and vomiting multiple times within a typical lifespan. Causes are numerous and varied but may include viral or bacterial, environmental (certain foods, alcohol), various disease states, pharmacological agents, and post-operative conditions[4]. Although a common condition, lack of proper treatment can lead to serious conditions, most often associated with fluid and electrolyte imbalances[4]. Promethazine is also among the most effective agents for treating balance disorders[4]. Motion sickness and other balance disorders are common and may be associated with a variety of clinical conditions[4]. Promethazine is also indicated for inducing light sedation, treating various allergic conditions, and as adjunctive therapy for anaphylactic reactions and pain[3].

Promethazine HCl dosage forms commercially available within the United States include tablets (12.5, 25, and 50 mg), a syrup (6.25 mg/5 ml), suppositories (12.5, 25, and 50 mg), and injections (25 mg/ml and 50 mg/ml)[5]. The average effective Promethazine adult dose for nausea and vomiting or motion sickness is 25 mg[3, 5]. The dose for children is typically 0.5 mg/pound of body weight. Promethazine is contraindicated in patients less than two years of age[3]. Dosing may be repeated at four to six hour intervals for nausea and vomiting. Dosing for motion sickness is typically twice a day.[3, 5]

The injection dosage forms are limited primarily to inpatient use. The other dosage forms have many disadvantages in the outpatient setting. Oral tablets have a

delayed onset of action[3] which is undesirable for acute treatment of emesis, motion sickness, or adjunctive treatment of anaphylaxis or pain. For the treatment of nausea and vomiting, tablets and syrups are inconsistent with the cornerstone of treatment, nothing by mouth in the initial treatment period[4]. In fact, ingestion of these dosage forms and the accompanying required liquids may worsen the condition, resulting in vomiting and expulsion of a portion or the entire dose administered. The amount remaining in the body is now uncertain but further action may result in over dosing. In addition, syrups are currently available only in pediatric concentrations[5]. Although suppositories circumvent some of these specific problems, this is a very undesirable dosage form for the majority of the patient population.

Other experimental Promethazine dosage forms have been considered. An experimental nasal spray resulted in mucosal irritability [6]. Although topical Promethazine is of interest in the area of compounding pharmacy[7], the potential for local irritation and systemic toxicity is a concern with transdermal delivery of any compound[8]. This is especially true in children because of variability in skin thickness and dermal blood flow[8]. In fact, systemic poisoning resulting from topical Promethazine has been reported[9].

An orally disintegrating dosage form overcomes the numerous limitations encountered with the above described dosage forms. An orally disintegrating tablet (ODT) can be taken by children or adults, anytime and anywhere, without the need for water. As previously noted, fluid intake in the initial stages of nausea and vomiting may result in further complications. An ODT gives the benefits of a suppository without the unpleasant experience of administration. In addition, oral administration of Promethazine

results in a much shorter (2-3 hours) time to peak plasma concentration (t_{max}) than rectal administration (7-8 hours)[10, 11]. In addition, any Promethazine absorbed transmucosally would avoid the first-pass effect, which is significant (approximately 75%) for Promethazine[10, 11].

One factor to consider in dosage form development is the chemical stability of the compound to be utilized. Promethazine undergoes both thermal and photolytic oxidation via free radical formation[1, 2]. Commercially available conventional tablets are available in brand and generic versions[3, 5]. This indicates stable solid dosage forms can be formulated and manufactured. The innovator tablets (Phenergan, Wyeth) contain very common tableting excipients; Lactose, Magnesium Stearate, Methylcellulose, Saccharin Sodium, and dyes (in two of three available strengths)[3].

Another important factor in formulation development is the availability of analytical methods. Compendial methods of analysis are available for all commercially available Promethazine dosage forms[5]. Conventional tablet methods are expected to be readily adaptable to an orally disintegrating tablet dosage form.

2.2 Orally Disintegrating Tablets

2.2.1 Overview

Orally Disintegrating Tablets (ODTs) may be defined as a tablet which disintegrates and/or dissolves rapidly (< one minute) in the saliva without the need for water or other liquid[12]. The United States Food and Drug Administration Center for Drug Evaluation and Research defines an ODT as a “dosage form containing medicinal substances, which disintegrates rapidly, usually in a matter of seconds, when placed upon

the tongue"[12]. As reflected in Table 2.2 , this dosage form has become extremely popular in recent years[13].

Orally Disintegrating Tablets offer the convenience of a tablet with the ease of swallowing a liquid[14]. These dosage forms are of particular advantage in certain patient groups such as children, elderly, and psychiatric patients[14-16]. Certain medical conditions such as pain, migraine, nausea, panic attack, allergic conditions, cough/cold, and Alzheimer's may benefit from these dosage forms[14-16]. A review of Table 2.2 reflects these patient groups and disease states. Product life cycle management has led pharmaceutical companies to be very interested in using these dosage forms to extend brand name use after the initial dosage forms become available generically[15].

Although the official name for this dosage form is Orally Disintegrating Tablets (ODTs)[17], many other names have been utilized. These include[14, 16, 18-20], but are not limited to, "fast-dissolve", "fast-melt", " rapidly disintegrating", "quick-melt", "quick-dissolve", "crunch-melt", "bite-dispersible", "mouth-dissolve", and orodispersible.

An ODT dosage form should possess certain ideal properties. These include no water required for administration, disintegration within seconds, pleasant taste and mouthfeel, porous, bioequivalent if a line-extension, sufficient strength to withstand manufacturing/packaging/shipping/environmental factors, adaptable to standard manufacturing and packaging equipment and materials, allow high drug-loading, and be cost effective (directly compressible, royalty-free, etc.) [16, 20]. No current ODT product or manufacturing method possesses all of the above qualities[13].

Table 2.2. Examples of ODT Products, Applications, and Technologies[5, 13, 14]

Brand Name	**Active Ingredient**	**Application**	**General Technology**	**Specific Technology**
Claritin RediTabs®	Loratadine	Antihistamine	Freeze-Drying	Zydis®
Feldene Melt®	Piroxicam	NSAID	as above	as above
Maxalt-MLT®	Rizatritpan	Migraine	as above	as above
Pepcid ODT®	Famotidine	Heartburn	as above	as above
Zyprexa® Zydis®	Olanzapine	Anti-psychotic	as above	as above
Zofran® ODT®	Ondansetron	Anti-emetic	as above	as above
Risperdal® M-Tab	Risperidone	Schizophrenia	as above	as above
Zubrin™	Tepoxalin	Dog NSAID	as above	as above
Klonopin® Wafers	Clonazepam	Anxiety/panic	as above	as above
Childrens Dimetapp® ND	Loratadine	Antihistamine	as above	as above
Imodium Instant Melts	Loperamide	Anti-diarrheal	as above	as above
Propulsid® Quicksolv®	Cisapride	GI prokinetic	Freeze-Drying	Quicksolv®
Tempra Quicklets	Acetaminophen	Pain/Fever	Tableting	OraSolv®
Remeron® SolTab®	Mirtazapine	Depression	as above	as above
Triaminic® Softchews®	Various	Cold/Cough/ Allergy	as above	as above
Zomig-ZMT®	Zolmitriptan	Migraine	Tableting	DuraSolv®
Alavert®	Loratadine	Antihistamine	as above	as above
NuLev®	Hyoscyamine	GI spasms	as above	as above
Kemstro™	Baclofen	Muscle Relaxer	as above	as above
Niravam® ODT	Alprazolam	Anxiety/panic	as above	as above
Benadryl® Fastmelt®	Diphenhydramine	Antihistamine	as above	WOWTAB®
Nasea OD	Ramosetron	Anti-emetic	as above	as above
Gaster D	Famotidine	Heartburn	as above	as above
Excedrin® QuickTabs	Acetaminophen	Pain/Fever	Tableting	QuickTabs™
Prevacid® SolTab	Lansoprazole	GERD/Ulcer	Tableting	Flashtab®
Ralivia FlashDose®	Tramadol	Pain	Cotton Candy	FlashDose®
Zolpidem ODT	Zolpidem	Sleep	as above	as above
Fluoxetine ODT	Fluoxetine	Depression	as above	as above
Aricept® ODT	Donepezil	Alzheimer's	-	-

2.2.2 Current Methods of Manufacture

a) Freeze-Drying

Methods of manufacturing ODTs can be divided into three broad categories, freeze-drying, molding, or compaction. Freeze-drying or lyophilization was the first technology resulting in a commercialized ODT[5, 13, 14]. Table 2.2 reflects the extensive use of this methodology. In lyophilization, the drug and excipients are dissolved and/or suspended in a liquid which is dosed into a pre-formed blister that forms the tablet shape and serves as the immediate product package. Cryogenic freezing followed by sublimation removes the liquid from the product and the blisters are sealed and further packaged[5, 13]. This results in a very porous, rapidly (as fast as 3 seconds) disintegrating dosage form which has an excellent mouthfeel[5, 14-16, 21]. However, these lightweight units are fragile, moisture sensitive, and require complex packaging and patient handling[5, 14-16, 21]. In addition, the manufacturing process is specialized, expensive, and is often patented and requires outsourcing/partnering[14, 15, 21].

Within the area of freeze-drying, the Zydis® (Cardinal Health, Dublin, Ohio) technology is the most well known[13]. In this method, the drug is physically trapped in a two component (saccharide and polymer) matrix. Mannitol is a common saccharide employed and carrier polymers used include partially hydrolyzed gelatin, hydrolyzed dextran, dextrin, alginates, acacia, polyvinylpyrrolidone (PVP), and poly(vinyl alcohol) (PVA)[13]. The drug, saccharide, and polymer are combined with other ingredients (flavors, sweeteners, collapse protectants, flocculating agents, etc.); then dissolved and/or dispersed in water. This liquid is then dosed into a pre-formed blister cavity which forms the final tablet shape and immediate product packaging. The package is then passed

through a liquid nitrogen freezing tunnel to achieve freezing. The packages are further frozen under vacuum in large scale freeze-dryers to remove the water. The now formed lightweight porous wafer is covered with a peelable foil and further packaged in an outer single-dose foil sachet-like package.[5, 13, 14, 16].

This extremely porous, small-particle size dosage form results in excellent mouthfeel and extremely rapid (as little as 3 seconds) disintegration. Taste-masking can also be achieved as part of the process. However, the dosage form is extremely fragile and moisture sensitive. The patient must deal with multiple packaging layers and must peel away the packaging without pushing the dosage form. Any minor damage to the package, humidity above 65%, or wet or sweaty hands may lead to collapse of the dosage form. In addition, the manufacturing method is patented, expensive, and requires partnering with Cardinal. The method requires a chemically stable drug with a preferred particle size below 50 microns. Doses above 60 milligrams are difficult to achieve with water soluble drugs.[13, 14, 16]

The Quicksolv® (Janssen Pharmaceutica, Beese, Belgium)) method utilizes two different solvent systems and is said to yield a product with greater physical strength for handling[13]. The Lyoc® (Pharmalyoc, Lefon, Maisons-Alfort, France) system is based upon freeze-drying of an oil in water emulsion. This system requires a large amount of undissolved filler to maintain content uniformity. The resulting product is less porous, thus slower disintegrating, yet still fragile.[13]

The NanoCrystal™ (Elan, King of Prussia, PA) system is based upon lyophilization of mixtures of colloidal drug dispersions and water-soluble ingredients. This process can be performed on a small scale which is advantageous for clinical supply

manufacturing. This is also beneficial when working with potent or hazardous materials since processes (blending, tableting, etc.) which generate large quantities of aerosolized powder are avoided. The final product is durable enough for blister or bottle packaging and less moisture sensitive than Zydis® products.[13]

b) Molding

A second broad category of ODT manufacturing methods is molding. The traditional molding process is compression molding. In this process, the major components are water soluble and ethanol, water, or mixtures of the two, are the typical solvents employed. The powder mixture (drug, sugar(s), flavors, sweeteners, etc.) is moistened with solvent then molded into tablets under pressures lower than those used in conventional tablet compression. The tablets are then air-dried. This process is similar to tablet triturates in compounding pharmacy. Heat-molding (melt and pour) and no-vacuum lyophilization (pour and evaporate at standard pressure) are more recent methods of molding tablets. [13, 16, 22]

Molded tablets disintegrate rapidly (5-15 seconds), have a good taste, and are less expensive to manufacture than freeze-dried products. However, the product has a low mechanical strength making packaging and handling difficult. The manufacturing process is sometimes proprietary, typically requires partnering, and is more expensive than direct compression[13, 16, 22].

c) Compaction

Compaction is a third major category of ODT manufacturing methods. The ability to produce ODTs using a conventional tableting press is very attractive due to the availability of equipment and the low processing costs. Products made using a

conventional tablet press are more robust, but high porosity and rapid disintegration are more difficult to achieve [13-15, 21]. Current tableting methods are complex and require pre-tableting treatments such as wet granulation, dry granulation, melt granulation, spray-drying, or flash-heating; or require post-tableting treatments such as sublimation, effervescence, sintering, or humidity treatment[13]. Although direct compression methods using superdisintegrants and/or other excipients exist[13], a separate taste-coating process is required for unpleasant tasting active ingredients.. Methods to date[12-16, 20-24] rely upon complex and/or multiple processes to accomplish both taste-masking and rapid disintegration. Various methods are reviewed below.

Granulation

Wet granulation has been utilized to produce ODTs. Wet granulations formed in a fluid bed yield low density, high porosity granules which lead to rapid disintegration of the finished tablet. The use of effervescence, surfactants, and nanoparticles has been combined with wet granulation methods. Taste-masking is typically achieved in the wet granulation process through the use of sugars and polymers.[13]. Wet granulation is more labor intensive, requires more equipment and energy, and is more expensive than direct compression. In addition, moisture and heat-sensitive drugs do not lend themselves to wet granulation[25, 26].Melt granulation and dry granulation have also been utilized[13], but suffer many of the same disadvantages as wet granulation[25, 26].

Spray Drying

Spray drying can be used to make very porous particles with a large surface area. Active ingredients may be sprayed together with saccharides, flavors, and sweeteners to achieve taste-masking. The use of two polypeptides of the same charge (to promote

repulsion) such as non-hydrolyzed and hydrolyzed gelatin combined with an acidifying or alkalinizing agent has been utilized to further increase porosity. Effervescent agents have also been included in spray dried mixtures to further promote rapid disintegration[13, 16]. Although effective, the manufacture of ODTs by spray drying requires several processing steps as well as the use of heat. Some spray drying processes may also utilize organic solvents.

Cotton Candy Process

Fuisz Technologies (Chantilly, Virginia) has manufactured ODTs utilizing a Cotton Candy type process also known as the Shearform® or Flashdose® technology. Drug, saccharides, and polysaccharides are flash melted while subjected to centrifugal force and a temperature gradient. This process yields a floss-like crystalline structure similar to cotton candy. This floss creates a very high surface area for disintegration and dissolution. The floss is re-crystallized to form freely flowing granules with self-binding properties. These granules are combined with other excipients and compressed into tablets. These tablets disintegrate rapidly, are of acceptable strength, and can accommodate high drug loading. However, this is a specialized, multi-step process. In addition, this process is inappropriate for heat sensitive drugs.[13, 14, 16, 20, 22]

Direct Compression

Direct compression is the simplest and least expensive tableting process[13]. Direct compression uses conventional blending and tableting equipment as well as commonly available excipients. ODTs made by direct compression are robust and can be easily packaged and handled. However, *in vivo* disintegration time is longer (30-60 seconds) and good taste and mouthfeel are harder to achieve. For unpleasant tasting drugs, current

direct compression methods require a separate taste-coating process for the active ingredient prior to introduction into the direct compression process[13, 16, 20, 22].

Separate processes used for taste-masking include wet granulation, roller compaction, spray-drying, and coating. Taste-coating may be based upon time or pH dependent dissolution of the coating polymer.[12] Other taste-masking methods include the use of cyclodextrins, encapsulation using coacervation, electrochemical coating, and the use of supercritical fluids[12].

For direct compression ODT processes, sugar based excipients (mannitol, sorbitol, xylitol, maltose, etc.) are routinely used for their high water solubility, sweet taste, and pleasant mouthfeel[13, 16, 20, 22]. In addition to taste and mouthfeel, disintegration time is a primary concern. Some ODT technologies use effervescent couples alone or in combination with other disintegrants to achieve rapid disintegration[13, 16, 20, 22]. The use of disintegrants, and especially the more modern superdisintegrants, has made the advent of compression based ODTs possible[16].

Various materials have been utilized as disintegrants. Starches and modified starches have a long history of use as disintegrants[25, 27]. Within this group, the superdisintegrant Sodium Starch Glycolate is of most interest today[25]. This material is commonly used in levels of 2-8% by weight and its primary mechanism of action as a disintegrant is via swelling[25, 27].

Crospovidone, cross-linked polyvinylpyrrolidone, is another superdisintegrant of choice[13, 25, 27]. Although historically used in a range of 2-5%[25, 27], one manufacturer recommends up to 15% by weight in ODT formulations[28]. In fact, a specific grade featuring a smaller and more narrow particle size distribution has been developed

specifically to yield better mouth feel in ODT formulations[28]. Crospovidone is said to promote both wicking and swelling[28]. Crospovidone's disintegrant action is dependent upon compression force[27]. A certain tablet hardness is required for the swelling and expansion to be effective.

Modified celluloses are another common group of disintegrants[13]. Most recommended among this group is Croscarmellose Sodium, an internally cross-linked Sodium Carboxymethycellulose[25, 27]. Typical use levels range from 2-4% although lower and higher amounts have been utilized[25, 27]. This disintegrant works via both wicking and swelling[25, 27].

Calcium Silicate in amounts up to 30% by weight has also been used to promote disintegration[27, 29]. RxCipients® FM 1000® Calcium Silicate from Huber Engineered Materials (Havre de Grace, Maryland) is extremely hydrophobic[29]. When combined with superdisintegrants, the superdisintegrants are said to expand against this hydrophobic material. This expansion against another material is said to promote the tablet rapidly breaking down into primary particles.[29] Other disintegrants employed in ODTs are Alginic Acid, Sodium Alginate, Microcrystalline Cellulose, Methacrylic Acid-Divinylbenzene Copolymer Salts, and Poly(Acrylic Acid) Superporous Hydrogel (SPH)[13].

Inorganic excipients have also been utilized in direct compression ODTs. Disintegration is aided by the combination of disintegrant, insoluble materials, and soluble materials in specific ratios[13]. Di-basic and Tri-basic Calcium Phosphate have been utilized as an insoluble inorganic material. Other insoluble excipients commonly used in tablets may contribute to the total amount of insoluble material used[13].

Lubrication is another important concern when making ODTs. Historically, Magnesium Stearate has been the most effective and most commonly used lubricant used in tableting processes to prevent tablets from sticking to the punch faces and to reduce friction between the die wall and the tablet during compression and ejection[25, 26]. It is commonly used in amounts of less than 2% with 1% or less being the preferred amount[25, 26]. Increases in the amount of Magnesium Stearate or the Magnesium Stearate mixing time tend to retard disintegration and dissolution and increase friability[25, 26]. In fact, some sources recommend against the use of Magnesium Stearate in ODTs because of its hydrophobic nature and tendency to increase disintegration time[30]. Sodium Stearyl Fumarate, a less hydrophobic material not sensitive to blending time, is generally recommended for use in ODTs[30]. One method of producing ODTs is to use a method of lubricating the tablet and press external to the tablet formulation[24, 31]. One patent recommended levels of Magnesium Stearate up to 2.5% be used as a tablet lubricant in ODTs[23].

d) Post-Tableting Treatments

Various post-tableting treatments have been used to yield rapidly disintegrating tablets. These methods are described below.

Sublimation

Sublimation has been used to speed disintegration by increasing tablet porosity[13, 16] A volatile substance is used as part of the tablet composition; the tablets are then compressed followed by sublimation of the volatile substance. Substances used include menthol, camphor, thymol, organic and lower fatty acids, urea, ammonium carbonate, ammonium bicarbonate, and hexa methylene tetramine. Both vacuum and/or

heat may be used to sublime the volatile material[13, 16]. Sublimation has been combined with a molding process as well[13].

Humidity Treatment

Tablets with low mechanical strength disintegrate rapidly but may be too friable for packaging and handling. Humidity treatment allows a lightly compressed, rapidly disintegrating tablet to gain the ruggedness required for packaging and handling. The weak tablets are placed in a high humidity area then subsequently dried. The humidity results in the formation of liquid bridges which become solid bridges after drying. Humidification and drying may also promote the change of sugars from an amorphous to a crystalline state. This results in an increase in tablet strength[13].

Sintering

Sintering is a process of using pressure and heat below the melting point to bond and partly fuse particles. This process has been used to increase tablet strength of rapidly disintegrating tablets which would otherwise be too friable to withstand packaging and handling.[13] In addition to being unsuitable for heat labile drugs, this is a complex, multi-step process.

2.2.3 Specific Examples

OraSolv® and DuraSolv®

OraSolv® (Cima Labs, Eden Prairie, MN) technology is based upon producing tablets at low compression pressures using an effervescent couple to further speed disintegration[13]. Acid sources include citric acid, tartaric acid, malic acid, fumaric acid, adipic acid, and succinic acids. Carbonate sources include sodium bicarbonate, sodium carbonate, potassium bicarbonate, and potassium carbonate. The effervescent couple

comprises 20-25% of the total tablet weight. The liberated carbon dioxide not only speeds the breaking apart of the tablet, but also the mild fizzing sensation results in a positive organoleptic sensation.[13] These tablets are fragile and a special packaging system (PakSolv®) was developed for use with these tablets. A dome-shaped blister package prevents the vertical movement of the tablet within the package as well as provides light, moisture, and child resistance[13].

Cima also developed a second generation technology, DuraSolv®, which results in stronger tablets suitable for packaging in bottles or blisters. This technology is based upon compressing tablets using non-compression grade polysaccharides, such as dextrose, mannitol, sorbitol, lactose, and sucrose, along with up to 2.5% of a hydrophobic lubricant such as Magnesium Stearate[13, 23]. However, taste-coating of unpleasant tasting actives must be achieved in a separate process[23]. DuraSolv tablets are said to disintegrate *in vivo* in less than 60 seconds[13].

WOWTAB®

WOWTAB® (Yamanouchi Pharma Technologies, Inc., Japan), (With Out Water Tablet) technology is based upon granulating a saccharide with low moldability (mannitol, glucose, sucrose, xylitol) using a dissolved saccharide with high moldability (maltose, maltitol, sorbitol) as a binder. Tablets are then compressed with these granules then further subjected to humidity treatment[13, 14]. This is obviously a multiple step process without the advantages of direct compression.

Flashtab®

Flashtab® (Ethypharm, France) produces ODTs by compression of granular excipients prior granulated by either dry or wet granulation. The drug may be granulated

or coated with time or pH dependent polymers such as methylmethacralate copolymers (Eudragit®)[13, 14, 19, 32]. One example of this technology is Prevacid® SolTab which is an ODT containing enteric coated granules used to deliver an acid labile drug[14, 19, 32]. This type of ODT is said to disintegrate *in vivo* within 30 to 60 seconds[13, 14, 19, 32]. This technology can be applied to high dose drugs and is not limited by drug taste or solubility[32]. However, again it can be seen that this technology is more labor and time intensive than simple direct compression.

AdvaTab™

AdvaTab™ (Eurand, Milan, Italy) is a tableting method of making ODTs based upon the use of an external lubricant[13, 24, 31]. Rather than the tableting blend containing a hydrophobic lubricant, a small amount of lubricant is sprayed onto each tablet during the tableting process. This method results in 10-30 times less hydrophobic lubricant. Since internal lubrication both decreases tablet strength and retards fluid entry, avoiding this process results in a non-friable, rapidly disintegrating tablet[13, 24, 31]. These tablets are rugged enough for blister or bottle packaging. However, this is a patented process using specialized equipment. In addition, unpleasant tasting actives must be taste-coated or otherwise taste-masked in a separate process[13, 24, 31].

Pharmaburst™

Pharmaburst™ (SPI Pharma, New Castle, Delaware) is an off-the-shelf directly compressible blend of co-processed materials which can be mixed with active and flavors/sweeteners then compressed into an ODT[13, 30]. This method can accommodate high drug loading with *in vivo* disintegration times of less than 40 seconds. The typical amount of Pharmaburst™ ranges from 50-80% of the total tablet weight. A lubricant is

also required[13, 30] and Sodium Stearyl Fumarate is recommended[30]. Tablets may be manufactured and packaged under normal conditions[13, 30]. Taste-coating or masking by an independent process is required for unpleasant tasting drugs. Due to high demand, agreements are required with the supplier to prevent a second manufacturer from easily duplicating an original Pharmaburst™ product.

Frosta®

Frosta® (Akina Inc., West Lafayette, IN) technology is based upon wet granulation of a porous and plastic material, a water penetration enhancer, and a binder. These granules are then compressed at low pressures into rugged tablets which disintegrate in 30 seconds or less[13, 24, 33]. This is a patented, multi-step process.

OraQuick™

OraQuick™ (KV Pharmaceuticals, St. Louis, MO) is based upon the sintering process reviewed above[24, 34].

2.3 Specific Aims of Current Study

As can be seen from the reviewed literature, no simple manufacturing method exists which accomplishes both taste-masking and fast (< one minute) *in vivo* disintegration. The specific aim of this study is to develop a simple method of manufacturing Orally Disintegrating Tablets. Additional information with regard to hypothesis, experimental design, and specific aims is covered in the Introduction section of this dissertation. This method should utilize conventional, routinely available manufacturing equipment as well as simple and economical processing methods. Simple blending followed by direct compression is the preferred method. This is the simplest, most economical process of manufacturing any tablet, conventional or rapidly

disintegrating. Materials used should be those with a history of safe use in the pharmaceutical industry. Compendial status is preferred for all materials to be utilized. Tablets produced by this method should be rugged enough to be packaged using conventional packaging materials (bottle or blister) and conventional packaging equipment. Tablets should meet friability requirements for conventional tablets. Complicated shipping, dispensing, and patient handling procedures should not be required.

Promethazine was chosen as a model drug for these studies. Its offensive taste and anesthetic effect coupled with its high water solubility enable it to be an excellent model for testing an ODT formulation and manufacturing method. In addition, alternative dosage forms of Promethazine are needed to overcome the limitations of current dosage forms, especially in the outpatient setting. Conventional tablets require fluid intake which may worsen acute nausea and vomiting. In addition, this fluid intake may lead to vomiting and expulsion of the drug delivered via a conventional tablet. This may result in under-dosing whereas repeating the dose may result in over-dosing. Currently available syrups not only share these problems, but also are limited due to their availability only in a single pediatric strength. Suppositories are an undesirable dosage form for the majority of the patient population. An Orally Disintegrating Tablet could overcome many of the above described limitations. The ability to take anytime, anywhere, without fluid, offers numerous advantages in the treatment of nausea and vomiting. Its portability and ease of administration also enable it to be very helpful in the treatment of motion sickness or allergic conditions.

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3. TASTE-MASKING

Abstract

Taste-masking is a critical component of formulation and process development for Orally Disintegrating Tablets (ODTs). The specific aim of this study was to develop a simple process for taste-masking which yields a blend which can be further diluted and directly compressed into an ODT dosage form. Promethazine HCl was chosen as a model drug for these studies. Promethazine HCl is a highly water soluble drug with an offensive, bitter taste and an unpleasant anesthetic effect in the oral cavity. Dissolution testing was utilized to evaluate taste-masking since only dissolved drug is tasted. The USP method for conventional Promethazine HCl tablets was modified to conditions (pH 6.4, paddles, 50 rpm) recommended for this dosage form. Initially, loss of Promethazine HCl to the end-filter of the sampling probe occurred. Use of a filter needle overcame this problem. A linear, reproducible method based upon UV analysis at 249 nm was achieved for dissolution analysis. Excipients did not produce interference. Numerous materials were evaluated for their ability to achieve taste-masking via simple blending. Magnesium Stearate V-blended in a 1:1 ratio with drug proved to be effective based upon dissolution testing and taste screening. Tablets were compressed by diluting this mixture with Pharmaburst, an off-the-shelf ODT platform. The taste-masking was not compromised by final blending and compression. Formulation trials to develop a suitable tablet will proceed using this taste-masking method.

3.1 Introduction

Orally Disintegrating Tablets (ODTs) have become a popular dosage form. An ODT may be defined as a tablet which disintegrates and/or dissolves rapidly (< one minute) in the saliva without the need for water or other liquid[1]. These readily transportable dosage forms are intended to be taken anytime and anywhere without the need for water or other liquid[1, 2]. Certain patient groups such as children, elderly, and psychiatric patients greatly benefit from this technology[3-5]. This dosage form is especially beneficial in certain medical conditions such as pain, migraine, nausea, panic attack, allergic conditions, cough/cold, and Alzheimer's[3-5].

Market research has shown a significant amount of consumers prefer an ODT over a conventional tablet. This research has also shown that taste is a very important factor. Longer disintegration times were acceptable if the taste was good. However, the converse was not true; fast disintegration times were not acceptable if taste was bad[1]. Although some drugs have little taste and a simple addition of flavor will result in an acceptable taste, most drugs to be incorporated into an ODT formulation require taste-masking [1].

Although some ODT manufacturing methods allow for taste-masking as part of the manufacturing process, many do not[2-7]. In those methods which do accomplish taste-masking, the steps which do so are often the same or similar processing methods as those used to accomplish taste-masking in independent processes[2-7]. These processes include wet granulation, roller-compaction, spray-drying, and coating[1, 2]. Taste-coating may be achieved using polymers which dissolve based upon time and/or pH[1].

Other taste-masking methods include the use of cyclodextrins, encapsulation using coacervation, electrochemical coating, and the use of supercritical fluids[1].

Direct compression is the fastest, simplest, and least expensive method of manufacturing conventional tablets or ODTs[2, 8, 9]. In its true form, direct compression consists of simple blending followed by compression of the powder blend using a conventional tablet press[8, 9]. Many methods of manufacturing ODTs which are listed as direct compression methods[2] require steps beyond this definition. Otherwise, taste-masking of unpleasant tasting drugs must be accomplished via a separate process. No current method accomplishes both taste-masking and rapid disintegration via simple blending followed by direct compression[2-5, 7, 10-21]. The specific aim of this study was to develop a taste-coating method which could be accomplished by simple blending alone with the resulting blend being suitable for direct compression into a rapidly disintegrating tablet. The hypothesis is that a material or combination of materials exist which when simply blended with Promethazine HCl, will result in an acceptable degree of taste-coating. The taste-coating must withstand the compression process and be effective in the final dosage form.

Promethazine HCl was chosen as a model drug for this study. Promethazine HCl is highly water soluble (500mg/ml)[22, 23] and has a very bitter taste as well as an unpleasant anesthetic effect in the oral cavity. These factors combined result in Promethazine HCl being a very challenging model drug for ODT formulation and manufacturing method development. Compendial methods of analysis exist for Promethazine HCl[24]. In addition to taste testing, dissolution is a key method for evaluating taste-masking. Since only dissolved drug is tasted, a reduction in the initial

dissolution is an appropriate method for evaluating taste-masking. In addition, it is important to establish that taste-masking does not retard dissolution to the extent that bioequivalence to the conventional dosage form is compromised[1].

Various hydrophobic materials in various concentrations were examined for their ability to mask the bitter taste of Promethazine HCl. The selected material, concentration, and blending method were utilized to produce tablets to insure the taste-masking method withstood the compression process. Dissolution data from powder blend and tablets are compared.

One hydrophobic material chosen for extensive study was Magnesium Stearate. Magnesium Stearate is an extremely hydrophobic material used in concentrations below 2% as a tablet lubricant in conventional tablets[8, 9]. In fact, Magnesium Stearate is the most effective and most commonly used tablet lubricant[8, 9]. Magnesium Stearate is more effective than Stearic Acid and other metallic stearates, probably due to its smaller particle size[8]. However, Magnesium Stearate tends to increase tablet friability and retard disintegration, especially as the amount of Magnesium Stearate increases and/or as the Magnesium Stearate blending time increases[8, 9]. For these reasons, some have recommended against the use of Magnesium Stearate in rapidly disintegrating dosage forms[21]. However, one method of producing ODTs utilizes up to 2.5% Magnesium Stearate as a lubricant in combination with non-direct compression grades of diluents[25].

3.2 Materials

The materials listed below were used as received:

-Promethazine HCl, USP; Gallipot; Lot 0101139;

-Promethazine HCl, USP; Honeywell (Ireland); Lot BPMH119117;

-Precirol ATO 5; atomized Glyceryl Dipalmitostearate Type I EP; C16-C18; melting point (drop point, Mettler) 53-57 °C; HLB 2; Gattefosse lot 28950; fine powder; lubricant, taste-masking, sustained release agent;

-Gelucire 33/01; Hard Fat, USP; semi-synthetic glycerides consisting of saturated fatty acids from C8 to C18 triglycerides; melting point 33-37 °C; HLB 1; Gattefosse lot 27328; semi-solid oily carrier for hard gelatin capsules, protects against light, moisture, and oxidation;

-Gelucire 43/01; as per 33/01 with a higher melting point of 42-46 °C; waxy solid (pellets or blocks);

-Compritrol 888 ATO; Glyceryl Behenate USP; Glyceryl Dibehenate EP; >83% C22; melting point 69-74 °C; HLB 2; Gattefosse lot 31463; fine powder; lubricant, binder, sustained-release agent;

-VP AEROPERL 300 Pharma; Colloidal Silicon Dioxide USP/NF, EP; hydrophobic; Degussa lot 315404042191.

-Pharmaburst C1; SPI Polyols; Lot 04C139;

-Calcium Silicate; RxCipients FM 1000; Huber Lot 294/102;

-Stearic Acid, NF, Triple Pressed Powder; Amend, Lot G18042A29;

-Magnesium Stearate, NF, Impalpable Powder; Mallinckrodt; Lot SC13325.

Other materials used in informal trials included Zinc Stearate, Calcium Stearate, Menthol, Vegetable Shortening, Petrolatum, and Sodium Saccharin.

3.3 Methods

3.3.1 UV Method

All solutions were prepared using a 0.2 M pH 6.4 Phosphate Buffer. Preliminary trials were conducted by diluting a single 30 mg/100 ml Promethazine HCl stock solution to concentrations of 5.4, 10.8, 32.4, 54.0, 75.6, 97.2, and 118.8 % label claim. In this case, label claim is 25 mg (product strength) per 900 ml (quantity of dissolution media). These concentrations correlate to a range from 0.00150 to 0.03300 mg/ml. Preliminary trials were conducted using a raw material source (Gallipot) other than that planned for use in formulation trials.

Initial unfiltered samples were collected by rotating the volumetric then immediately pouring sample into a glass collection tube. Filtered samples were withdrawn into a five ml B-D Luer-Lok plastic syringe via a manual sample probe kit (HR Easi-Probe Kit PN 72-300-305, Hanson Research) with a ten micron sintered polyethylene end filter (HR PN 27-101-074) attached to the sample end of the probe cannula. The sample probe kit consists of a stainless steel cannula with plastic connectors. Each concentration solution utilized a separate, unused filter and probe kit. An initial three ml filtered sample was withdrawn, expressed into a collection tube, followed by the withdrawal and collection of a second three ml sample. Absorbance of all samples was determined at 249 nm using a Beckman Model DU-65 (S/N 4293550) Spectrophotometer.

Additional work was conducted the following day using the same diluted solutions. Solutions and samples were stored at ambient lab conditions (21-22 °C). Standard lighting was employed while measuring, mixing, or analyzing. When not in

use, solutions and samples were stored on the lab bench with lighting turned off. An unfiltered sample was collected as done on Day 1. A four ml sample was then withdrawn via the sample probe-syringe system without the end filter. This sample was then expressed via a five micron filter needle (B-D 305200). The first ml expressed was discarded with the remaining three ml collected in a glass collection tube. Samples for the three highest concentrations were diluted with an equal volume of buffer prior to reading.

Final UV trials were conducted using the Promethazine HCl (Honeywell) to be used in formulation trials. Two independent trials (labeled as A and B) were conducted by weighing 30 mg quantities of Promethazine HCl and diluting each to 100 ml with filtered (Millipore sintered glass filter apparatus) buffer. These stock solutions were further diluted into two separate sets of dilutions in the same concentrations previously employed (seven dilutions ranging from 5.4 to 118.8 % label claim).

Unfiltered samples for each dilution were collected by inverting the volumetric and pouring directly into the glass sample collection tube. Filtered samples were collected by withdrawing five ml into a ten ml plastic B-D Luer-Lok syringe via a Hanson Research manual dissolution sample probe with no end filter. A five micron B-D filter needle (BD Item 305200, 19G, 1.5TW) was attached, two ml was expressed and discarded, and the subsequent three ml was expressed into the sample collection tube.

After a spectrophotometer bulb warm-up time of greater than one hour, the absorbance of each sample was read at 249 nm using buffer as a reference solution. Samples for the three highest concentrations were diluted with an equal volume of buffer prior to determining absorbance and the resulting absorbance value was multiplied by two.

A solution containing all excipients initially planned for use in formulation trials was prepared and the absorbance determined. Later, a solution was prepared using the final formulation excipients in the concentrations used and the absorbance of a filtered sample was determined.

3.3.2 Dissolution Method

For conventional Promethazine HCl tablets, USP dissolution (<711>) is performed in 900 ml of 0.01 N Hydrochloric Acid at 37°C using Apparatus 1 (baskets) at 100 rpm[24]. The USP limit is not less than (NLT) 75% (Q) dissolved in 45 minutes. The amount dissolved is determined by employing UV absorption at a wavelength of about 249 nm on filtered portions of the test solution, suitably diluted, in comparison with a standard solution of known concentration in the same media[24].

Certain modifications were made to the above referenced method based upon current guidelines[26] for dissolution testing of Orally Disintegrating Tablets. A 0.2 Molar pH 6.4 Phosphate Buffer was utilized. Molarity was as per USP[24] recommendations and pH was chosen based upon the pH of the oral cavity as recommended by current guidelines[26, 27]. Volume was unchanged at 900 milliliters. Apparatus 2 (paddles) at a speed of 50 rpm was utilized as per current recommendations[26, 27]. There is concern that baskets might be clogged by a rapidly disintegrating tablet. Also, 50 rpm with paddles is considered to be equivalent to 100 rpm with baskets[27]. Standard curve and filtration studies were performed as described in UV Methods above to insure this method was accurate and reproducible.

The equipment used for dissolution testing included a Beckman Model DU-65 Spectrophotometer (Serial # 4293550) and a Hanson Research SRII 6-Flask Dissolution

Test Station (Model 46-100-040, S/N 0196-2364) with HR Validata Control Module (Model 47-200-202, S/N 0196-2366). Test media was 900 ml of 0.2M pH 6.4 (±0.05) Phosphate Buffer. Specific conditions included using Apparatus 2 (paddles) at 50 rpm with a media temperature of 37.0 ± 0.5 °C. Paddles were centered and the distance from the bottom of each paddle to the bottom of each vessel was 2.5 cm. The sampling point was approximately one-half the distance from the top of the paddle to the surface of the media. The water bath level was maintained above the level of the dissolution media. The buffer was de-aerated by heating in a lab oven to approximately 41°C, followed by vacuum filtration using a Millipore sintered glass apparatus. The buffer was stirred (magnetic stir bar) vigorously under vacuum for 5 minutes. The buffer was then immediately transferred to the dissolution flasks in a pre-heated water bath. Covers were added and stirring started and continued until sample addition. Media temperature was confirmed prior to sample addition. Stirring was stopped for sample addition then immediately restarted. Samples (5 ml) were withdrawn at specified times via a Hanson Research Manual Sample Probe (HR Easi-Probe Kit PN 72-300-305) using a B-D 10 ml plastic syringe. Media was replaced after each sampling. Absorbance was determined for each sample at 249 nm. For each sample, a new 5 micron filter needle (B-D Item 305200, 19G, 1.5TW) was attached to the syringe. The first two ml expressed were discarded and the remaining 3 ml collected in a glass sample tube. For absorbance readings above 1.5, the sample was diluted with an equal volume of buffer, re-read, and the resulting absorbance value was multiplied by two. Percent Dissolved values were determined using a standard curve equation. Media temperature was rechecked and recorded at the

end of dissolution. Although not done initially, the media volume remaining was recorded for later trials.

3.3.3 Taste-Masking Trials (Blends)

Blending equipment used was as follows:

-PK Twin Shell (V) Dry Blender, S/N LB853S, tabletop unit with interchangeable shells, using an approximately two quart acrylic shell (actual volume equals 1820 ml), speed equals 22 rpm;

-Planetary Mixer, Kitchen- Aid Artisan 5-quart, single standard attachment;

-Planetary Mixer, Sunbeam Mixmaster, dual dough-hook attachments or dual egg-beater attachments as specified, 1580 ml freely rotating bowl.

The effectiveness of taste coating was evaluated primarily by dissolution testing. Ideally, the dissolution profile would consist of no drug dissolved at the initial time-point followed by subsequent rapid dissolution. Although this type of profile is attainable with true coating processes such as fluid bed coating, a more gradual increase in dissolution rate may be realized with a simple physical mixture. The acceptance criteria were an initial decrease in dissolution rate as compared to Promethazine HCl powder alone followed by subsequently meeting compendial dissolution requirements for Promethazine HCl tablets. Although this requirement for subsequent dissolution rate was quantitative, the assessment of dissolution at the initial time point was a mixture of qualitative and quantitative assessment. Although a numerical value was obtained, an absolute limit was not pre-established.

So as not to rely solely on dissolution data, taste screening was also performed by taste testing by two researchers, one of which was blinded. A small amount of powder

was tasted then expectorated. This qualitative testing was limited due to the limited number (2) of tasters and possible bias. Therefore, a large sample size of blinded, independent subjects would be required to fully evaluate taste. However, it should be noted that no decisions were based upon the lack of bitter taste alone without supporting dissolution data.

Initial trials were performed with Precirol ATO 5 Glyceryl Dipalmitostearate. Promethazine HCl (100 grams, 80.6% of mixture by weight) and Precirol (24 grams, 19.4% of mixture) were separately passed through a 30 mesh sieve and added to the V-blender in this order. This mixture was blended for 120 minutes with samples removed and internal blend and ambient temperatures recorded at 30 minute intervals. The final blend was subjected to dissolution testing (n=3, 31 mg blend equivalent to 25 mg active ingredient). Unprocessed Promethazine HCl, 25 mg, was also tested. Dissolution samples were taken at 5, 10, 15, and 30 minute time points. The final blend from the V-blender was then blended for 30 minutes in a Kitchen-Aid 5-quart planetary mixer (speed setting two).

An attempt was made to screen Gelucire 43/01 Hard Fat pellets through a 20 and 30 mesh sieve. Fifty grams (66.7%) of Promethazine HCl was mixed for approximately thirty minutes with five grams (6.7%) of Gelucire 33/01 Hard Fat in a Sunbeam Planetary Mixer (speed setting seven) with dual dough hook attachments. A total of twenty-five grams (26.7%) of Compritrol 888 ATO Glyceryl Behenate was added incrementally over a total additional mixing time of two hours. An ambient and blend temperature was recorded after the longest uninterrupted blending interval of one hour. One gram samples were taken after various additions and the final blend (n=3, 37.5 mg blend equivalent to

25 mg active) was subjected to dissolution testing. Samples were taken at 2, 5, 10, and 15 minute time-points. The dissolution stirring speed was then increased to 100 rpm and samples withdrawn after an additional 10 minutes. The final blend was then mixed for three minutes (speed setting two) with five grams of VP AEROPERL 300 Pharma hydrophobic colloidal silicon dioxide.

A number of materials were screened determine what materials to utilize in additional trials. These materials and methods included:

- Menthol + Precirol (mortar and pestle);
- Stearic Acid : Promethazine HCl 0.2:1 (mixed in rotating bottle);
- Pre-heated (69°C) Precirol ATO 5 (Glyceryl Dipalmitostearate) : Promethazine HCl 0.75:1 (pre-heated planetary mixer bowl and dough hooks);
- Precirol : Promethazine HCl 0.75:1 heated (69°C, beaker in water bath);
- Vegetable Shortening : Promethazine HCl 1:1 (mortar and pestle);
- Petrolatum: Promethazine HCl 1:1 (mortar and pestle), also with flavor added;
- Promethazine HCl : Petrolatum Mixture (petrolatum + starch + HPMC) 1:1 (mortar and pestle);
- Stearic Acid : Promethazine HCl 1:1 (mortar and pestle);
- Sodium Saccharin : Promethazine HCl 0.3 : 1 (mortar and pestle);
- Stearic Acid + Promethazine HCl + Sodium Saccharin (mortar and pestle).

Additional trials with stearates were then performed. Promethazine HCl (screened 30 mesh) 25 grams and Stearic Acid (screened 40 mesh) 12.5 grams were mixed in a Sunbeam Planetary Mixer (dual egg-beater attachments), Speed 2, for 0.75 hours. An additional 12.5 grams of Stearic Acid was added and

mixing was continued for 1.5 hours. This 1:1 Stearic Acid: Promethazine HCl blend (total blend time 2.25 hours) was subjected to dissolution testing (n = 3, 50 mg blend = 25 mg active).

One gram of Promethazine HCl was mixed in a mortar and pestle with one gram of Calcium Stearate, Magnesium Stearate, or Zinc Stearate. Each sample was taste screened by two researchers.

Promethazine HCl and Magnesium Stearate, 25 grams of each, were added to the planetary mixer. An attempt to blend, even at low speed, resulted in too much dust generation in this open system. This material was transferred to the V-Blender and mixed (22 rpm) for 1.0 hour. This 1:1 blend was subjected to dissolution testing (n = 3, 50 mg blend = 25 mg active).

Magnesium Stearate: Promethazine HCl (25 grams) blending was repeated with 12.5 grams and 16.7 grams of Magnesium Stearate. This corresponds to Magnesium Stearate: Promethazine HCL ratios of 0.5:1 and 0.67:1, respectively. An extensive screening process was added in these trials. Each material was screened (40 mesh) prior to weighing. The two materials were then co-screened (40 mesh) ten times prior to being added to the V-Blender. After 0.5 hours of blending, the material was discharged and passed five additional times through a 40 mesh screen. Blending was continued for an additional 0.5 hours (total blend time 1.0 hour). The blend was screened twice more before being subjected to dissolution testing (n = 3 for each blend, 37.5 mg and 41.7 mg respectively for the 0.67:1 and 0.5:1 blends = 25 mg active).

3.3.4 Tablet Taste-Masking Trial

Equipment utilized for testing taste-masking in compressed tablets included:

-Stokes Single-Station Tablet Press, Model 519.2, Serial Number 662673, Lot 562134, speed = 50 tablets/minute;

-Tooling: 9/32 (0.2812) inch diameter round flat-faced beveled edge (FFBE), Natoli Engineering Co., Inc. (Drawing Number 99073);

-Hardness Tester, J H DeLamar & Son, Inc., Model PT 102, Serial Number 39;

-V-Blender- as previously described (22 rpm).

Tablet formulations are shown in Table 3.3 below.

Table 3.3 Tablet Formulations

Ingredients per Tablet (theoretical tablet weight = 125 mg)

Formula/Description	Magnesium Stearate	Promethazine	Pharmaburst	Calcium Silicate
A. 0.67:1	16.7 mg (13.4%)	25.0 mg (20%)	83.3 mg (66.6%)	
B. 0.67:1 + $CaSiO_n$	16.7 mg (13.4%)	25.0 mg (20%)	58.3 mg (46.6%)	25 mg (20%)
C: 1:1	25.0 mg (20%)	25.0 mg (20%)	75.0 mg (60.0%)	

Ingredients per Batch (g)

Formula/Description	Magnesium Stearate	Promethazine	Pharmaburst	Calcium Silicate
A. 0.67:1	6.0	9.0	30.0	
B. 0.67:1 + CaSiOn	6.0	9.0	21.0	9.0
C: 1:1	15.0	15.0	45.0	

Magnesium Stearate: Promethazine HCl blends from previous taste-masking trials were utilized for the initial tablet trials. These pre-blends were V- blended with Pharmaburst for five minutes. Formulation B which included Calcium Silicate was prepared by first V-blending the pre-blend with Calcium Silicate for two minutes followed by the addition of Pharmaburst with three additional minutes of blending.

These blends were compressed on the single-station tablet press. Hardness and weight values (n=5) were determined. Three tablets from the Magnesium Stearate: Promethazine HCl-Pharmaburst formulas (A and C) were subjected to dissolution testing.

3.4 Results and Discussion

3.4.1 UV Method

Absorbance versus concentration data are shown numerically in Table 3.4a and graphically in Figure 3.4a. These results indicate that a notable loss occurs to the filter and/or sample probe. The second three ml filtered sample results indicate this loss is partially, but not adequately, saturated. In addition, it appears samples with an absorbance value above 1.5 should be diluted prior to measuring.

Upon review of these results, additional work was conducted the following day using the same diluted solutions. Hanson Research Technical Support was contacted and suggested that filtering not be employed or filtering be performed with another type filter after the sample is withdrawn into the syringe. The USP method does state to analyze a filtered sample. This also would appear to be the preferred method from a scientific standpoint. The important criterion in filtering after withdrawal is that in actual dissolution trials, this filtering must be performed immediately to reduce the likelihood of dissolution of particles occurring in the sample after the withdrawal time.

The results for Day 1 and Day 2 unfiltered data are presented graphically in Figure 3.4b. These results indicate stability of absorbance of drug in solution under ambient conditions for the intended formulation studies and dissolution testing. In addition, dilution of samples with absorbance above 1.5 to fifty percent concentration is sufficient for the range employed in these studies.

Table 3.4a. Absorbance Data

Absorbance Data at 249 nm

	DAY 1 HR End Filter				DAY 2** 0.5 µ Filter Needle			
					Initial readings		Second readings***	
% label*	Unfiltered	1st 3 ml	2nd 3 ml	2nd 3 ml/ Unf. X 100	Unfiltered	Filtered	Unfiltered	Filtered
5.4	0.116	0.050	0.088	75.9	0.063	0.054	0.075	0.062
10.8	0.227	0.156	0.211	93.0	0.180	0.178	0.194	0.187
32.4	0.766	0.514	0.709	92.6	0.718	0.718	0.734	0.734
54.0	1.283	0.997	1.239	96.6	1.247	1.255	1.269	1.263
75.6	1.750	1.436	1.689	96.5	1.700	1.684	1.738	1.722
97.2	2.113	1.823	2.034	96.3	2.200	2.232	2.294	2.294
118.8	2.119	2.119	2.119	100.0	2.730	2.766	2.822	2.880

*After Day 1, samples for the 3 highest concentrations were diluted with an equal amount of buffer, read, and absorbance multiplied by 2 to obtain the reported values.
**4 ml sample, 1st ml discarded
***Re-read after additional bulb warm-up time.

Figure 3.4a. Effect of End Filter Filtration on Absorbance Values

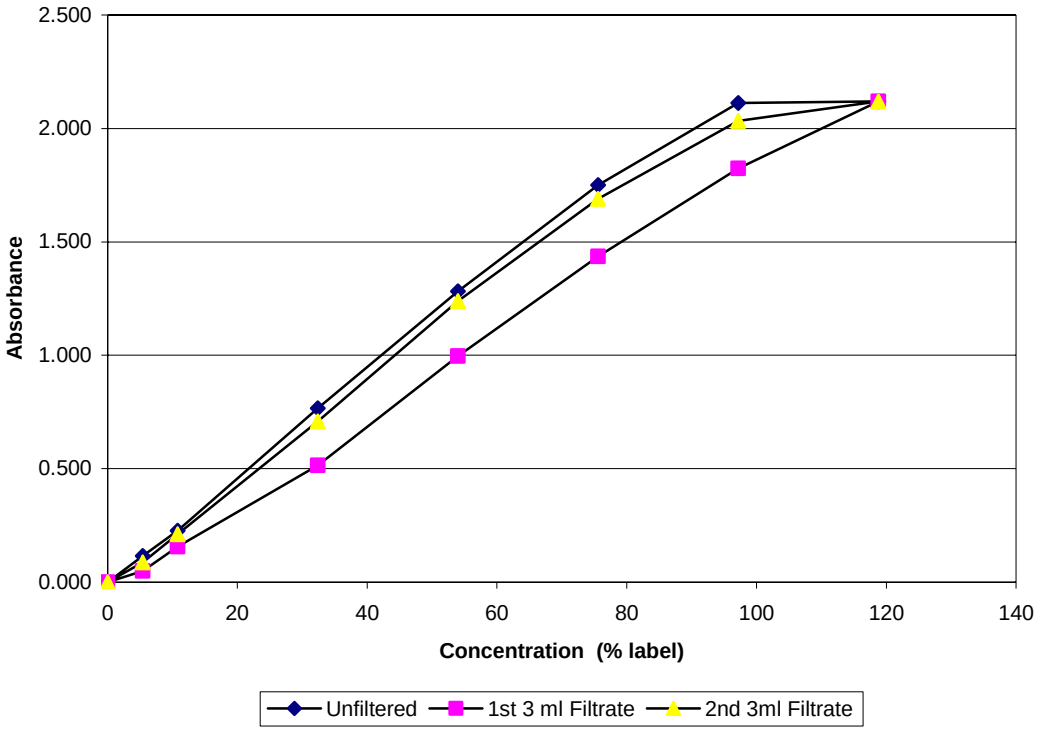


Figure 3.4b. Effect of Time and Dilution on Absorbance Values

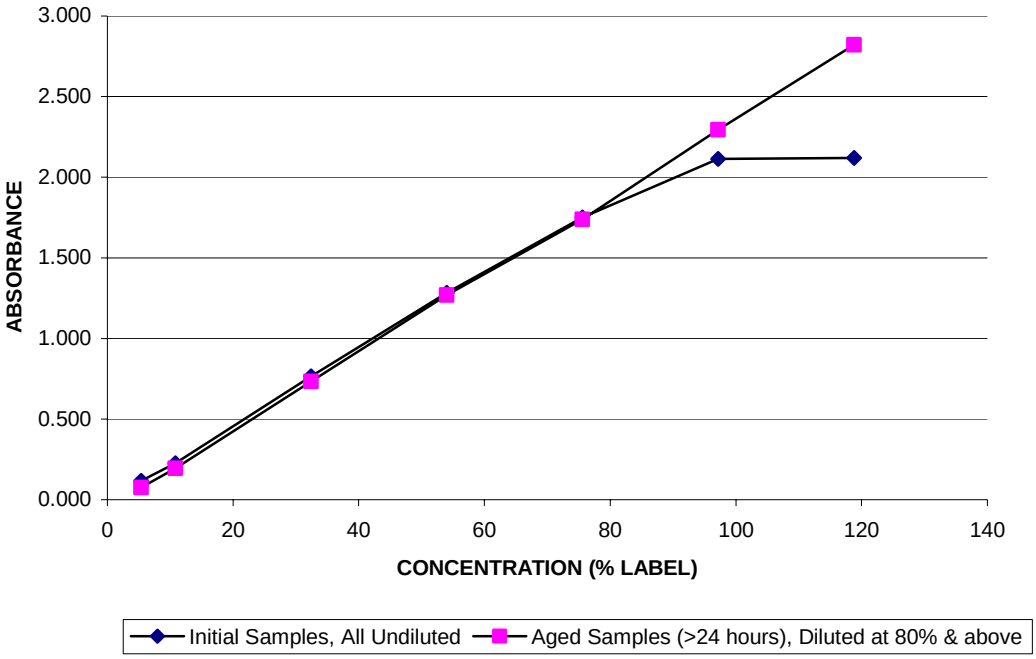


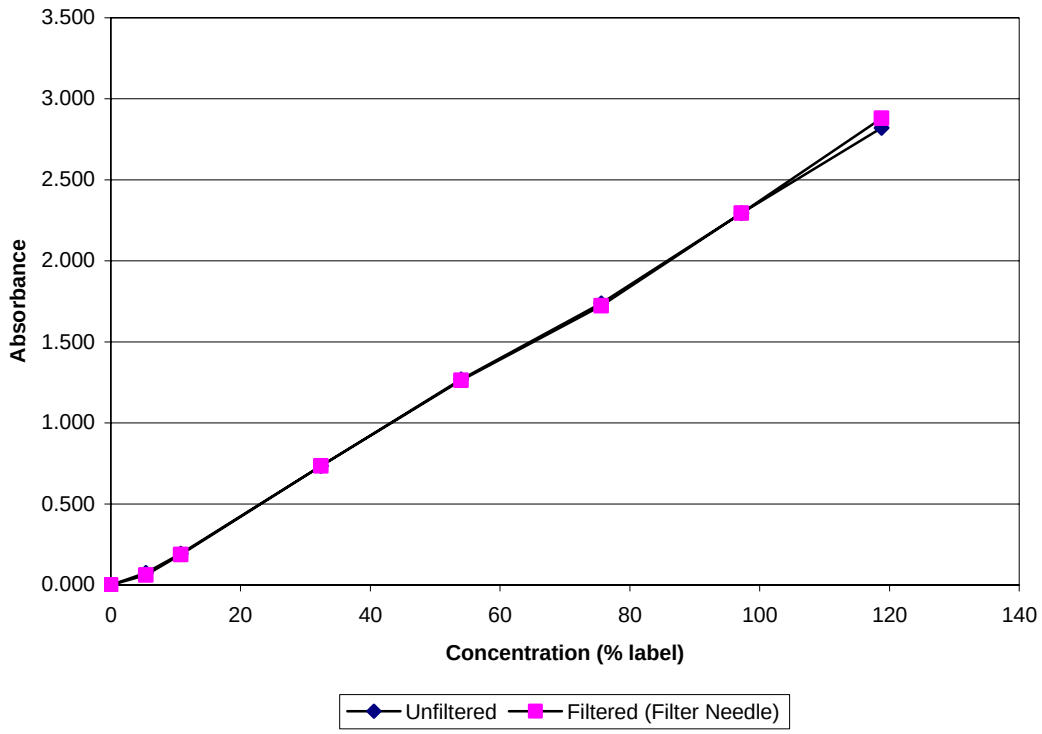
Figure 3.4c presents a graphical comparison of Day 2 filtered and unfiltered absorbance data. In this case a four milliliter sample was filtered with a filter needle and the first milliliter discarded, the filtered versus unfiltered curves are nearly identical. This indicates the previous loss on Day 1 was to the end filter. The use of a filter needle did not result in a significant loss at concentrations at or above 10.8 percent label claim.

Some loss did occur to the filter needle at the lowest concentration. A single trial where the first two ml rather than one ml expressed were discarded yielded identical readings for unfiltered and filtered and appeared to solve this problem. A closer look at the raw data indicates this concentration may also be below the accurate, reproducible absorbance range for this compound. Lack of precision at the lowest concentration does not invalidate the method. In addition, it was noted that allowing one hour rather than the minimum fifteen minute instrument bulb warm-up time is recommended for more accuracy and reproducibility**.**

Final trials conducted in duplicate were undertaken. These trials incorporated all recommendations from the initial trials. These recommendations included a minimum one hour UV bulb warm-up time, use of a filter needle, withdrawal of five ml with the first two milliliters discarded, and sample dilution when absorbance was above 1.5.

Final trials absorbance data are presented in Table 3.4b. Figure 3.4d is a graphical representation comparing absorbance data before and after filtering of samples. This data indicate a slight loss to the filter occurs. The loss is much less dramatic than that seen with the use of a Hanson Research end filter. For example, for this method (filter needle) the maximum loss is about five percent whereas with the end filter the loss at the lowest

Figure 3.4c Effect of Filtration with Filter Needle on Absorbance Values



concentration was over sixty percent for the first three milliliters of filtrate and still approximately twenty-five percent for the second filtrate.

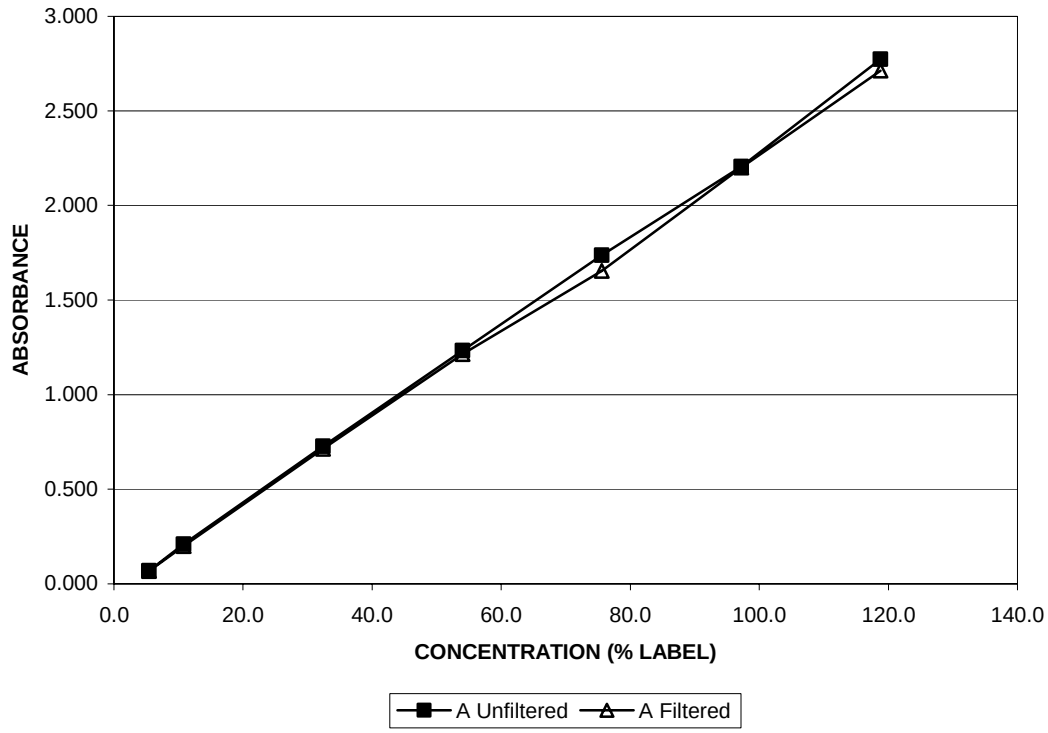
Figure 3.4e graphically presents average absorbance versus concentration plots for filtered samples. One graph reflects the lines for individual trials A and B whereas the second plot presents average data. The results for A and B unfiltered are very similar as reflected by the indistinguishable lines on the graph comparing these values. This indicates the method is very reproducible, especially when considering that some samples are diluted prior to measurement. This introduces an additional step for potential error. This similarity between the data sets also indicates good technique by the lab personnel.

The average values for filtered samples are used to prepare the absorbance versus concentration plot which will be utilized to determine percent dissolved based upon absorbance values of filtered dissolution samples. The trend line indicates the actual concentration values (y) are very similar to predicted concentration values. The coefficient of determination (R^2) of 0.9995 indicates a high degree of linearity for this method. This absorbance versus concentration line is described by the equation: **y = 0.0231x – 0.0493 where y = absorbance and x = concentration (% label claim).** Absorbance readings at 249 nm were zero for solutions prepared with excipients planned for use and with excipients at concentrations in the final tablet formulation. This indicates

Table 3.4b. Final Trials Absorbance Data

% Label	A Unfiltered	A Filtered	B Unfiltered	B Filtered	Average Unfiltered	Average Filtered	F/U x 100 (%)
5.4	0.069	0.067	0.076	0.071	0.073	0.069	94.5
10.8	0.210	0.199	0.209	0.204	0.210	0.202	96.2
32.4	0.727	0.714	0.753	0.717	0.740	0.712	96.2
54.0	1.232	1.215	1.273	1.233	1.253	1.224	97.7
75.6	1.736	1.654	1.738	1.662	1.737	1.658	95.5
97.2	2.206	2.200	2.220	2.180	2.213	2.190	99.0
118.8	2.774	2.712	2.654	2.726	2.714	2.719	100.2

Figure 3.4d. Effect of Filtration on Absorbance (Duplicate Trials, Filter Needle)



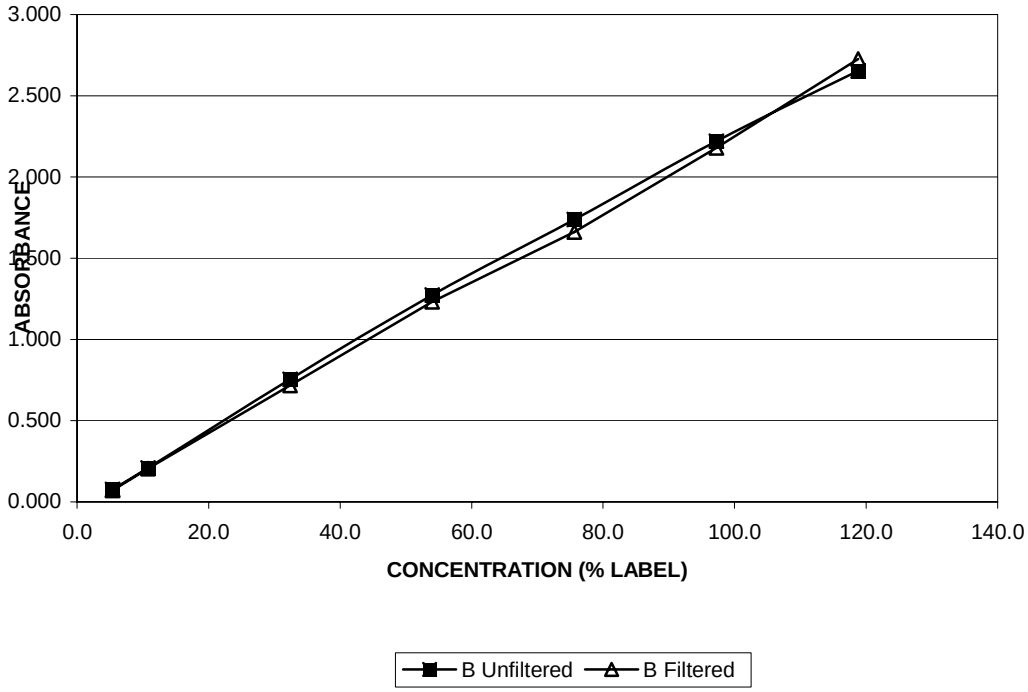
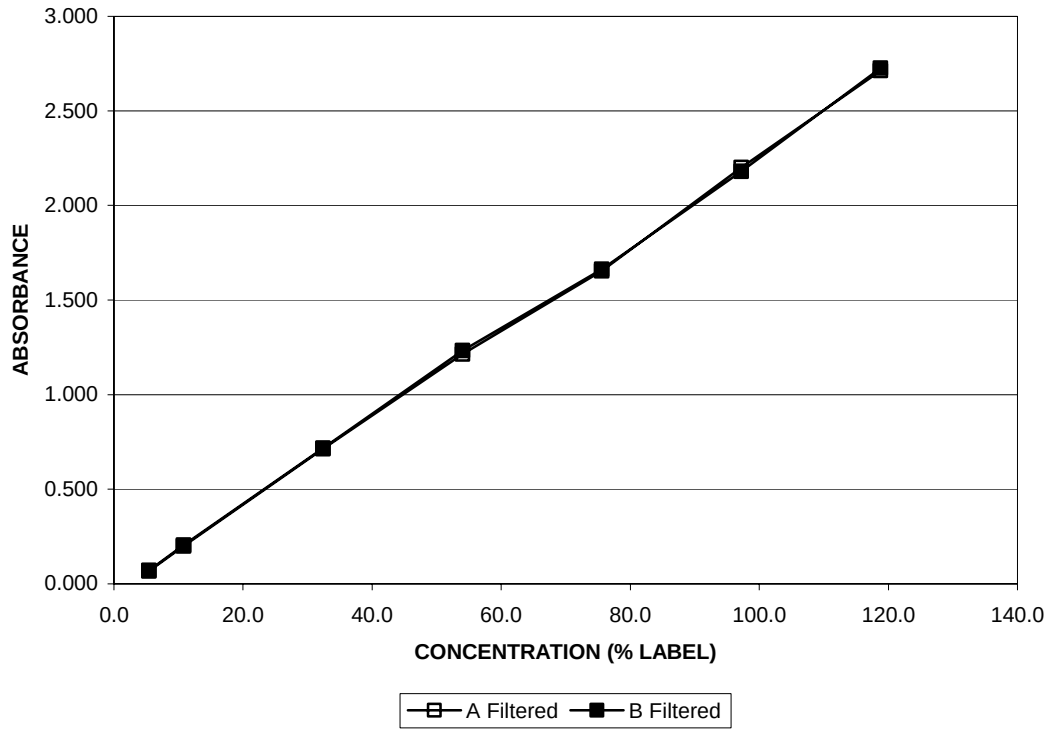
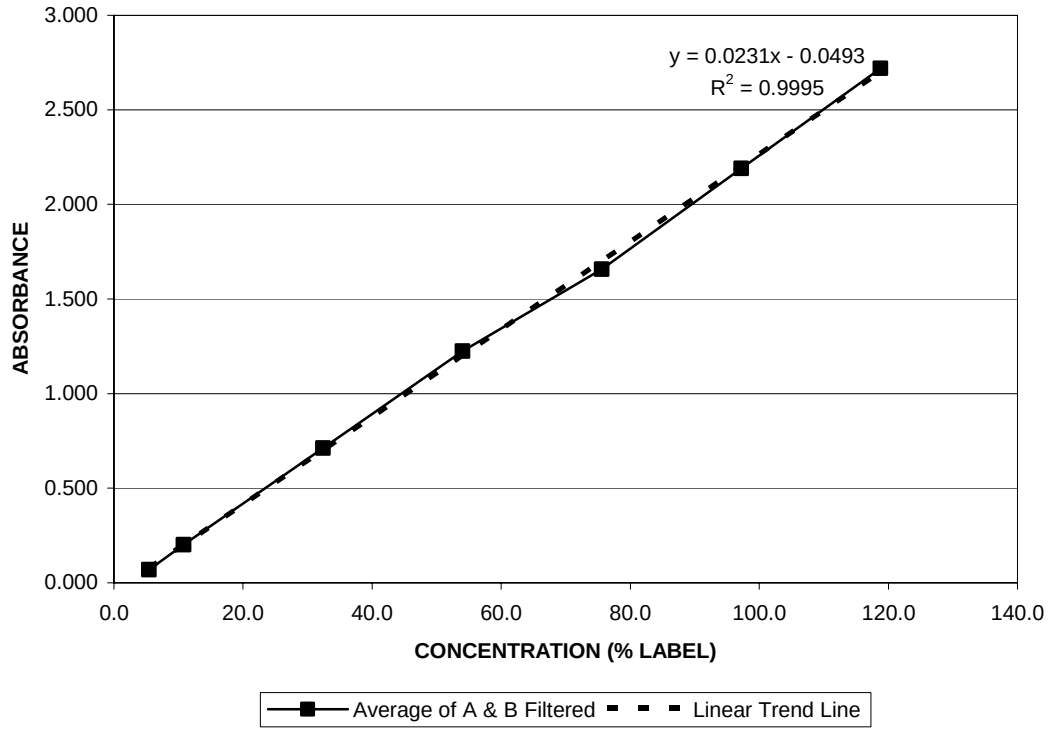


Figure 3.4e. Relationship of Absorbance and Concentration





inactive ingredients should not interfere with UV analysis of Promethazine HCl at 249 nm. The method as used in the final trials is suitable for use in formulation development trials. The method is linear, reproducible, corrected for minor drug loss, and lacks interference by inactive ingredients.

3.4.2 Taste Masking

Dissolution data from initial taste masking trials are presented in Tables 3.4c, 3.4d, and 3.4e. These same data are presented graphically in Figure 3.4f. Dissolution of Promethazine HCl powder and Promethazine HCl blended (two hours, V-Blender) with approximately twenty percent Precirol ATO 5 Glyceryl Dipalmitostearate was rapid and complete. This blending did not retard dissolution. Further blending of this blend in a Kitchen-Aid planetary blender did not visually appear to result in any intimate mixing of these materials. As expected, no notable heat build-up occurred during this blending as indicated by the lack of an internal blend temperature difference from ambient temperature of more than one degree Celsius.

At this point, Gelucire Hard Fat materials were considered. These materials are labeled by the manufacturer as more semi-solid in nature and used to protect against light, moisture, and oxidation. Gelucire 43/01 has a melting point of approximately 43 °C and would be preferred for taste-masking since this temperature is above the temperature of the oral cavity. However, this material supplied as pellets was too hard to hand screen and could not be simply mixed with Promethazine HCl. Gelucire 33/01 (melting point around 33 °C) is a semi-solid with a texture similar to softened margarine. This material would appear to mix and potentially coat better. However, the lower melting point is a concern

Table 3.4c Promethazine HCl Dissolution Data

Flask #	Abs @ 5 min	Conc @ 5 Min	Abs @ 10 min	Conc @ 10 min	Abs @ 15 min	Conc @ 15 min	Abs @ 30 min	Conc @ 30 min
F1	2.114	93.6	2.510	110.8	2.488	109.8	2.366	104.6
F2	2.268	100.3	2.426	107.2	2.416	106.7	2.380	105.2
F3	2.298	101.6	2.602	114.8	2.646	116.7	2.606	114.9
Mean		98.5		110.9		111.1		108.2
SD		4.3		3.8		5.1		5.8
%RSD		4.4		3.5		4.6		5.4

Table 3.4d. Promethazine HCl + Precirol Dissolution Data*

Flask #	Abs @ 5 min	Conc @ 5 min	Abs @ 10 min	Conc @ 10 min	Abs @ 15 min	Conc @ 15 min	Abs @ 30 min	Conc @ 30 min
F1	2.402	106.1	2.392	105.7	2.392	105.7	2.422	107.0
F2	2.320	102.6	2.242	99.2	2.348	103.8	2.376	105.0
F3	2.384	105.3	2.316	102.4	2.334	103.2	2.380	105.2
Mean		104.7		102.4		104.2		105.7
SD		1.9		3.2		1.3		1.1
%RSD		1.8		3.2		1.3		1.0

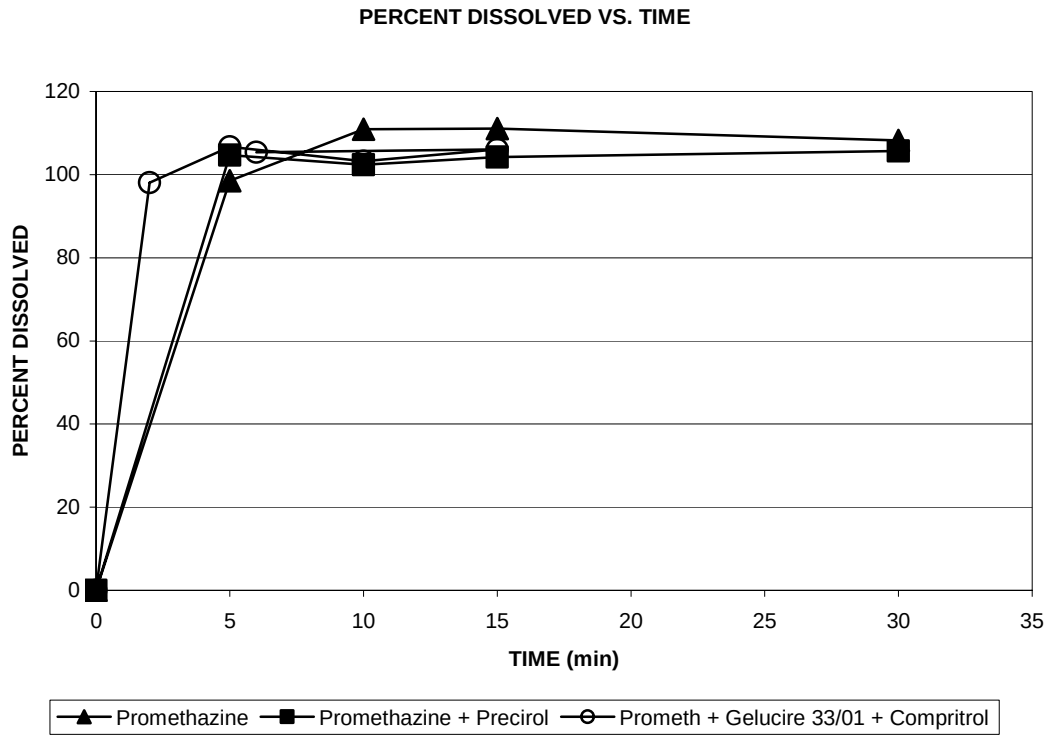
* Promethazine HCl (80.6%) + Precirol ATO 5 Glyceryl Dipalmitostearate (19.4%)

Table 3.4e. Promethazine HCl + Gelucire + Compritrol Dissolution Data*

Flask #	Abs @ 2 min	Conc @ 2 min	Abs @ 5 min	Conc @ 5 min	Abs @ 10 min	Conc @ 10 min	Abs @ 15 min	Conc @ 15 min	Abs @ + 10 min 100rpm	Conc @ + 10 min 100 rpm
F1	2.172	96.2	2.384	105.3	2.310	102.1	2.312	102.2	2.334	103.2
F2	2.240	99.1	2.406	106.3	2.352	104.0	2.462	108.7	2.452	108.3
F3	2.238	99.0	2.452	108.3	2.344	103.6	2.428	107.2	2.372	104.8
Mean		98.1		106.7		103.2		106.1		105.4
SD		1.7		1.5		1.0		3.4		2.6
%RSD		1.7		1.4		0.9		3.2		2.5

* Promethazine HCl (66.7%) + Gelucire 33/01 Hard Fat (6.7%)
+ Compritrol 888 ATO Glyceryl Behenate (26.7%)

Figure 3.4f. Initial Taste-Masking Dissolution Plot



with regard to taste-masking. A small amount (6.7%) of this material was blended with Promethazine HCl in an attempt to create a “sticky” surface. This was followed by the addition of Compritrol 888 ATO Glyceryl Behenate (26.7%), a very fine powder lipid with a higher melting point (around 70 °C). As before, no notable build-up of heat occurred. The graphed profile differs because an earlier (two minute) time point was tested to see if any delay occurred.

This blend was then mixed at a slower speed for three minutes with VP AEROPERL 300 Pharma hydrophobic Colloidal Silicon Dioxide. This rapidly converted the waxy appearing blend into a fine, free-flowing powder. This information may be helpful in future trials.

For all dissolution trials, percent dissolved values of greater than one hundred percent were obtained. For the first trial with unprocessed Promethazine HCl powder, a long (two-hour) equilibration time was employed between adding media to the flasks and starting the dissolution test. Since excessive evaporation can lead to higher concentrations, subsequent trials were conducted with minimal yet adequate equilibration times of less than thirty minutes and final media volumes were measured and recorded. The trend of these latter trials was lower yet still above ideal. The measurable media loss ranged from one to two percent. This alone would not explain the high percent dissolved results. It was considered, especially with a powder that does not sink before dissolving as a typical tablet would, that slow diffusion at 50 rpm could result in higher concentrations near the sampling point (midway between surface of media and top of paddle). At the completion of the third dissolution test, the stirring rpm was increased to 100 rpm for ten additional minutes. Although the higher speed is visually more effective

in mixing, the percents dissolved for these samples were not lower. The high numbers do not appear to be the result of inadequate mixing. It should be noted that the numbers in the latter two trials are not beyond the range sometimes observed in dissolution testing. The shorter dissolution equilibration times employed in the latter trials were employed in all subsequent trials. These materials or and process did not retard dissolution by simple blending without heat, high-shear, or solvents.

Subsequent screening trials were conducted. Menthol did not influence the physical form of Precirol. The pre-heated Precirol cooled rapidly and resulted in an uneven mixture of granules, large agglomerates, and uncoated powder. The melted Precirol mixture did not readily appear to mask the drug taste upon cooling (Taste was informally evaluated by the investigator touching a minute portion to the side of the tongue.). A review of solubility data for Promethazine HCl reflects the challenge in masking this bitter tasting drug. Although highly water soluble, Promethazine HCl exhibits lipid soluble properties as well[22, 23].

Vegetable shortening did appear to slightly delay the bitter taste of Promethazine HCl. Petrolatum and petrolatum mixtures helped slightly but less so than shortening. Stearic Acid, Sodium Saccharin, and the combination of these ingredients showed promise in masking this bitter taste. It was decided to pursue formal blending trials with Stearic Acid and metallic stearates. Saccharin or another sweetening agent would be added in later formulations.

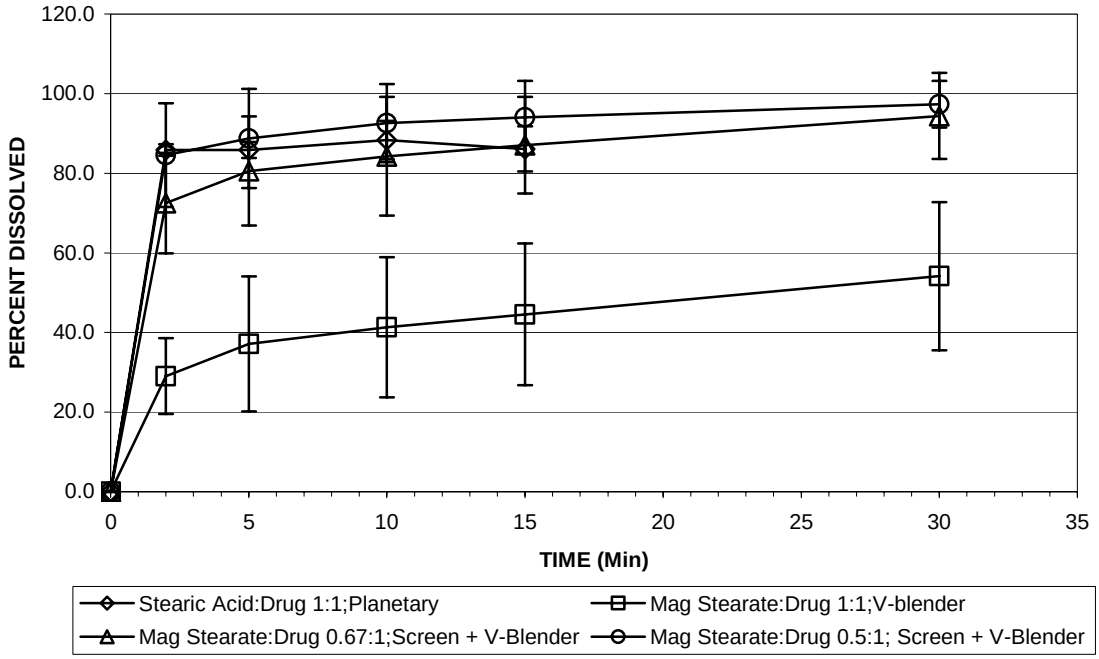
Dissolution results for Stearic Acid and metallic stearate trials are shown in Table 3.4f. A graphical representation of these same data is presented in Figure 3.4g. Stearic Acid did slow Promethazine HCl dissolution to approximately eighty-five percent at two

Table 3.4f. Stearate Trials Dissolution Data

PROMETHAZINE DISSOLUTION DATA (PERCENT DISSOLVED)

Time (min)	0	2	5	10	15	30
Sample Description						
Stearic Acid: Drug 1:1						
SAF1	0.0	87.2	86.1	92.4	88.2	
SAF2	0.0	84.3	83.7	83.0	79.7	
SAF3	0.0	86.0	87.7	89.6	90.4	
AVG SA	0.0	85.8	85.8	88.3	86.1	
SD	0.0	1.5	2.0	4.8	5.7	
%RSD	0.0	1.7	2.3	5.5	6.6	
Magnesium Stearate: Drug 1:1						
1:1 F1	0.0	30.4	34.4	38.5	42.6	54.9
1:1 F2	0.0	18.9	21.7	25.3	27.8	35.2
1:1 F3	0.0	37.8	55.3	60.2	63.3	72.4
AVG 1:1	0.0	29.0	37.1	41.3	44.6	54.2
SD	0.0	9.5	17.0	17.6	17.8	18.6
%RSD	0.0	38.0	45.6	42.7	40.1	34.4
Magnesium Stearate: Drug 0.67:1						
0.67:1 F1	0.0	58.1	65.4	67.2	73.2	82.2
0.67:1 F2	0.0	78.0	84.3	90.9	92.1	98.4
0.67:1 F3	0.0	81.4	92.0	94.7	95.8	102.6
AVG 0.67:1	0.0	72.5	80.6	84.3	87.0	94.4
SD	0.0	12.6	13.7	14.9	12.1	10.8
%RSD	0.0	17.4	17.0	17.7	13.9	11.4
Magnesium Stearate: Drug 0.5:1						
0.5:1 F1	0.0	86.9	90.7	93.1	96.3	98.3
0.5:1 F2	0.0	70.5	75.4	82.5	84.0	91.0
0.5:1 F3	0.0	96.2	100.1	102.1	101.9	102.6
AVG 0.5:1	0.0	84.5	88.7	92.6	94.1	97.3
SD	0.0	13.0	12.5	9.8	9.2	5.9
%RSD	0.0	15.4	14.0	10.6	9.8	6.0

Figure 3.4g. Stearate Trials Percent Dissolved vs. Time Plot



minutes. However, dissolution did not notably increase with time. Since this profile did not show the desired effect of initially slowing dissolution followed by subsequent complete dissolution, the use of metallic stearates was examined. For later trials, an additional thirty minute dissolution sample was taken.

Informal mortar and pestle trials indicated Magnesium Stearate and Calcium Stearate were more effective in masking taste than Zinc Stearate. Magnesium Stearate appeared to be slightly more effective than Calcium Stearate. Magnesium Stearate and Calcium Stearate have a smaller particle size and better coating properties than Stearic Acid. Magnesium Stearate is considered to be a more efficient lubricant than Calcium Stearate[8]. Based upon observed results and theoretical considerations, blending trials with Magnesium Stearate were undertaken.

In a 1:1 ratio, Magnesium Stearate reduced the average Promethazine HCl percent dissolved to below thirty percent at two minutes and below fifty-five percent at thirty minutes. This was by far the greatest reduction in dissolution observed to date. The variation between samples (i.e., between dissolution flasks) was large and did not decrease with time. The blending process incorporated a very small portion of the blender capacity and the Magnesium Stearate appeared to adhere to the acrylic blender shell walls and form small agglomerates at times. This observation coupled with the large variation in percent dissolved between blend samples led to a concern that the blend was potentially not uniform. Therefore, the extensive screening steps were added in subsequent trials.

The lower ratio (0.67:1 and 0.5:1) Magnesium Stearate: Promethazine HCl blends both slowed initial dissolution, but dissolution increased with time. As expected, the

greater the amount of Magnesium Stearate, the lower the dissolution profile. Variation between samples decreased as the amount of Magnesium Stearate decreased. For the lower ratio blends, variation decreased as time (and subsequently dissolution) increased. It should be noted that the increase in dissolution with time occurred for each flask. The variation in samples correlated with the variation between flasks in initial dissolution. Based upon these observations, the agglomeration of powder on the surface of the dissolution medium may affect initial dissolution. Therefore, this variation may be a phenomenon associated only with powder testing and should decrease when testing a finished dosage form (tablet) which sinks. In addition, the variation in the initial trial was likely not related to blend uniformity.

Magnesium Stearate slowed the initial dissolution of Promethazine HCl. Taste screening supported this observation. How this will translate to final blends and compressed tablets is unknown. In order to evaluate the effects of final blending and compression, blending with additional excipients and compression was undertaken with Magnesium Stearate: Promethazine HCl blends. Although some screening is prudent, the extensive amount of screening was reduced.

Pharmaburst, a commercially available ODT platform, was chosen as a system which would allow the quick evaluation of the effects of final blending and compression on dissolution of Magnesium Stearate: Promethazine HCl blends. Physical test data for compressed tablets are shown in Table 3.4g. Dissolution test data are shown in Table 3.4h. Graphical representations of dissolution data are shown in Figures 3.4h, 3.4i, and 3.4j. Formula A (0.67:1 Magnesium Stearate: Promethazine HCl- Pharmaburst) tablets

Table 3.4g. Tablet Physical Test Data

0.67:1 Magnesium Stearate: Promethazine HCl-Pharmaburst Tablets (Formula A)

Parameter	Hardness	Weight (mg)
	4.0	126
	4.0	125
	5.0	126
	5.5	125
	4.5	125
Average	4.6	125.4
SD	0.7	0.6
%RSD	14	0.4

1:1 Magnesium Stearate: Promethazine HCl- Pharmaburst Tablets (Formula C)

Parameter	Hardness	Weight (mg)
	4.0	121
	4.0	119
	4.0	117
	4.0	119
	4.0	121
Average	4.0	119.4
SD	0	1.5
%RSD	0	1.3

Table 3.4h. Tablet Dissolution Data

Promethazine 25 mg Tablet Dissolution Data						
Magnesium Stearate: Promethazine 0.67:1 + Pharmaburst						
Sample Description	**Percent Dissolved**					
Time (min)	0	2	5	10	15	30
F1	0.0	85.9	88.4	95.0	96.9	95.3
F2	0.0	31.4	64.3	79.5	83.3	88.2
F3	0.0	77.3	86.5	89.2	90.4	93.3
Average	0.0	64.9	79.7	87.9	90.2	92.3
SD	0.0	29.3	13.4	7.9	6.8	3.7
%RSD	0.0	45.2	16.8	9.0	7.6	4.0
0.67:1 Blend Data(AVG)	0.0	72.5	80.6	84.3	87.0	94.4
SD	0.0	12.6	13.7	14.9	12.1	10.8
%RSD	0.0	17.4	17.0	17.7	13.9	11.4
Magnesium Stearate: Promethazine 1:1 + Pharmaburst						
Sample Description	**Percent Dissolved**					
Time (min)	0	2	5	10	15	30
F1	0.0	65.1	75.5	79.2	81.4	85.8
F2	0.0	85.9	81.4	80.7	81.6	86.3
F3	0.0	70.4	80.4	83.2	85.9	89.4
Average	0.0	73.8	79.1	81.0	83.0	87.2
SD	0.0	10.8	3.2	2.0	2.5	2.0
%RSD	0.0	14.7	4.0	2.5	3.0	2.3
1:1 Blend Data (AVG)	0.0	29.0	37.1	41.3	44.6	54.2
SD	0.0	9.5	17.0	17.6	17.8	18.6
%RSD	0.0	38.0	45.6	42.7	40.1	34.4

Figure 3.4h. 0.67:1 Individual Tablet Dissolution Plot

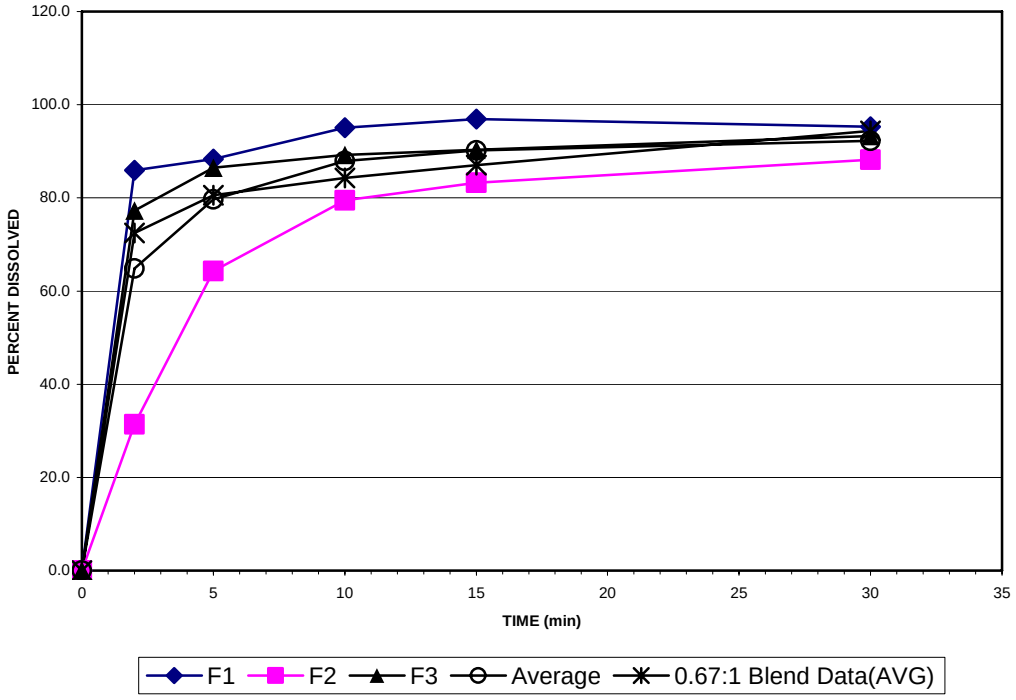


Figure 3.4i. 1:1 Individual Tablet Dissolution Plot

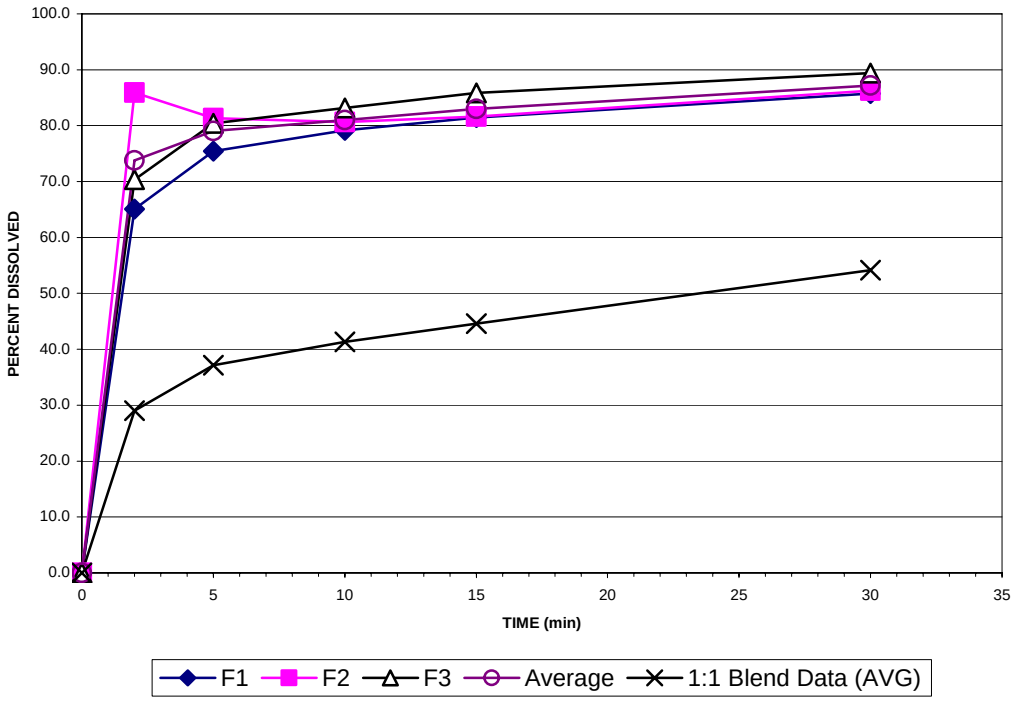
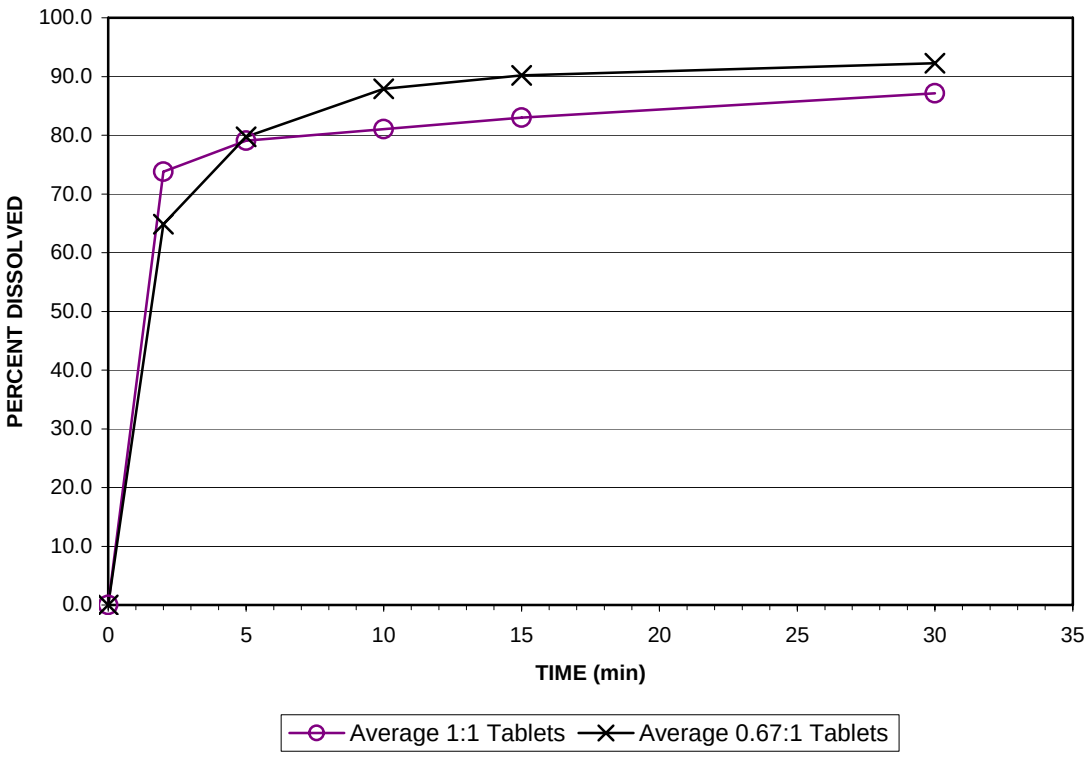


Figure 3.4j. 0.67:1 and 1:1 Average Tablet Dissolution Plot



compressed with no apparent problems. Formula B, which included Calcium Silicate, was very light and fluffy (high bulk volume) and did not flow well. Weight control was difficult and this formula was abandoned. Formula C (1:1 Magnesium Stearate: Promethazine HCl- Pharmaburst) tablets containing a higher ratio of Magnesium Stearate also did not flow well. Enough tablets were compressed for the testing performed with only a small quantity to spare. The weight of these tablets was low (range 117-121 mg, average = 119.4 mg, theoretical = 125 mg). Tablets at the upper end of this range (121mg, 96.8% of theoretical) were selected for dissolution. It should be noted that the addition of an agent such as Colloidal Silicon Dioxide to improve flow at later stages is expected to solve this problem. However, for these trials, the goal was to observe the effect of final blending and compression on dissolution. Therefore, changes from the pre-blends previously tested were kept at a minimum.

The 0.67:1 ratio tablets did exhibit some delay (average 65% at two minutes) in dissolution. Flask two was notably slower than flasks one and three. All tablets sunk and the tablets in vessels one and three quickly and completely disintegrated in less than one minute. The tablet in flask two appeared to stick to the bottom of the vessel and disintegrated much slower. After the testing was complete, when cleaning flask two, a residue in the shape of the tablet was evident on the bottom of the vessel. There appeared to be a permanent ring etched in the glass. This flask was removed from service at this point. Also, due to a faulty syringe, the two minute flask one sample was actually drawn at three minutes after replacing the defective syringe. This value was higher than the flask three value. Overall, the average tablet dissolution profile appeared to match the

corresponding average pre-blend dissolution profile. This to indicate final blending and compression did not affect dissolution.

The 1:1 ratio tablets briefly floated then rapidly disintegrated while sinking. The tablets were completely disintegrated in less than one minute and before the sinking process was completed. A re-examination of these tablets indicated they were soft as compared to the 0.67:1 A tablets. Although the difference in average hardness was not great (4.0 vs. 4.6), further investigation indicates 4.0 may be the minimum reading obtained with the hardness tester utilized (Note: Testing of subsequent batches indicated this was not the case. Re-testing of these tablets at a later date yielded a similar average of 3.6 with variability (2.0-5.5) from tablet to tablet.). Dissolution was very fast as compared to the corresponding pre-blend and dissolution at two minutes was actually faster (74% vs. 65%) than that observed for the 0.67:1 ratio tablets as would be expected, dissolution at the latter time points and the overall profile was lower than for the 0.67:1 tablets. The variation between flasks, especially at five minutes and beyond, was very low (< 4%) as compared to the variation observed with blends and the 0.67:1 tablets, all of which varied more in powder dispersion or tablet disintegration.

Based upon observations with blend and tablet dissolution testing, the initial percent dissolved is greatly related to the sample dispersion or disintegration and dispersion, respectively. Overall dissolution trends do correlate with the level of coating agent, Magnesium Stearate. Although both 0.67:1 and 1:1 ratio tablets were better tasting than uncoated drug, informal taste tests indicated the 1:1 ratio tablets were notably better tasting than the 0.67:1 ratio tablets.

Although not completely correlated with initial time point dissolution data, Magnesium Stearate does notably improve the taste of both Promethazine HCl blends and tablets. The 1:1 ratio does afford taste improvement while meeting USP dissolution requirements (NLT 75% in 45 minutes) for conventional Promethazine HCl tablets[24]. Higher levels of Magnesium Stearate may adversely affect compressibility and disintegration. Formulation trials proceeded utilizing a 1:1 Magnesium Stearate: Promethazine HCl ratio.

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4. ORALLY DISINTEGRATING TABLET FORMULATION

Abstract

Orally Disintegrating Tablets (ODTs) which rapidly dissolve in the saliva without the need for water have become a very popular dosage form. This is especially true in certain disease states and/or patient populations. For offensive tasting drugs, no method of simple blending followed by direct compression has resulted in achieving both taste-masking and a robust, rapidly disintegrating tablet. Previous trials indicated Magnesium Stearate V-blended in a 1:1 ratio with Promethazine HCl resulted in taste-masking of this highly soluble, offensive tasting drug. However, a large amount of hydrophobic Magnesium Stearate has a tendency to increase both tablet friability and disintegration time. This is of special concern with ODTs where it is a difficult balance to produce a tablet which both disintegrates rapidly and is robust enough for packaging, shipping, and handling. Formulation trials were undertaken to produce such a tablet via simple blending and direct compression in the presence of this large amount of Magnesium Stearate. The combination of Dextrates, NF as the diluent with multiple disintegrants with different mechanisms of action did yield a robust, pleasant tasting, rapidly disintegrating tablet. This method yielded a tablet with a friability of 0.17%, an *in vitro* disintegration time of 21 seconds, and an *in vivo* disintegration time of less than one minute. Although this method overcame the bitter taste of Promethazine, the unpleasant anesthetic effect of this drug in the oral cavity was only greatly reduced, not eradicated.

4.1 Introduction

Orally Disintegrating Tablets (ODTs) have become a popular dosage form. An ODT may be defined as a tablet which disintegrates and/or dissolves rapidly (< one minute) in the saliva without the need for water or other liquid[1]. These readily transportable dosage forms are intended to be taken anytime or anywhere[1, 2]. Certain patient groups such as children, elderly, and psychiatric patients greatly benefit from this technology[3-5]. This dosage form is especially beneficial in certain medical conditions such as pain, migraine, nausea, panic attack, allergic conditions, cough/cold, and Alzheimer's[3-5].

Market research has shown a significant number of consumers prefer an ODT over a conventional tablet. This research has also shown that taste is a very important factor. Longer disintegration times were acceptable if the taste was good. However, the converse was not true; fast disintegration times were not acceptable if taste was bad[1]. Although some drugs have little taste and a simple addition of flavor will result in an acceptable taste, most drugs to be incorporated into an ODT formulation require taste-masking [1].

Although some ODT manufacturing methods allow for taste-masking as part of the manufacturing process, many do not[2-7]. In those methods which do accomplish taste-masking, the steps involved are often the same or similar processing methods as those used to accomplish taste-masking in independent processes[2-7]. These processes include wet granulation, roller-compaction, spray-drying, and coating[1, 2]. Taste-coating may be achieved using polymers which dissolve based upon time and/or pH[1].

Other taste-masking methods include the use of cyclodextrins, encapsulation using coacervation, electrochemical coating, and the use of supercritical fluids[1].

Direct compression is the fastest, simplest, and least expensive method of manufacturing conventional tablets or ODTs[2, 8, 9]. In its true form, direct compression consists of simple blending followed by compression of the powder blend using a conventional tablet press[8, 9]. Many methods of manufacturing ODTs which are listed as direct compression methods[2] require steps beyond this definition. For example, taste-masking of unpleasant tasting drugs must often be accomplished via a separate process. No current method accomplishes both taste-masking and rapid disintegration via simple blending followed by direct compression[2-5, 7, 10-16]. Previous studies in our labs indicated Magnesium Stearate V-blended in a 1:1 ratio with Promethazine HCl was effective in masking the bitter, offensive taste of this drug. Preliminary tableting trials with Pharmaburst, an off-the-shelf ODT platform[2, 16], indicated this taste-masking method was not compromised by additional blending followed by direct compression. The large quantity of Magnesium Stearate resulted in poor tableting and soft tablets. The specific aim of this study was to develop a direct compression formulation with this Magnesium Stearate: Promethazine blend which would yield rugged yet rapidly disintegrating tablets. If successful, this would yield a simple method of producing ODTs which accomplishes both taste-masking and rapid disintegration via simple blending followed by direct compression. This process would be much simpler and less expensive than currently available multi-step ODT manufacturing methods.

Magnesium Stearate is an extremely hydrophobic material used in concentrations below 2% as a tablet lubricant in conventional tablets[8, 9]. In fact, Magnesium Stearate is

the most effective and most commonly used tablet lubricant[8, 9]. Magnesium Stearate is more effective than Stearic Acid and other metallic stearates, probably due to its smaller particle size[8]. However, Magnesium Stearate tends to increase tablet friability and retard disintegration, especially as the amount of Magnesium Stearate increases and/or as the Magnesium Stearate blending time increases[8, 9]. For these reasons, some authors have recommended avoiding the use of Magnesium Stearate in rapidly disintegrating dosage forms[16]. However, one method of producing ODTs utilizes up to 2.5% Magnesium Stearate as a lubricant in combination with non-direct compression grades of diluents.

For direct compression ODT processes, sugar based excipients (mannitol, sorbitol, xylitol, maltose, etc.) are routinely used for their high water solubility, sweet taste, and pleasant mouthfeel[2, 5-7]. In addition to taste and mouthfeel, disintegration time is a primary concern. Some ODT technologies use effervescent couples alone or in combination with other disintegrants to achieve rapid disintegration[2, 5-7]. The use of disintegrants, and especially the newer superdisintegrants, has made the advent of compression based ODTs possible[5].

Various materials have been utilized as disintegrants. Starches and modified starches have a long history of use as disintegrants[9, 17]. Within this group, the superdisintegrant Sodium Starch Glycolate is of most interest today[9]. This material is commonly used in levels of 2-8% by weight and its primary mechanism of action as a disintegrant is via swelling[9, 17].

Crospovidone (cross-linked polyvinylpyrrolidone) is another superdisintegrant of choice[2, 9, 17]. Although historically used in a range of 2-5%[9, 17], one manufacturer recommends up to 15% by weight in ODT formulations[18]. In fact, a specific grade

featuring a smaller and more narrow particle size distribution has been developed specifically to yield better mouth feel in ODT formulations[18]. Crospovidone is said to promote both wicking and swelling[18]. Crospovidone's disintegrant action is dependent upon compression force[17]. A certain tablet hardness is required for the swelling and expansion to be effective.

Modified celluloses are another common group of disintegrants[2]. Most recommended among this group is Croscarmellose Sodium, an internally cross-linked Sodium Carboxymethycellulose[9, 17]. Typical use levels range from 2-4% although lower and higher amounts have been utilized[9, 17]. This disintegrant works via both wicking and swelling[9, 17].

Calcium Silicate in amounts up to 30% by weight has also been used to promote disintegration[17, 19]. RxCipients® FM 1000® Calcium Silicate from Huber Engineered Materials (Havre de Grace, Maryland) is extremely hydrophobic[19]. When combined with superdisintegrants, the superdisintegrants are said to expand against this hydrophobic material. This expansion against another material is said to promote rapid tablet break down into primary particles.[19] Other disintegrants employed in ODTs are Alginic Acid, Sodium Alginate, Microcrystalline Cellulose, Methacrylic Acid-Divinylbenzene Copolymer Salts, and Poly(Acrylic Acid) Superporous Hydrogel (SPH)[2].

Various methods will be utilized to evaluate the ODT formulations. Traditional tablet tests such as hardness, thickness, friability, and disintegration[8, 9] will be performed. Key among these is disintegration and friability testing. A critical balance in formulating ODTs is achieving a rapid disintegration time with a tablet rugged enough to withstand packaging, shipping, and handling. A harder, stronger tablet typically has a longer

disintegration time[2, 8, 9]. USP methods for conventional tablets will be utilized[20]. It is assumed that a tablet rugged enough to meet friability requirements for conventional tablets can be packaged, shipped, and handled using conventional materials, equipment, and methods. Although *in-vitro* disintegration times may differ from *in vivo* disintegration times[2], when comparing similar formulations, a reduction in *in vitro* disintegration time would likely correspond to a reduction in *in vivo* disintegration time. Informal *in vivo* disintegration and taste testing will also be performed.

4.2 Materials

-Promethazine HCl, USP; Honeywell (Ireland); Lot BPMH119117;

-Magnesium Stearate, NF, Impalpable Powder; Fisher Scientific, Lot 974493;

-Dextrates, NF; EMDEX, JRS Pharma, LP, Lot 04H502X;

-Colloidal Silicon Dioxide, NF; AEROSIL VV 200 Pharma, Degussa, Lot 4020513;

-Colloidal Silicon Dioxide, NF; VP AEROPERL 300 Pharma, Degussa, Lot 3154042191;

-Croscarmellose Sodium, NF; Ac-Di-Sol, FMC Biopolymer, Type SD-711, Lot T442N;

-Crospovidone, NF; Polyplasdone XL-10, ISP Technologies, Inc., Lot 03400117085;

-Crospovidone, NF; Polyplasdone XL, ISP Technologies, Inc., Lot 03300106081;

-Sodium Chloride, USP; Morton Salt, Hutchinson Plant;

-Silicified Microcrystalline Cellulose (Microcrystalline Cellulose, NF + Colloidal Silicon Dioxide, NF); ProSolv HD-90, JRS Pharma, LP, Lot D9B4033X;

-Compressible Sucrose; Sugartab, JRS Pharma, LP, Lot 47X;

-Copovidone, USP; Plasdone S-630, ISP Technologies, Inc., Lot 05400118999;

-Maltodextrin, NF; Maltrin QD M500, Grain Processing Corporation, Lot M031329001;

-Sodium Starch Glycolate, NF; Explotab, JRS Pharma LP, Lot 4111034021X;

-Microcrystalline Cellulose, NF (PH 102 and PH 105); FMC Biopolymer, Lot 7303C (PH 102) and Lot 5416C (PH 105);

-Polyethylene Glycol 8000, NF, Granular, Carbowax Sentry Grade; Dow, Lot SG075557D1(167020);

-Mannitol, USP, Spray-dried; Pearlitol 200SD, Roquette, Lot 755074;

-STARLAC (spray-dried mixture of 85% Lactose Monohydrate, NF and Corn Starch, NF); Roquette, Lot Y9165;

-Microcrystalline Cellulose/Guar Gum, Co-processed; Avicel CE-15, FMC Biopolymer, Lot RH322;

-Calcium Silicate; RxCipients FM 1000, Huber, Lot 294/102;

-Saccharin Sodium, USP, Powder; Syncal-S, PMC Specialties Group, Inc Lot 3891 (manufacturer); Mutchler (supplier);

-Natural Wild Cherry Flavor; WONF FAFW075, WILD Flavors, Inc, Lot F050103382;

-Alginic Acid, NF; Satialgine H8, JRS Pharma LP, Lot 2700393X;

-Soy Polysaccharides; Emcosoy STS IP, JRS Pharma LP, Lot P660002580X;

-Calcium Carbonate DC; Type CS 90L, SPI Pharma, Lot 0408001;

-Citric Acid, USP, Monohydrate, Granular; Mallinckrodt, Lot A20613;

-Saccharin Sodium, USP, Granular; City Chemical LLC, Lot 01L185;

-Artificial French Vanilla Flavor; FAFW079, WILD Flavors, Inc, Lot S05020416H;

-Sodium Lauryl Sulfate, NF/FCC; Fisher, Lot 735986-60;

-Citric Acid, USP/FCC, Anhydrous; Humco, Lot 519072E;

-Masking Flavor, Natural; Flavors of North America, Inc., #936-780/PM, Lot SR-05-00038744;

-Sucralose, NF, Micronized; Tate & Lyle Sucralose, Inc, Lot H3004B36MA;

-Bentonite, Powder, Purified Grade; Fisher B-235, Lot 730257B;

-Key Lime Flavor, Natural & Artificial (N&A), FAGJ869; WILD, Lot F080901Z;

-Lemon Flavor, N&A, 862.001/EN; FONA, SR# SR-05-0041750;
-Citrus Flavor, Natural, 828.112/EN; FONA, SR# SR-05-0041750;

-Cherry Pineapple Flavor, N&A, FAGJ872; WILD, Lot S05050302B;

-Orange Cream Flavor, N&A, FAGJ866; WILD, Lot F0508322.

4.3 Methods

4.3.1 General Methods

Blending

Blending was performed using a Patterson-Kelley Twin Shell (V) Dry Blender, Serial Number LB853S, tabletop unit with interchangeable shells. An approximately two quart (actual volume equals 1820 ml) acrylic shell with a speed of 22 rpm was used. Specific blend times and procedures are described in the appropriate specific method.

Tableting

Tableting was performed using a Stokes Single-Station Tablet Press, Model 519.2, Serial Number 662673, Lot 562134, speed equals 50 tablets/minute. Tooling for 125 mg target weight tablets was 9/32 (0.2812) inch (7.1 mm) diameter round, plain, flat-faced beveled edge (FFBE). Tooling for 250mg, 300 mg and 350 mg target weight tablets was 7/16 (0.4375) inch (11.1 mm) diameter, round, plain, standard concave. The one exception was lot GGG which employed 11/32 (0.3438) inch (8.7 mm) diameter, round, plain, standard concave tooling.

Hardness, Thickness, and Weight Testing

All tablets for testing were randomly selected from each finished lot or sub-lot. Tablet Hardness was determined for ten tablets using a J. H. DeLamar & Son, Inc. Model PT 102, Serial Number 39, Hardness Tester. Although not listed on this instrument, one

literature souce[21] lists kg/cm^2 as the units for this tester. Thickness was determined by manually measuring the thickest point of ten individual tablets using a Fisher Scientific battery-operated, digital dial caliper. Ten tablets were weighed individually using an analytical balance. Average and Standard Deviation values were determined and reported for each parameter.

Friability

Friability was determined as per USP <1216> Tablet Friability method[20] using a Roche-type friabilator rotated at 25 rpm for four minutes for a total of 100 revolutions. Drop-height was 156.0 ± 2.0 mm (6.1 inches). Ten randomly selected tablets were de-dusted, weighed, and placed in the friabilator. After 100 rotations, the tablets were removed, de-dusted, and re-weighed. Percent Friability was determined as: ((Initial Weight – Final Weight)/ (Initial Weight)) * 100. A maximum weight loss of not more than 1.0 % was considered acceptable. Broken tablets were noted and considered a test failure. Initially, friability was performed on select batches only since early trials produced tablets which were obviously not rugged enough to be friability tested. Beyond this point, friability testing was performed on each lot or sub-lot.

Disintegration

Disintegration testing was performed as per USP <701> Disintegration[20] for uncoated tablets. Purified water at 37 ± 2 °C was used as the test media. Six randomly selected tablets were placed into each of the six tubes of the apparatus. The apparatus was operated and the time for the last tablet to disintegrate was recorded as the disintegration time. Notable observations were also recorded.

Flavor Testing

Individual solutions of flavors were prepared. Concentrations were such that 0.5 ml solution included the amount of the ingredient projected in a 350 milligram tablet. These projections were based upon 25 milligrams Promethazine, 0.4% Flavor, 1.5% Citric Acid, 0.5% Saccharin Sodium, and 0.25% Sucralose. Initially, 1.0 ml of each flavor solution was combined with 1.0 ml drug solution and purified water was added to bring the final volume to 4.0 ml. The mixtures were randomly sorted and 250 microliters of each were independently and blindly tasted by two researchers. A lemon juice in water mixture was used to rinse between each tasting.

A single flavor was selected for further testing. Solutions of Saccharin Sodium, Citric Acid, Promethazine + Citric Acid, Promethazine + Saccharin Sodium, and Promethazine + Saccharin Sodium + Citric Acid + Key Lime Flavor were prepared and tasted. The combination of Drug + Flavor + Citric Acid was tasted with the addition of Saccharin Sodium, Sucralose, ½ Strength Saccharin Sodium, Saccharin Sodium + Sucralose, and ½ Strength Saccharin Sodium + Sucralose.

4.3.2 Initial Active Ingredient Tablet Trials

Initial formulations included a Pharmaburst control and four in-house formulations which differed in choice or level of disintegrant. These trials employed materials commonly used in direct compression ODT products to assess the challenges to be encountered with this method. In addition to drug and Magnesium Stearate, in-house formulas contained the following:

-Flavors/Sweeteners- Saccharin Sodium, Masking Flavor, Wild Cherry Flavor;

-Disintegrants- Sodium Starch Glycolate (2 or 4%), or Crospovidone XL-10 (5 or 10%);

-Taste/Mouthfeel Excipients- Maltodextrin and Microcrystalline Cellulose/Guar Gum;

-Glidant- Colloidal Silicon Dioxide 200 VV Pharma;

-Diluent- Mannitol, Spray-Dried.

Specific formulations are shown in Table 4.3a. Individual batch sizes were 1000 tablets (125 grams). Pre-blends for all batches were made together to decrease variables and to save labor. Batch quantities are shown in Table 4.3b. The blending procedure and description of pre-blends follow.

1. Weigh all raw materials and pass individually (except Maltodextrin) through a 20 mesh sieve.

    - Flavor/Flow Pre-Blend

2. Add ITEMS, (8) MCC/Guar Gum (skip item 8 for Pharmaburst Control), (2B) Saccharin Sodium, (4B) Nat Wild Cherry Flavor, and ITEM (9) Colloidal Silicon Dioxide to V-Blender;

3. Blend for TEN minutes;

4. Add ITEM (7) Maltodextrin (For Pharmaburst Control, Skip Steps 4 & 5);

5. Blend FIVE minutes;

6. Discharge Flavor/Flow Pre-Blend into a suitable container and retain.

    - Drug/Sweetener/Flavor/Magnesium Stearate Blend

7. Add ITEM (1) Promethazine to V-Blender;

8. Add ITEM (2A) Saccharin Sodium;

9. Blend FIVE minutes;

10. Add ITEM (3) Masking Flavor and ITEM (4A) Nat Wild Cherry Flavor;

11. Blend FIFTHTEEN minutes;

12. Add ITEM (5) Magnesium Stearate and Blend SIXTY minutes.

Table 4.3a. Initial Tablet Formulations

Promethazine 25mg ODT Formulations

Item No.	Ingredient	Weight Percent	Quantity (mg/tablet) *D.Pharmaburst Control*	*E.SSG* Low*	*F. SSG* High*	*G.Crospovidone Low*	*H. Crospovidone High*
1	Promethazine HCl, USP	20.0	25.000	25.000	25.000	25.000	25.000
2A	Sodium Saccharin, USP	2.4	3.000	3.000	3.000	3.000	3.000
3	Masking Flavor, FONA	0.2	0.250	0.250	0.250	0.250	0.250
4A	Nat Wild Cherry Flavor	0.3	0.375	0.375	0.375	0.375	0.375
5	Magnesium Stearate,NF	20.0	25.000	25.000	25.000	25.000	25.000
6E	Sod Starch Glycolate,NF	2.0		2.500			
6F	Sod Starch Glycolate,NF	4.0			5.000		
6G	Crospovidone, NF	5.0				6.250	
6H	Crospovidone, NF	10.0					12.500
7	Maltodextrin, NF	10.0		12.500	12.500	12.500	12.500
8	MCC/Guar Gum	5.0		6.250	6.250	6.250	6.250
2B	Saccharin Sodium, USP	0.8	1.000	1.000	1.000	1.000	1.000
4B	Nat Wild Cherry Flavor	0.3	0.375	0.375	0.375	0.375	0.375
9	Colloidal Silicon Dioxide,NF	1.0	1.250	1.250	1.250	1.250	1.250
	Subtotal		56.250	77.500	80.000	81.250	87.500
10A	Mannitol	30.0-38.0		47.500	45.000	43.750	37.500
10B	Pharmaburst	55.0	68.750				
	Total		125.000	125.000	125.000	125.000	125.000

* SSG = Sodium Starch Glycolate, NF

Table 4.3b. Batch Quantities

Batch Quantities				
Item	**Ingredient**	**Weight**	**mg/tablet or**	**g/6000 tablets**
No.		**Percent**	**g/1000 tabs**	
	Drug/Sweetener/Flavor/Magnesium Stearate Blend			
1	Promethazine HCl, USP	20.0	25.000	150.00
2A	Sodium Saccharin, USP	2.4	3.000	18.00
3	Masking Flavor, FONA	0.2	0.250	1.50
4A	Nat Wild Cherry Flavor	0.3	0.375	2.25
5	Magnesium Stearate, NF	20.0	25.000	150.00
	Total	42.9	53.625	321.75
	Disintegrant (varies by formula)			
6E	Sod Starch Glycolate, NF	2.0	2.500	
6F	Sod Starch Glycolate, NF	4.0	5.000	
6G	Crospovidone, NF	5.0	6.250	
6H	Crospovidone, NF	10.0	12.500	
	Flavor/Flow Pre-Blend (for all batches except Pharmaburst Control)			
7	Maltodextrin, NF	10.0	12.500	75.00
8	MCC/Guar Gum	5.0	6.250	37.50
2B	Saccharin Sodium, USP	0.8	1.000	6.00
4B	Nat Wild Cherry Flavor	0.3	0.375	2.25
9	Colloidal Silicon Dioxide, NF	1.0	1.250	7.50
	Pre-Blend Total	17.1	21.375	128.25
10B	Pharmaburst	55.0	68.750	
10A	Mannitol E. SSG Low	38.0	47.500	
	Mannitol F. SSG High	36.0	45.000	
	Mannitol G. Crospovidone. Low	35.0	43.750	
	Mannitol H. Crospovidone. High	30.0	37.500	
Individual Batch Size = 1000 tablets (125 grams)				
Pre-blends made together for all batches				

- Final Blending

14. Add ITEM 6 Sodium Starch Glycolate ***or*** Crospovidone to blend in V-Blender (Drug/Sweetener/Flavor/Magnesium Stearate Blend from Step 13);

15. Blend FIVE minutes;

16. Add Flavor/Flow Pre-Blend (from Step 6);

17. Blend THREE minutes;

18. Add ITEM 10 Pharmaburst ***or*** Mannitol;

19. Blend FIVE minutes;

20. Discharge, weigh, calculate yield, and retain in a suitable container.

Tablets were compressed using the Stokes Single-Station Tablet Press and the previously described tooling and speed setting. After some initial adjustment trials, a single setting for weight and compression force was used to compress each blend. Tablets were immediately subjected to weight, thickness, and hardness testing. Ten tablets were randomly selected for testing and each tablet was individually tested for weight, thickness, and hardness.

Tablets from each blend were randomly selected for disintegration testing per USP methodology (1 trial, 6 tablets, distilled water, 37 °C).

4.3.3 Placebo Tablet Trials

The placebo blends shown in Table 4.3c below were compressed to evaluate the effects of no or different glidants. Magnesium Stearate (20%) and Dextrates (78-80%) alone or with two percent hydrophobic (VP AEROPERL 300 Pharma) or hydrophilic (AEROSIL VV 200 Pharma) Colloidal Silicon Dioxide were prepared and compressed.

Table 4.3c. Glidant Trial Formulations

Ingredient	I. No Glidant	J. AEROPERL	K. AEROSIL
Magnesium Stearate, NF	12.5 g (20%)	12.5 g (20%)	12.5 g (20%)
Dextrates, NF (EMDEX)	50.0 g (80%)	48.75 g (78%)	48.75 g (78%)
Colloidal Silicon Dioxide, NF; AEROPERL or AEROSIL	N/A	1.25 g (2%)	1.25 g (2%)
Total (62.5 g = 500 tabs)	62.5 g	62.5 g	62.5 g

Blending instructions were as follows:

1. Weigh raw materials;
2. Screen 20 mesh;
3. Blend all materials except Magnesium Stearate in V-Blender (22 rpm) for 4 minutes;
4. Add Magnesium Stearate and blend 6 additional minutes;
5. Discharge, compress (125 mg), and test (weight, thickness, hardness, disintegration).

Compression was performed using the Stokes Single-Station Tablet Press and the previously described speed setting and tooling. One set of weight and hardness settings established for the first blend (No Glidant) was utilized for all three blends.

Additional trials were undertaken. Individual formulations and target or theoretical tablet weights are shown in Table 4.3d. Formula I from the previous glidant trials is included for comparative purposes. Blend batch sizes were 62.5 grams (500 tablets) and 60.0 grams (200 tablets) for the 125 milligram and 300 milligram tablets respectively.

Table 4.3d. Additional Placebo Formulations

Formula & Target Weight	Ingredient (% w/w) Magnesium Stearate	Dextrates	Coll. Silicon Dioxide	Croscar-mellose Na	Cros-povidone	NaCl	Co-povidone	Other
I 125 mg	20	80						
L "	20	70	2	8				
M "	20	60	2	8	XL-10 10			
N "	20	58	2	20				
O "	20	60	2	8		10		
P "	20	55	2	8	XL 5	10		
Q "	20	50	2	8				SMCC 20
R "	18	77	1	4				
S "	18	72	1	4		5		
T 300 mg	8.3	82.7	1	8				
U "	8.3	62.7	1	8				Sucrose 20
V "	8.3	77.7	1	8			5	
W "	8.3	67.7	1	8			15	
X "	8.3	62.7	1	8		10	10	
Y "	8.3	62.7	1	8				Maltrin 10
Z1 Hi "	8.3	81.3						Drug 8.3
Z2 Med "								SSG 2
Z3 Lo "								
Notes:								
Z: Hi, Med, and Lo refers to high, medium, and low compression force, respectively.								
I-Q: Final Blending Time = 6 minutes;								
R-Y: Final Blending Time = 3 minutes;								
Z: Final Blending Time = 2 minutes.								

SSG = Sodium Starch Glycolate
SMCC = Silicified Microcrystalline Cellulose

All materials were weighed and passed through a 20 mesh sieve except for Dextrates and Maltodextrin which were passed through a 14 mesh sieve. All materials other than Magnesium Stearate were placed in the V-blender and blended for four minutes. Magnesium Stearate was then added and blending was performed as per the final blending times noted in Table 4.3d. Formulation Z is different in that it contains active ingredient. In this case, Magnesium Stearate: Promethazine 1:1 blend from previous taste making trials was utilized in place of Magnesium Stearate alone.

Final blends were discharged, weighed, and compressed into tablets. Tablets were compressed at a single compression force with the exception of Formulation Z which was compressed and tested at low, medium, and high compression force adjustments. Weight, thickness, hardness, and disintegration testing was performed on each lot or sub-lot. Selected batches were subjected to friability testing.

4.3.4 Active Ingredient Tablet Trials

Various trials employing active ingredient were undertaken. Formulations are shown in Table 4.3e. Each formulation with a theoretical tablet weight of 300 milligrams consisted of 8.3% w/w each Magnesium Stearate and Promethazine HCl. The exceptions were formulations with a 250 or 350 milligram tablet weight where these percentages were 10.0% and 7.1% respectively. The primary diluent used was Dextrates with its weight percentage varying from 55.8% to 88.3%. Remaining ingredients and their percentages are included in tables and Formula Z2 from previous trials and corresponding results are included for comparison purposes.

Table 4.3e. Active Formulations

Formula	% SSG	% Croscar-	% Calcium	% Other
		mellose Na	Silicate	
Z2	2			
AA	4			
BB	8			
CC	2	2		
CC Low	2	2		
DD	2	3		
DD Low	2	3		
EE	3	2		
EE Low	3	2		
FF	3	3		
FF Low	3	3		
GG	3	3		3 Copovi-
GG Low	3	3		3 done
HH	4	4		
HH Low	4	4		
II	3	3	1.5	
II Low	3	3	1.5	
JJ	3	3	2.0	
JJ Low	3	3	2.0	
KK	3	3		2 MCC PH102
KK Low	3	3		2 MCC PH102
LL	3	3	1.5	2 MCC PH102
LL Low	3	3	1.5	2 MCC PH102
MM	3	3	1.5	2 PEG
MM Low	3	3	1.5	2 PEG
NN	3	3	1.5	<mix time
NN Low	3	3	1.5	<mix time
OO	3	3	1.5	10 Mannitol
OO Low	3	3	1.5	10 Mannitol
PP	3	3	1.5	20 STARLAC
PP Low	3	3	1.5	20 STARLAC
QQ	3	3	1.5	4 Avicel CE
QQ Low	3	3	1.5	4 Avicel CE
RR	3	3	4.5	< mix time
RR Low	3	3	4.5	< mix time

SSG = Sodium Starch Glycolate

MCC PH 102 = Microcrystalline Cellulose PH 102

Represents a notable improvement and serves as control for subsequent trials.

Table 4.3e. Active Formulations (continued)

Formula	% SSG	% Croscar-mellose Na	% Calcium Silicate	% Other
All formulas below based on NN, changes/additions noted				
SS	1% Saccharin Na Powder,0.6% Cherry			
SS Low	Flavor & Change Blend Procedure			
TT	4% MCC PH 105			
TT Low	4% MCC PH 105			
UU	2.5% Alginic Acid			
UU Low	2.5% Alginic Acid			
VV	2.5% Soy Polysaccharides			
VV Low	2.5% Soy Polysaccharides			
WW	1.25% Soy Polysaccharides			
WW Low	1.25% Soy Polysaccharides			
All formulas below based on WW, changes/additions noted				
XX	2% Calcium Carbonate, DC			
XX Low	2% Calcium Carbonate, DC			
YY	4% Calcium Carbonate, DC			
YY Low	4% Calcium Carbonate, DC			
All formulas below also contain 2% Calcium Carbonate, changes/additions noted				
ZZ	0.5% Colloidal Silicon Dioxide (AEROSIL)			
ZZ Low	0.5% Colloidal Silicon Dioxide (AEROSIL)			
AAA	1% Saccharin Na,Powder,0.6% Cherry Flavor			
AAA Low	1% Saccharin Na,Powder,0.6% Cherry Flavor			
BBB	AAA + 2% Citric Acid,Monohydrate,Granular			
BBB Low	AAA + 2% Citric Acid,Monohydrate,Granular			
CCC	2% Citric Acid,Monohydrate,Granular			
CCC Low	2% Citric Acid,Monohydrate,Granular			
DDD	0.5% Saccharin Na,Granular, 0.2% Vanilla Flavor			
DDD Low				
EEE	CCC - Calcium Silicate			
EEE Low	CCC - Calcium Silicate			
FFF	DDD + 1% Citric Acid,Monohydrate, Granular			

Table 4.3e. Active Formulations (continued)

GGG	XX with smaller diameter (11/32") tooling
GGG Low	XX with smaller diameter (11/32") tooling
HHH	XX + 25% Mannitol SD 200
HHH Low	XX + 25% Mannitol SD 200
III	XX + 0.1% Sodium Lauryl Sulfate
III Low	XX + 0.1% Sodium Lauryl Sulfate
Calcium Carbonate Removed, WW as control	
JJJ	WW, change blend procedure
JJJ Low	WW, change blend procedure
KKK	WW + 2% Citric Acid Anhydrous, USP-FCC
KKK Low	WW + 2% Citric Acid Anhydrous, USP-FCC
LLL	WW + 0.3% each sucralose,vanilla,and
LLL Low	masking flavors
MMM	WW, Tablet Weight 350 mg
MMM Low	WW, Tablet Weight 350 mg
NNN	WW, Tablet Weight 250 mg
NNN Low	WW, Tablet Weight 250 mg
OOO	MMM + 1% Citric Acid,Monohydrate,Granular
OOO Low	MMM + 1% Citric Acid,Monohydrate,Granular
PPP	Drug:Mag Stearate/Pharmaburst(86%),350mg
PPP Low	Drug:Mag Stearate/Pharmaburst(86%),350mg
QQQ	MMM + 1% Bentonite
QQQ Low	MMM + 1% Bentonite
RRR	MMM + 1% Crospovidone, NF XL-10
RRR Low	MMM + 1% Crospovidone, NF XL-10
SSS	MMM + 20% Maltodextrin, NF (QD M500)
SSS Low	MMM + 20% Maltodextrin, NF (QD M500)

Magnesium Stearate: Promethazine HCl 1:1 pre-blends were prepared as shown below. Subsequent blending steps for individual tablet batches are also below.

Each fifty gram pre-blend was sufficient to prepare approximately five batches of tablets. Beginning with batch MMM, pre-blend batch sizes were doubled to 100 grams which prepares approximately ten tablet batches. Individual tablet batch sizes were 200 tablets or 50, 60, and 70 grams, respectively, for 250, 300, and 350 milligrams theoretical tablet weight formulas.

Blending procedures are described below.

Magnesium Stearate: Promethazine Pre-Blend Blending Procedure:

1. Weigh raw materials;
2. Screen 20 mesh;
3. Blend, V-Blender (22 rpm) for sixty (60**)** minutes;
4. Discharge, record weight/yield information.

Individual Batch Blending Procedure:

1. Weigh raw materials and pre-blend;
2. Screen raw materials 20 mesh (14 mesh for Dextrates, Citric Acid, and Maltodextrin);
3. Blend all materials except Magnesium Stearate: Promethazine pre-blend in V-Blender (22 rpm)

   for four (4) minutes;
4. Add pre-blend and blend for the time noted for each batch (120 or 80 seconds);
5. Discharge, weigh, record yield, compress, and test.

Preliminary friability testing with a couple of tablets was performed during tablet press set-up to determine an initial compression force level. Compression force levels which yielded tablets which passed this preliminary test did not insure a finished product that passed friability since manual set-up and actual running of the press do not yield the same product. Initially, tablets were compressed at one compression force level. After the first two batches (AA and BB), each subsequent blend was compressed at two compression force levels. The Low designation represents the lowest compression force at which preliminary testing indicated the tablets might pass friability testing. The second level with no designation was a slightly higher compression force that typically resulted in a tablet at least 0.03 mm thinner. Random samples from each sub-batch were tested as previously described. Testing included weight, thickness, hardness, friability, and disintegration time.

4.4 Results and Discussion

4.4.1 Initial Active Ingredient Tablet Trials

Initial formulations included a Pharmaburst control and four in-house formulations which differed in choice or level of disintegrant. These trials employed materials commonly used in direct compression ODT products to assess the challenges to be encountered with this method. In addition to drug and Magnesium Stearate, in-house formulas contained flavors/sweeteners, disintegrants (one of two at two different levels), taste/mouthfeel excipients, a glidant, and the primary diluent, spray-dried mannitol. A summary of physical test results is presented in Table 4.4a. Compressibility was poor for all blends. In all cases, a large percentage of tablets laminated at the point of ejection or

Table 4.4a. Initial Trials Summary of Physical Test Results

Summary of Physical Test Results

		Weight (mg)	Thickness(mm)	Hardness	Disintegration Time (USP) min:sec
D.Pharmaburst Control	Average	126.2	2.85	3.3	1:53
	SD	5.3	0.114	0.5	
	%RSD	4.2	4.01	16.6	
	Range	120-134	2.73-3.03	2.0-4.0	
E.SSG Low (2%)	Average	129.8	2.85	3.6	14:21
	SD	2.3	0.046	0.6	
	%RSD	1.7	1.62	15.8	
	Range	127-133	2.77-2.92	2.5-4.0	
F.SSG High (4%)	Average	130.4	2.85	3.5	8:31
	SD	3.9	0.073	0.7	
	%RSD	3.0	2.55	19.9	
	Range	125-138	2.77-2.97	2.5-4.0	
G. Crospovidone Low (5%)	Average	126.8	2.85	3.2	3:25
	SD	5.7	0.124	0.6	
	%RSD	4.5	4.34	18.3	
	Range	121-136	2.71-3.06	2.0-4.0	
H.Crospovidone High (10%)	Average	123.0	2.81	3.3	2:18
	SD	4.6	0.083	0.4	
	%RSD	3.7	2.96	12.8	
	Range	117-131	2.69-2.93	3.0-4.0	

SSG = Sodium Starch Glycolate

thereafter upon handling. Hardness and thickness values for all blends were similar which further indicates the compressibility is comparable for each formulation.

Average tablet weight did vary between blends. Sodium Starch Glycolate (SSG) blends resulted in higher average tablet weights (approximately 130 mg) than crospovidone blends. The higher concentration Crospovidone blend had the lowest average tablet weight (123 mg). However; the weight variation was higher than desired for all batches except E. (SSG Low). This is especially notable when viewing the weight range data which was equal to or greater than ten percent of theoretical weight (125 mg) for all batches except SSG Low. This variability indicates formulation flow needs further improvement.

Disintegration time varied dramatically between batches. Crospovidone produced much better results than SSG. Crospovidone wicks and swells versus SSG which primarily swells[17]. The swelling action of SSG may also require a harder tablet for maximum effect[17]. The higher (10%) concentration Crospovidone resulted in a disintegration time (2 min 18 sec) very close to the Pharmaburst Control (1 min 53 sec). All of the tablets appear to disintegrate by slowly eroding without any rapid breakup into smaller particles. The tablets exhibited a pleasant taste. A more rapid disintegration would aid in this area as well.

As might be expected, the high level of Magnesium Stearate results in formulations which resist flow, compressibility, and disintegration[8, 9]. Although still not as rapid as desired, disintegration is acceptable for this point in the formulation process. Equivalence to the Pharmaburst Control is a positive result at this stage. Crospovidone appeared to be superior to SSG for this basic formulation. The Magnesium Stearate tends

to produce waxy, non-porous tablets which may clearly benefit from a wicking plus swelling action (Crospovidone) versus a swelling only action (SSG). The addition of Croscarmellose Sodium, an excellent wicking and swelling type superdisintegrant[17], was evaluated in later trials.

Subsequent trials were conducted utilizing Dextrates, NF Hydrated (EMDEX; JRS Pharma, LP) as the diluent. Dextrates, NF is spherical in nature and exhibits better flow and compressibility than mannitol[22]. It has a sweet taste (equivalent to dextrose), a negative heat of solution, and a high solubility (1g/ml); all of which contribute to its usefulness in chewable and orally disintegrating tablets[9, 22].

New blending methods included lending together all materials other than the Promethazine: Magnesium Stearate blend. These two blends were blended together for a minimal time. It was thought this might result in a less hydrophobic, more compressible final blend. In addition; flavor(s), sweetener(s), and disintegrant(s) may be more rapidly and thoroughly available if less intimately blended with the Magnesium Stearate.

Since Magnesium Stearate has the predominate effect on this product, subsequent trials were initially conducted using Magnesium Stearate only rather than a Promethazine: Magnesium Stearate blend. This conserved active ingredient for later trials.

4.4.2 Placebo Tablet Trials

Trials employing Dextrates and glidants were undertaken to evaluate the use of Dextrates with and without glidants. These placebo trials consisted solely of Magnesium Stearate and Dextrates with and without one of two glidants. A summary of physical test results are presented in Table 4.4b.

Table 4.4b. Glidant Trials Summary of Physical Test Results

Summary of Physical Test Results

		Weight (mg)	Thickness(mm)	Hardness	Disintegration Time (USP) min:sec
I.Magnesium Stearate (20%)	Average	122.4	2.58	2.9	>30:00
Dextrates (80%)	SD	5.7	0.088	0.6	
	%RSD	4.7	3.42	21.2	
	Range	116-132	2.48-2.76	2.0-4.0	
J.Magnesium Stearate (20%)	Average	116.1	2.59	2.3	>30:00
Dextrates (78%)	SD	2.9	0.022	0.6	
VP AEROPERL 300	%RSD	2.5	0.85	27.5	
Pharma CSD (2%)	Range	112-120	2.56-2.62	2.0-4.0	
K.Magnesium Stearate (20%)	Average	111.4	2.53	2.2	>30:00
Dextrates (78%)	SD	2.0	0.029	0.6	
AEROSIL VV 200	%RSD	1.8	1.14	28.7	
Pharma CSD (2%)	Range	109-114	2.46-2.56	2.0-4.0	

VP AEROPERL 300 Pharma CSD = Hydrophobic Colloidal Silicon Dioxide
AEROSIL VV 200 Pharma CSD = Hydrophilic Colloidal Silicon Dioxide

The tablet weight setting used for the previous mannitol formulations resulted in a very high tablet weight (188 mg) for the Magnesium Stearate: Dextrates (formulation I, No Glidant) blend. The machine was readjusted using this blend. The effects of glidants were evident even in the blending stage. The blend without glidant had a tendency to adhere to the acrylic blender shell wall. The addition of AEROPERL (blend J) resulted in a better flowing blend which did not adhere to the blender walls at all. The visual difference was dramatic. AEROSIL (blend k) resulted in some minimal blend adherence to the blender wall. The percent yield values calculated from the amount of blend discharged for the various formulas supported these observations (95.5 %, 99.2%, and 98.7% for No Glidant (I),AEROPERL (J), and AEROSIL (K), respectively).

Compression of the blend with No Glidant proceeded well with no lamination of tablets. A small percentage of the AEROPERL tablets capped upon ejection whereas a small percentage of the AEROSIL tablets capped while handling after compression. In all cases, lamination was much less prominent than in the earlier trials with mannitol and other excipients.

Weight control was much better with glidants. For the No Glidant, AEROPERL, and AEROSIL tablets, respectively, percent relative standard deviation values decreased from 4.7 to 2.5 to 1.8 and the range values decreased from 16 to 8 to 5 milligrams. These results indicate a glidant is required and AEROSIL is the better form of Colloidal Silicon Dioxide to use in this formulation.

No notable comparisons are drawn from the hardness or thickness data. Greater thickness variation was observed with AEROSIL, but this is due to one tablet with a value of 1.46 mm. The other nine tablets tested yielded an average of 2.53 mm with a

standard deviation of 0.019 mm (%RSD = 0.73%). In all cases, disintegration was greater than thirty minutes. This is perhaps not surprising given the high amount of Magnesium Stearate and the lack of a disintegrant. In all cases the tablets slowly eroded and did not break into pieces. Examination of the remaining cores revealed the No Glidant and AEROSIL tablets left behind only a small, collapsible core whereas the remaining AEROPERL core was larger. The hydrophobic nature of AEROPERL likely explains this difference. This further indicated that proceeding with AEROSIL was the appropriate choice.

At this point it was concluded that a glidant was required for this system and AEROSIL at a level of two percent was acceptable. Compression was better than previous trials but still less than optimal due to lamination. As expected, the addition of disintegrant(s) was required. Compression trials were next undertaken with Croscarmellose Sodium, NF (Ac-Di-Sol, FMC Biopolymer). This superdisintegrant also has excellent compression properties[9]. If compression is acceptable and disintegration is still slow, Crospovidone could be added. Crospovidone was shown in earlier trials to be an effective disintegrant. If compression is still unacceptable, other diluent combinations must be evaluated.

Compositions and test results for additional placebo trials are shown in Table 4.4c. The last batch, Z, contains active ingredient as well. Physical examination of the tablets from the glidant trials revealed the tablets containing only Magnesium Stearate and Dextrates (Formulation I) to be very robust in nature. The formulations containing a glidant capped during compression. However, the weight variation (%RSD = 4.7) for the formulation without a glidant was notably higher than for the formulation containing the

Table 4.4c. Additional Placebo Trial Formulations and Test Results

Formula	Ingredient (% w/w)							
Target	Magnesium	Dextrates	Coll. Silicon	Croscar-	Cros-	NaCl	Co-	Other
Weight	Stearate		Dioxide	mellose Na	povidone		povidone	
I 125 mg	20	80						
L "	20	70	2	8				
M "	20	60	2	8	XL-10 10			
N "	20	58	2	20				
O "	20	60	2	8		10		
P "	20	55	2	8	XL 5	10		
Q "	20	50	2	8				SMCC 20
R "	18	77	1	4				
S "	18	72	1	4		5		
T 300 mg	8.3	82.7	1	8				
U "	8.3	62.7	1	8				Sucrose 20
V "	8.3	77.7	1	8			5	
W "	8.3	67.7	1	8			15	
X "	8.3	62.7	1	8		10	10	
Y "	8.3	62.7	1	8				Maltrin 10
Z1 Hi "	8.3	81.3						Drug 8.3
Z2 Med "								SSG 2
Z3 Lo "								
Notes:								
Z: Hi, Med, and Lo refers to high, medium, and low compression force, respectively.								
I-Q: Final Blending Time = 6 minutes;								
T-Y: Final Blending Time = 3 minutes;								
Z: Final Blending Time = 2 minutes.								

SMCC = Silicified Microcrystalline Cellulose SSG = Sodium Starch Glycolate

Formula	Average (SD)(%RSD), n=10					
& Target	Weight (mg)	Thickness (mm)	Hardness	Disintegration	Friability (%)	Observations
Weight				Time (min:sec)	(25 rpm, 4 min)	
I 125 mg	122.4 (5.7)(4.7)	2.58 (0.088)(3.42)	2.9 (0.6)(21.2)	> 30:00	none broken	From glidant trials, robust tablet
L "	121.9 (2.1)(1.7)	2.57 (0.035)(1.35)	2.1 (0.2)(7.7)	10:00:00		Capping when handled
M "	124.9 (2.0)(1.6)	2.64 (0.042)(1.58)	3.0 (0.9)(30.4)	4:38:00		Capping during compression
N "						Intact tablet not attained, did not compress
O "	124.5 (1.6)(1.3)	2.54 (0.018)(0.71)	3.8 (0.5)(14.4)	6:00		Better tablet, capping when dropped
P "	127.0 (4.3)(3.4)	2.61 (0.083)(3.18)	3.2 (0.7)(22.3)	3:10		Capping when handled
Q "	123.2 (1.9)(1.6)	2.56 (0.030)(1.15)	3.8 (0.6)(16.9)	4:44		Harder tablet but still caps
R "	123.1 (1.7)(1.4)	2.53 (0.040)(1.60)	4.1 (0.2)(3.9)	10:00	all broken	Compressed well w/o capping but fails friability
S "	126.5 (1.1)(0.9)	2.57 (0.013)(0.53)	4.1 (0.2)(3.9)	9:32		Compressed well
T 300 mg	297.2 (1.5)(0.5)	3.34 (0.035)(1.06)	4.1 (1.0)(23.6)	5:19	all broken	Compressed well w/o capping but fails friability
U "	301.3 (1.6)(0.5)	3.27 (0.025)(0.78)	4.1 (0.5)(12.3)	6:45		Compressed well
V "	297.3 (1.8)(0.6)	3.42 (0.019)(0.56)	4.5 (1.0)(22.2)	4:36	all broken	Compressed well w/o capping but fails friability
W "	297.4 (3.3)(1.1)	3.41 (0.032)(0.94)	4.8 (1.3)(26.1)	8:44	all broken	Compressed well w/o capping but fails friability
X "						Weak tablets, compression abandoned
Y "	291.7 (2.3)(0.8)	3.39 (0.021)(0.61)	6.0 (1.4)(22.6)	8:00	9/10 broken	Compressed well w/o capping but fails friability
Z1 Hi "	300.6 (1.6)(0.5)	3.29 (0.013)(0.39)	7.1 (1.4)(20.1)	9:43	1.2	Excellent compression, better friability
Z2 Med "	299.7 (2.1)(0.7)	3.40 (0.008)(0.25)	8.4 (1.7)(20.4)	7:32	0.6	Excellent compression, passes friability
Z3 Lo "	297.6 (2.2)(0.7)	3.38 (0.010)(0.31)	9.1 (2.4)(26.9)	7:47	0.6	Excellent compression, passes friability

AEROSIL VV 200 Pharma Colloidal Silicon Dioxide (%RSD = 1.8%). It was decided to proceed using Colloidal Silicon Dioxide (CSD). A base formulation (L) was produced containing Magnesium Stearate (20%), Dextrates (70%), CSD (2%), and Croscarmellose Sodium (8%). Croscarmellose Sodium (Ac-Di-Sol, FMC Biopolymer) is a wicking and swelling disintegrant known to have favorable compression properties[9, 17]. This addition did result in better compression. The tablets did not cap during compression. However, the tablets did cap when handling (de-dusting, etc.). These tablets yielded a disintegration time of approximately ten minutes.

Formulation M was produced by replacing ten percent of the Dextrates with Crospovidone XL-10, a wicking and swelling[9, 17] disintegrant. This did reduce the disintegration time to below five minutes. However, this blend did not compress as well with capping occurring during compression. Another formulation (N) containing a higher amount (20%) of Croscarmellose Sodium did not compress. All additions to formulations were offset by a corresponding reduction in Dextrates, the primary diluent.

Sodium Chloride has excellent compression properties[8] and is very water soluble. The addition of ten percent NaCl (formulation O) to the base formulation did yield a harder tablet with a faster disintegration time (six minutes). These tablets compressed well yet still capped when dropped. Five percent Crospovidone XL was added to this formulation to further reduce disintegration time. It was hoped that this larger particle size grade of Crospovidone would not adversely affect compression as previously seen with the smaller particle size XL-10 grade. Although disintegration time was shortened to three minutes, the tablets appeared to be less hard and capped when handled. Neither particle size grade had good compression properties in these formulations.

Silicified Microcrystalline Cellulose (SMCC) is a material reported by its manufacturer to have excellent flow and compressibility. The addition of 20% SMCC (formulation Q) to the base formulation yielded a harder tablet yet capping occurred during compression.

At this point, no formulation produced a strong tablet which would rapidly disintegrate. None of the tablets produced were as rugged as Formulation I containing only Magnesium Stearate and Dextrates. At this point, a trial was conducted using less Magnesium Stearate (18% vs. 20%), a shorter blending time (3 minutes vs. 6 minutes), and one-half as much CSD and Croscarmellose Sodium (Formulation R). The same formula was tried with the addition of five percent NaCl (Formulation S) since NaCl had previously aided compression and disintegration. Both formulations compressed well without notable differences. However, when subjected to friability testing, all tablets broke. This indicated the tablet was still not robust enough to withstand packaging and shipping.

The problems encountered are not completely surprising considering the large amount (20%) of Magnesium Stearate. It was decided to undertake trials with a larger (300 mg. vs. 125 mg.) theoretical tablet weight in an attempt to dilute the effects of Magnesium Stearate. This corresponds with a drop from 20% Magnesium Stearate to 8.3%. This dilution does not affect the Magnesium Stearate: Promethazine 1:1 ratio.

A new base formulation (T) was produced comprising 8.3% Magnesium Stearate, 82.7% Dextrates, 1% CSD, and 8% Croscarmellose Sodium. This was compared to formulations with additions of either Compressible Sucrose 20%, Copovidone 5%, Copovidone 15%, or Copovidone 10% + Maltodextrin 10% (Formulations U, V, W, and

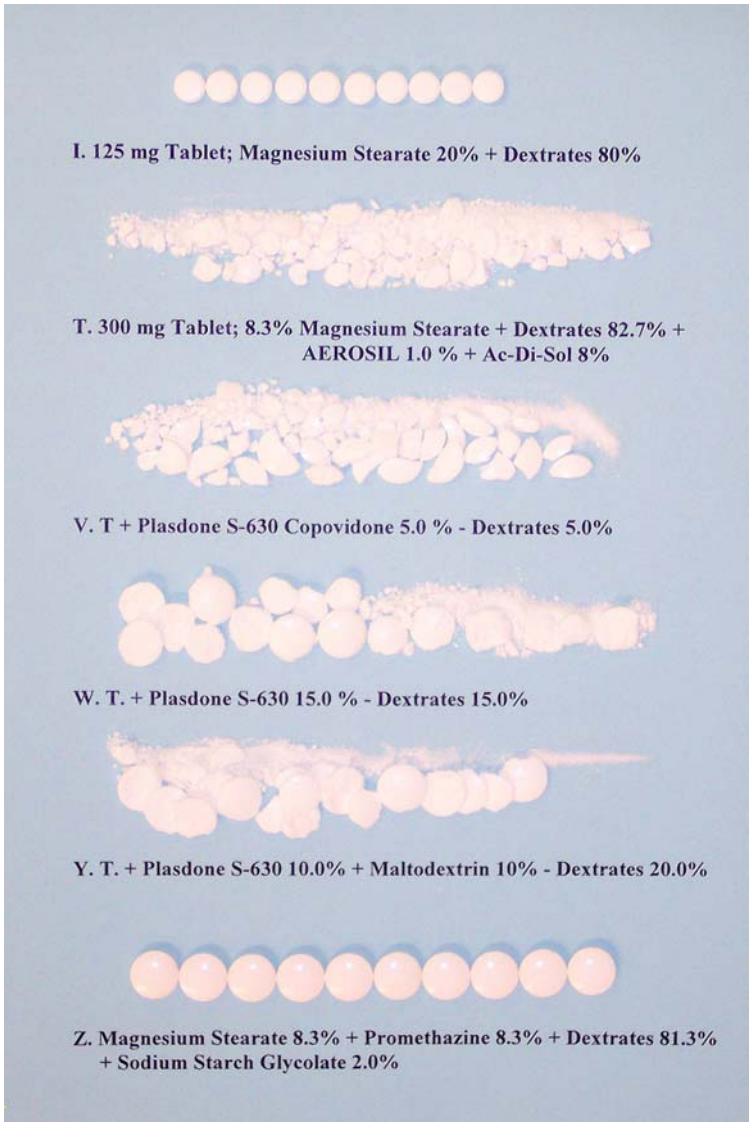
X, respectively). All formulations compressed well. The addition of Sucrose offered no apparent advantage. The addition of the binder Copovidone and the combination of binders Copovidone and Maltodextrin did produce a harder tablet.

A photograph of tablets post-friability testing is shown in Figure 4.1. This photo re-emphasizes the ruggedness of Formulation I containing only Magnesium Stearate and Dextrates. All additions result in a less rugged tablet. Although glidant was required in the smaller, 125 milligram tablet, it was unknown if the large amount of Dextrates in the larger 300 milligram tablet would result in adequate flow without the addition of Colloidal Silicon Dioxide. It was decided to conduct a trial with an active formulation containing minimal additions.

Formulation Z containing 8.3% Magnesium Stearate, 8.3% Promethazine HCl, 81.3% Dextrates, and 2% Sodium Starch Glycolate (SSG) was examined. Sodium Starch Glycolate is a swelling type disintegrant[9, 17] which exhibited good flow properties in initial tableting trials. Although SSG was less effective as a disintegrant in earlier trials, this may have been due to the inability to achieve a hard tablet. A certain hardness to expand against is required for optimal performance of a swelling type disintegrant[17]. The final blending time was also reduced in this formulation containing over 80% Dextrates. These large spherical particles have excellent flow and blending properties[22].

Compression was excellent for this minimal formulation with a wide range of compression forces producing acceptable tablets. No capping occurred during or after compression and no tablets broke when subjected to friability testing. The low and medium compression force levels produced tablets with a friability of 0.6%. This is well

Figure 4.1 Photograph of Tablets Post-Friability Testing (25 rpm, 4 min)



within our criteria of NMT 1.0% which is acceptable for conventional tablets[20] and excellent for an ODT. The high compression force tablets were more friable with a result of 1.2%. This is typical for most formulations in that beyond a certain point, further increases in compression force produce a less well bonded, brittle tablet[8, 9]. The coinciding decrease in average hardness for this higher compression force further supports this scenario.

Disintegration time was around eight minutes for these tablets. It should be noted that these tablets completely broke apart during disintegration whereas earlier tablets had small remaining cores which floated out prior to completely breaking apart. Weight variation was acceptable with %RSD values of 0.5, 0.7, and 0.7 for high, medium, and low compression force tablets, respectively. This larger tablet with a high percentage of Dextrates had adequate flow without the addition of Colloidal Silicon Dioxide.

4.4.3 Active Ingredient Tablet Trials

Initially, additional active ingredient tablet trials were undertaken primarily to evaluate the addition of additional disintegrants and various disintegrant levels. Formulations and a summary of test results are shown in Table 4.4d. Highlighted formulations represent notable improvements and serve as subsequent controls. Summary weight data is not included. Balancing hardness, thickness, disintegration, and friability was the main goal. No problems with weight variation were encountered. All individual data, including weight data, are included in the Appendix.

Table 4.4d. Disintegrant Trial Formulations and Results

					Average (SD) (%RSD)		Disintegration	Friability (%)
Formula	% SSG	% Croscar-	% Calcium	% Other	Thickness (mm)	Hardness	Time	(25 rpm, 4 min)
		mellose Na	Silicate				(min:sec)	
Z2	2				3.40(0.008)(0.25)	8.4(1.7)(20.4)	7:32	0.60
AA	4				3.37(0.005)(0.14)	14.6(4.6)(31.8)	8:25	0.66
BB	8				3.40(0.029)(0.84)	5.9(2.1)(36.0)	5:31	3 broke
CC	2	2			3.40(0.007)(0.20)	15.2(2.8)(18.3)	2:44	0.58
CC Low	2	2			3.49(0.019)(0.54)	12.7(2.1)(16.8)	0:54	0.87
DD	2	3			3.41(0.011)(0.32)	16.1(3.1)(19.0)	3:16	0.60
DD Low	2	3			3.50(0.005)(0.14)	13.8(2.6)(18.6)	1:15	0.59
EE	3	2			3.43(0.008)(0.24)	13.3(2.7)(20.5)	2:53	0.66
EE Low	3	2			3.47(0.007)(0.21)	13.3(2.4)(18.1)	1:59	0.70
FF	3	3			3.45(0.009)(0.27)	14.2(1.5)10.3)	2:36	0.66
FF Low	3	3			3.57(0.007)(0.20)	8.5(2.1)(24.6)	0:35	0.85
GG	3	3		3 Copovi-	3.49(0.014)(0.12)	8.2(1.6)(19.4)	1:34	0.70
GG Low	3	3		3 done	3.57(0.007)(0.20)	7.5(1.3)(17.5)	0:33	1.24
HH	4	4			3.40(0.007)(0.21)	9.4(2.4)(25.5)	3:08	0.63
HH Low	4	4			3.50(0.007)(0.21)	8.6(1.9)(22.1)	1:12	0.94
II	3	3	1.5		3.42(0.008)(0.25)	8.6(0.7)(8.0)	2:55	0.40
II Low	3	3	1.5		3.62(0.004)(0.12)	6.7(1.2)(17.7)	0:22	0.63 (1 broke)
JJ	3	3	2.0		3.53(0.011)(0.32)	10.4(1.4)(13.7)	0:41	0.70
JJ Low	3	3	2.0		3.59(0.007)(0.19)	8.8(1.9)(21.3)	0:29	0.82

SSG = Sodium Starch Glycolate

Increasing the amount of Sodium Starch Glycolate (SSG), a swelling type superdisintegrant[17], from two (lot Z2) to four (AA) percent did not improve disintegration time. A further increase to 8% (BB) resulted in a friable tablet. The addition of two percent of a second superdisintegrant, the wicking and swelling[9, 17] agent croscarmellose sodium, to 2% SSG reduced the disintegration time from over seven minutes (Z2) to less than one minute (CC Low). An increase in compression force increased disintegration time. This is not surprising since a harder tablet is generally more compacted and less porous. This may be even more pronounced in this system employing a large percentage of hydrophobic magnesium stearate. A corresponding decrease in thickness and increase in hardness was observed. This trend was evident throughout these trials and the compression force window yielding a non-friable yet quick disintegrating tablet was quite narrow. Thickness values proved to be the better indicator of disintegration time between these measures due to this parameter being much less variable than hardness.

Variations in the amounts of SSG and Croscarmellose were examined. Overall, equivalent amounts yielded the best combination of friability and disintegration time with 3% of each (FF Low) yielding a disintegration time of 35 seconds in a tablet which passed friability (< 1%, none broken). This combination (FF Low) was chosen as the control for subsequent trials. It should be noted that a further increase to 4% each (HH) resulted in a slower disintegration time. This is not unusual in that a point is commonly reached where additional swelling agent results in gelling and retardation of disintegration[9, 17].

A trial (GG) was conducted with 3% Copovidone added to this new control. This binder may allow a non-friable tablet to be produced with less compression force. In

addition, this Vinyl Acetate/Polyvinyl Acetate copolymer has some surfactant properties[23] In our case, the resulting tablet formulation that passed friability had a longer (94 seconds) disintegration time. It appears the binding property outweighed any beneficial properties.

RxCIPIENTS FM 1000 Calcium Silicate is produced in a manner that results in the particles being very hydrophobic and water repelling in nature. When mixed with superdisintegrants, this material acts as a background for other disintegrants to wick and swell against, resulting in the tablet more rapidly breaking up into prime particles[19]. The addition of 1.5% Calcium Silicate (II Low) resulted in a decrease in disintegration time to 22 seconds versus 35 seconds for the corresponding control (FF Low). In addition, visual observation of the in-vitro disintegration revealed that these tablets no longer had a core which was slower to disintegrate than the outer portion of the tablet. Informal taste testing reflected the same observation. This lack of a core is consistent with the disintegrant mechanism for Calcium Silicate.

One tablet from this sub-lot did break in the final seconds of friability testing. Otherwise the tablets had a good appearance and acceptable friability of 0.63%. It was decided that the friability problem was minor and the improvement in disintegration was notable, thus this formula (II Low) was selected as the new control after the completion of a series of trials. A higher level (2.0%) of this material did not appear to result in any further improvement.

Various approaches were tried to further improve disintegration. Formulations and results are shown in Table 4.4e. Microcrystalline cellulose is a multifunctional

Table 4.4e. Additional Formulations and Results I

					Average (SD) (%RSD)		Disintegration	Friability (%)
Formula	% SSG	% Croscar-	% Calcium	% Other	Thickness (mm)	Hardness	Time	(25 rpm, 4 min)
		mellose Na	Silicate				(min:sec)	
KK	3	3		2 MCC PH102	3.51(0.007)(0.19)	9.3(1.6)(17.3)	0:29	0.84 (1 broke)
KK Low	3	3		2 MCC PH102	3.59(0.005)(0.14)	7.2(0.9)(13.2)	0:16	all broke
LL	3	3	1.5	2 MCC PH102	3.51(0.009)(0.26)	9.0(1.9)(21.1)	1:02	0.43
LL Low	3	3	1.5	2 MCC PH102	3.58(0.005)(0.14)	6.7(2.1)(31.3)	0:30	4 broke
MM	3	3	1.5	2 PEG	3.61(0.006)(0.16)	5.1(0.9)(17.8)	0:26	0.13
MM Low	3	3	1.5	2 PEG	3.65(0.013)(0.37)	5.3(0.8)(14.4)	0:23	2 broke
NN	3	3	1.5	<mix time	3.60(0.007)(0.19)	6.8(0.9)(12.7)	0:24	0.27
NN Low	3	3	1.5	<mix time	3.68(0.015)(0.40)	4.8(0.8)(17.4)	0:18	all broke
OO	3	3	1.5	10 Mannitol	3.57(0.009)(0.26)	6.1(1.0)(16.8)	0:41	0.39
OO Low	3	3	1.5	10 Mannitol	3.64(0.014)(0.37)	6.2(1.8)(29.9)	0:21	0.43
PP	3	3	1.5	20 STARLAC	3.44(0.009)(0.25)	6.7(1.1)(16.3)	0:49	0.47
PP Low	3	3	1.5	20 STARLAC	3.52(0.009)(0.27)	5.3(0.9)(16.2)	0:30	8 broke
QQ	3	3	1.5	4 Avicel CE	3.53(0.009)(0.25)	6.9(1.5)(21.2)	0:45	0.23
QQ Low	3	3	1.5	4 Avicel CE	3.58(0.014)(0.38)	5.8(0.9)(16.4)	0:26	8 broke
RR	3	3	4.5	< mix time	3.48(0.008)(0.24)	8.4(1.7)(20.4)	0:26	0.26
RR Low	3	3	4.5	< mix time	3.58(0.012)(0.33)	6.9(1.0)(15.2)	0:41	0.26

SSG = Sodium Starch Glycolate
MCC PH102 = Microcrystalline Cellulose PH 102
PEG = Polyethylene Glycol 8000

tableting excipient with good compression and wicking properties[9]. Trials (KK-LL) were conducted with a large particle size grade (Avicel PH102) of this material since our formulation already contains many fines. This material with and without Calcium Silicate resulted in tablets which were either more friable or slower disintegrating.

Polyethylene Glycol (PEG 8000), a hydrophilic tablet lubricant with some binding properties[9] was tested (MM) to see if a more hydrophilic tablet would disintegrate faster . Although friability was very low (0.13%) disintegration was not improved.

As discussed above, friability was marginal with the new control (II Low) employing 1.5% Calcium Silicate in addition to 3% each SSG and Croscarmellose Sodium (also referred to as the 3-3-1.5 control). The final blend time was reduced by one-third from 120 to 80 seconds. Final blending time is known to be an important parameter when working with Magnesium Stearate[8, 9]. Extended blending times can not only retard disintegration, but may also adversely affect tablet bonding, resulting in increased friability, capping, laminating, and other compression problems. For this product, the drug is pre-blended with the Magnesium Stearate so a lower limit on blending time does exist to avoid content uniformity problems. The reduced blending time appeared adequate and uniformity will be further assessed in the final formulation. This did result in excellent friability of 0.27% with no broken tablets. This 3-3-1.5-<mixing time formula (NN) was adopted as the new control for further studies.

Other materials were examined to further reduce disintegration time. Trial OO replaced 10% of the Dextrates base with a small particle size spray-dried Mannitol

(Mannitol, USP, Spray-dried; Pearlitol 200SD, Roquette). This particular Mannitol has been shown[24] to be the fastest dissolving of many sugars employed in ODTs. Our main diluent, Dextrates, was shown to be the second fastest (16 seconds versus 5 seconds). This formulation produced results comparable to the control (for Low sub-lots, disintegration times of 21 seconds versus 24 seconds and friability values of 0.43% versus 0.27% with the latter values representing the control). Although roughly equivalent, this did not result in a strong advantage so the addition of this material was not pursued further at this point.

The use of 20% STARLAC was also examined. STARLAC is a co-spray dried compound consisting of 85% alpha-lactose monohydrate and 15% corn starch. The manufacturer (Roquette) states that this material combines the excellent flow and compressibility of lactose with the disintegration properties of starch. In addition, product literature for this material shows it to be less affected by Magnesium Stearate than physical blends of the same materials[25]. It was hoped that these properties would result in faster disintegration of our product. In our trial (PP), the tablets were less desirable in terms of both disintegration and friability.

The use of Avicel CE-15 was explored. This co-processed mixture of microcrystalline cellulose and guar gum is used in chewable tablets to both improve mouthfeel and decrease friability. It was hoped that this material in our formulation would allow a non-friable tablet to be made using less compression force which in turn would lead to a decrease in disintegration time. Favorable results were not obtained in our trial (QQ). A large increase from 1.5% to 4.5% (RR) in the previously beneficial Calcium Silicate also did not improve disintegration time.

Additional formulations and results are shown in Table 4.4f. For trial SS, Saccharin and Cherry Flavor were added to the previous control (NN) and the Calcium Silicate was blended less time with the other excipients. It was thought that the reduced blending time might yield the same action of the tablet breaking apart into prime particles with a less overall hydrophobic tablet nature. The water soluble sweetener and flavor could potentially also aid in this effect. This resulted in a thinner, poorly disintegrating (> one minute) tablet. Thinner tablets typically result when higher compression forces are required to yield tablets which pass friability. More compressible materials could also yield a thinner tablet. Whatever the cause, a thinner tablet in our trials typically resulted in a longer disintegration time. This may be due to a more compact, less porous tablet. Because two variables were changed, the exact cause was unknown.

Microcrystalline cellulose (MCC) is typically expected to improve disintegration and friability. Earlier trials had shown large particle size, very compressible microcrystalline cellulose did not improve this product. Trial TT was undertaken using 4% PH105 grade MCC. This grade has a small particle size and high bulk volume. It was believed that this might yield a thicker, more porous tablet. However, friability failed at both compression force levels.

Additional non-traditional disintegrants were examined next. Alginic Acid resulted in a thin tablet with very poor disintegration (range of three minutes or greater). Soy Polysaccharides is an all natural, high-fiber, low caloric, and kosher disintegrant popular in the nutritional product industry. Use of this material at a 2.5% level did not improve disintegration. However, observation of the disintegration test indicated a rapid

Table 4.4f. Additional Formulations and Results II

Formula	% SSG	% Croscar-	% Calcium	% Other	Thickness (mm)	Hardness	Time	(25 rpm, 4 min)
		mellose Na	Silicate				(min:sec)	
All formulas below based on Formula NN								
changes/additions noted								
SS	1% Saccharin Na Powder,0.6% Cherry				3.51(0.007)(0.20)	7.0(1.7)(23.8)	1:30	0.33
SS Low	Flavor & Change Blend Procedure				3.54(0.009)(0.25)	6.4(0.9)(14.6)	1:17	0.26
TT	4% MCC PH 105				3.55(0.005)(0.15)	7.3(1.5)(20.9)	0:32	2 broke
TT Low	4% MCC PH 105				3.59(0.005)(0.14)	6.8(0.9)(14.0)	0:23	4 broke
UU	2.5% Alginic Acid				3.37(0.007)(0.22)	7.9(1.2)(15.4)	3:59	0.27
UU Low	2.5% Alginic Acid				3.42(0.008)(0.25)	7.9(1.9)(24.6)	2:55	0.23
VV	2.5% Soy Polysaccharides				3.44(0.013)(0.39)	7.7(1.5)(19.7)	2:07	0.23
VV Low	2.5% Soy Polysaccharides				3.52(0.007)(0.20)	7.8(1.3)(17.3)	0:32	0.23
WW	1.25% Soy Polysaccharides				3.61(0.011)(0.31)	6.3(0.9)(14.1)	0:19	0.33
WW Low	1.25% Soy Polysaccharides				3.68(0.014)(0.37)	5.8(0.5)(9.4)	0:17	7 broke
All formulas below based on WW,								
changes/additions noted								
XX	2% Calcium Carbonate, DC				3.62(0.011)(0.30)	4.7(0.9)(18.2)	0:18	0.36
XX Low	2% Calcium Carbonate, DC				3.66(0.023)(0.62)	4.5(1.1)(24.5)	0:22	5 broke
YY	4% Calcium Carbonate, DC				3.61(0.007)(0.19)	5.7(1.1)(19.1)	0:22	0.42
YY Low	4% Calcium Carbonate, DC				3.65(0.010)(0.28)	5.0(0.8)(15.4)	0:18	8 broke

SSG = Sodium Starch Glycolate

initial wicking and breaking-up of the outer layer of the tablet. However, as might be expected, the core of the thinner tablet was slower to disintegrate. Based upon this observation, a trial (WW) was conducted with 1.25% Soy Polysaccharides. This yielded a notable improvement in disintegration time (19 seconds versus 24 seconds for control) with good friability (0.33%). This was selected as the new control.

Calcium Carbonate has been used in orally disintegrating tablets. Trials were conducted with 2% and 4% direct compression grade of Calcium Carbonate. The 2% formula (XX) yielded a good tablet (friability 0.36%) with an 18 second disintegration time. Although this was not a big improvement over 19 seconds in terms of disintegration time, these tablets had a notable (> 1.5 units) lower average hardness. It was believed a softer yet still robust tablet would be better for an ODT product. Tablets with 4% Calcium Carbonate (YY) which passed friability had a longer disintegration time (22 seconds). Therefore, the 2% Calcium Carbonate formula (XX) was chosen as the control for further study.

Additional formulations and results are shown in Table 4.4g. Trial ZZ was conducted by adding 0.5% Colloidal Silicon Dioxide (CSD). Earlier trials had shown larger amounts resulted in friable tablets. A small amount was employed to determine if this hydrophilic silica which typically improves disintegration by wicking would further improve disintegration in this product. In this case, disintegration time was higher (1:13 min) for tablets which passed friability testing. The addition of this hydrophilic agent may have offset the improvement yielded by the hydrophobic Calcium Silicate.

With a disintegration time of 18 seconds, attempts were made to flavor and sweeten the current control formulation, XX. The addition of 1% Sodium Saccharin

Table 4.4g. Additional Formulations and Results III

Formula	% SSG	% Croscar-mellose Na	% Calcium Silicate	% Other	Average (SD) (%RSD) Thickness (mm)	Average (SD) (%RSD) Hardness	Disintegration Time (min:sec)	Friability (%) (25 rpm, 4 min)
All formulas below also contain 2% Calcium Carbonate, changes/additions noted								
ZZ	0.5% Colloidal Silicon Dioxide (AEROSIL)				3.57(0.009)(0.26)	5.2(0.7)(13.0)	1:13	0.39
ZZ Low	0.5% Colloidal Silicon Dioxide (AEROSIL)				3.64(0.007)(0.19)	5.7(1.0)(17.6)	0:31	9 broke
AAA	1% Saccharin Na,Powder,0.6% Cherry Flavor				3.43(0.008)(0.24)	6.3(0.7)(11.5)	2:29	0.39
AAA Low	1% Saccharin Na,Powder,0.6% Cherry Flavor				3.48(0.011)(0.30)	5.5(0.9)(17.1)	1:29	0.26
BBB	AAA + 2% Citric Acid,Monohydrate,Granular				3.42(0.006)(0.17)	6.0(0.4)(6.8)	2:07	0.37
BBB Low	AAA + 2% Citric Acid,Monohydrate,Granular				3.48(0.007)(0.8)	5.2(0.8)15.9)	0:56	1 broke
CCC	2% Citric Acid,Monohydrate,Granular				3.60(0.016)(0.46)	5.3(1.1)(21.0)	0:21	0.50
CCC Low	2% Citric Acid,Monohydrate,Granular				3.60(0.020)(0.56)	4.9(1.2)(24.9)	0:19	9 broke
DDD	0.5% Saccharin Na,Granular, 0.2% Vanilla				3.50(0.006)(0.18)	7.5(1.3)(18.0)	0:37	0.37
DDD Low	Flavor				3.53(0.014)(0.39)	5.5(1.5)(28.1)	0:23	2 broke
EEE	CCC - Calcium Silicate				3.51(0.011)(0.30)	6.2(0.6)(10.2)	0:26	0.44
EEE Low	CCC - Calcium Silicate				3.53(0.007)(0.21)	4.5(0.6)(12.8)	0:19	6 broke
FFF	DDD + 1% Citric Acid,Monohydrate, Granular				3.52(0.016)(0.44)	6.4(0.9)(13.4)	0:35	0.73
FFF Low	DDD + 1% Citric Acid,Monohydrate, Granular				3.57(0.013)(0.35)	5.9(1.3)(21.4)	0:19	1 broke
GGG	XX With Smaller Diameter (11/32") Tooling				5.33(0.019)(0.35)	4.1(0.3)(7.7)	0:22	1 broke
GGG Low	XX With Smaller Diameter (11/32") Tooling				5.34(0.018)(0.34)	4.2(0.5)(11.5)	0:21	all broke
HHH	XX + 25% Mannitol SD 200				3.49(0.020)(0.58)	7.1(0.8)(1.3)	0:31	1 broke
HHH Low	XX + 25% Mannitol SD 200				3.55(0.009)(0.26)	7.8(0.9)(11.9)	0:34	0.42
III	XX + 0.1% Sodium Lauryl Sulfate				3.59(0.009)(0.24)	5.7(1.2)(21.3)	0:18	6 broke
III Low	XX + 0.1% Sodium Lauryl Sulfate				3.62(0.005)(0.13)	5.7(1.2)(21.3)	0:18	2 broke
Calcium Carbonate Removed, WW as control								
JJJ	WW, Change Blend Procedure				3.55(0.012)(0.35)	8.0(0.6)(7.2)	0:21	1 broke
JJJ Low	WW, Change Blend Procedure				3.55(0.008)(0.24)	7.8(1.2)(15.9)	0:21	1 broke after
KKK	WW + 2% Citric Acid Anhydrous, USP-FCC				3.52(0.010)(029)	4.3(0.6)(14.7)	0:17	five broke
KKK Low	WW + 2% Citric Acid Anhydrous, USP-FCC				3.59(0.018)(0.51)	6.4(1.7)(26.5)	0:20	three broke
LLL	WW + 0.3% each Sucralose,Vanilla,and				3.59(0.013)(0.37)	5.4(1.1)(20.4)	0:20	one broke
LLL Low	Masking Flavors				3.60(0.007)(0.19)	5.3(0.9)(17.5)	0:17	seven broke

SSG = Sodium Starch Glycolate

powder and 0.6% Cherry Flavor (AAA) had a surprisingly negative effect on disintegration time. The thinner tablets (higher compression force levels) required to yield a tablet that passed friability had poor disintegration (≥ 1.5 minutes). The earlier trial with flavor, saccharin, and a blend procedure change yielded similar results. In the same period, formula BBB was made employing the AAA plus 2% granular Citric Acid, Monohydrate. Citric acid is used in flavoring and in this case it also yielded a slight effervescence (visible in-vitro) when combined with Calcium Carbonate. These tablets also had a greatly increased (> 2 min) disintegration time. Surprisingly, the slight effervescence did not improve disintegration. This is one mechanism which has been successfully employed with some ODT products[2]. With regard to flavoring, the Cherry Flavor was too mild. Although the bitter taste was hidden by the Magnesium Stearate, some unpleasant delayed numbness did occur. The Citric Acid formulation seemed to prevent this numbness. It was unknown if this was due to the Citric Acid itself or due to Carbon Dioxide produced via effervescence.

Formulation CCC was made by adding only 2% Citric Acid to the control formulation. These tablets were much better (disintegration 21 seconds, friability 0.5%) in terms of disintegration than the previous batch containing Saccharin, Cherry Flavor, and Citric Acid. This indicated the sweetener/flavor effect was more deleterious than the effect of Citric Acid. Although on paper this Citric Acid only formulation appears acceptable, the tablets were crumbly when subjected to hardness testing. Again, the effervescence was observable but did not improve disintegration. The addition of Citric Acid again improved the problem with numbness.

A different form (granular rather than powder) and lower amount (0.5% vs. 1.0% in AAA) of Saccharin Sodium and a more potent flavor (0.2% Vanilla vs. 0.6% Cherry in AAA) was added to the control formulation. Although this formula (DDD) was better than AAA, disintegration time (37 seconds) was still greater than control (18 seconds).The Vanilla flavor was good, but mild, and the numbness was present in the absence of Citric Acid.

Formulation EEE consisted of the control plus Citric Acid to prevent numbness minus Calcium Silicate. This was undertaken to determine if the effervescence effect would perform the same function as Calcium Silicate in speeding disintegration by aiding in breaking apart the tablet into prime particles. If so, the absence of Calcium Silicate would result in a more hydrophilic tablet which could potentially disintegrate faster. This was not the case and disintegration time (26 sec) was slightly higher than control (18 sec).

Formula DDD with Vanilla and Saccharin had a pleasant taste but did exhibit numbness. The DDD Low compression force sub-lot failed friability and DDD had an increased disintegration time of 37seconds. Formulation FFF was made by adding 1% Citric Acid to this formula. This resulted in a reasonably pleasant taste but disintegration time was also higher (35 seconds) than desired.

Since attempts to sweeten and flavor the control resulted in increased disintegration times, trials were undertaken to see if fundamental changes could further improve the disintegration time of the control formulation. If successful, subsequent decreases upon sweetening and flavoring would potentially be acceptable. Trials GGG, HHH, and III looked at the effects of changing tablet geometry (smaller diameter, thicker

tablet), the addition of a large amount of spray dried Mannitol which had shown potential earlier in a smaller amount, and the addition of a wetting agent, Sodium Lauryl Sulfate. None of these changes resulted in a robust tablet with faster disintegration time.

At this point, all trials indicated a fragile formulation which could not be flavored and sweetened without losing ground in terms of disintegration and/or friability. Previous trials had shown this basic formulation to have poor dilution potential. Since the addition of Calcium Carbonate only yielded a softer tablet with no notable improvement in disintegration time, this was removed in subsequent trials. This once again made WW the control. This formulation is the 3-3-1.5-<mix time plus 1.25% Soy Polysaccharides.

In lot JJJ, only a blending procedure change was attempted. One-half of the Calcium Silicate was added to the Promethazine: Magnesium Stearate pre-blend and blended for an additional hour. The final blend time was reduced from 80 seconds to 60 seconds. The additional pre-blending in the presence of Calcium Silicate did not prevent numbness and disintegration was not improved. Friability testing resulted in one broken tablet for sub-lot JJJ and one tablet from JJJ Low broke upon removal from the friabilator.

Formulation KKK was made by adding 2% anhydrous Citric Acid to the control. This form of Citric Acid not only differed from that previously used in being anhydrous, but was also a finer powder versus granular. Although this also prevented numbing, even in the absence of Calcium Carbonate, compression characteristics were worse in that the tablets failed friability. Formulation LLL employed adding 0.3% each of Sucralose, Vanilla Flavor, and Masking Flavor. The Masking Flavor did not prevent numbness and

Table 4.4h. Additional Formulations and Results IV

					Average (SD) (%RSD)		Disintegration	Friability (%)
Formula	% SSG	% Croscar-	% Calcium	% Other	Thickness (mm)	Hardness	Time	(25 rpm, 4 min)
		mellose Na	Silicate				(min:sec)	
WW	Control				3.61(0.011)(0.31)	6.3(0.9)(14.1)	0:19	0.33
LLL	WW + 0.3% each Sucralose,Vanilla,and				3.59(0.013)(0.37)	5.4(1.1)(20.4)	0:20	one broke
LLL Low	Masking Flavors				3.60(0.007)(0.19)	5.3(0.9)(17.5)	0:17	seven broke
MMM	WW, Tablet Weight 350 mg				3.97(0.008)(0.20)	7.0(0.9)(13.3)	0:34	0.14
MMM Low	WW, Tablet Weight 350 mg				4.00(0.006)(0.14)	7.2(1.1)(15.1)	0:21	0.17
NNN	WW, Tablet Weight 250 mg				3.13(0.008)(0.25)	7.2(0.6)(8.8)	0:36	1 broke
NNN Low	WW, Tablet Weight 250 mg				3.15(0.005)(0.16)	6.5(0.5)(8.3)	0:30	1 broke
OOO	MMM + 1% Citric Acid,Monohydrate,Granular				4.01(0.006)(0.14)	6.5(0.8)(11.8)	0:21	0.51
OOO Low	MMM + 1% Citric Acid,Monohydrate,Granular				4.03(0.005)(0.12)	6.9(0.9)(13.6)	0:20	0.43
PPP	Drug:Mag Stearate/Pharmaburst(86%),350mg				4.86(0.008)(0.17)	5.4(0.6)(11.4)	0:18	2
PPP Low	Drug:Mag Stearate/Pharmaburst(86%),350mg				4.97(0.008)(0.16)	4.8(0.6)(12.4)	0:22	2.8
QQQ	MMM + 1% Bentonite				3.87(0.007)(0.18)	6.8(0.8)(12.2)	1:23	0.23
QQQ Low	MMM + 1% Bentonite				3.93(0.008)(0.21)	6.4(1.1)(17.4)	0:55	0.14
RRR	MMM + 1% Crospovidone, NF XL-10				3.88(0.005)(0.12)	7.2(0.6)(8.1)	1:23	0.28
RRR Low	MMM + 1% Crospovidone, NF XL-10				3.92(0.006)(0.14)	5.8(0.5)(9.3)	0:51	0.28
SSS	MMM + 20% Maltodextrin, NF (QD M500)				4.06(0.006)(0.16)	5.2(0.9)(17.2)	1:09	6 broke
SSS Low	MMM + 20% Maltodextrin, NF (QD M500)				4.09(0.007)(0.16)	4.9(0.7)(14.6)	1:24	3 broke
TTT	In-House Formulation				3.98(0.005)(0.12)	5.0(0.6)(11.1)	0:28	0.31
TTT Low	In-House Formulation				4.01(0.006)(0.14)	5.0(0.7)(14.9)	0:28	0.37
UUU	Pharmaburst Formulation				4.69(0.020)(0.42)	4.1(0.5)(12.6)	0:18	1.00
UUU Low	Pharmaburst Formulation				4.82(0.007)(0.14)	4.4(0.7)(17.2)	0:19	1.75

SSG = Sodium Starch Glycolate

the taste with Sucralose was less pleasant than with Saccharin Sodium. These tablets also failed friability.

The effect of tablet weight was examined. Formulations and results are shown in Table 4.4h. The control formulation WW is included for comparison. It was expected that further dilution of the Magnesium Stearate could yield a less friable tablet at lower compression forces resulting in faster disintegration. In addition, this dilution might enable the subsequent addition of sweeteners and flavors without the previously observed negative effects. Although it was generally believed a lower weight, less diluted tablet would yield a more friable, slower disintegrating tablet; it is also possible that less dilution could result in a less stable tablet that could disintegrate faster. The target weight of the control formulation was increased from 300 to 350 milligrams for formulation MMM. In this case, the Promethazine: Magnesium Stearate blend is a smaller percentage (7.1% each versus 8.3% each) of the formulation and the primary diluent Dextrates is a larger percentage of the formulation. All other percentages remain unchanged. Although the percentage change in Dextrates is small (increase from 74.6% to 77.0%), the increase in the amount of Dextrates per tablet (224 mg to 270 mg) is notable.

The resulting 350 milligram tablet yielded excellent friability results of 0.14% and 0.17% for MMM and MMM Low respectively. Corresponding disintegration times were 34 seconds and 21 seconds for MMM and MMM Low respectively. This value of 21 seconds was similar to the control (WW) value of 19 seconds, but friability was lower than the 0.33% value for WW. An increase in tablet size may increase disintegration time whereas further dilution of the Magnesium Stearate may improve friability. The taste of this tablet was good. No bitterness was observed and the sweetness was acceptable as is

without added sweetener. However, although less severe, the delayed numbness was present.

As expected, trial NNN with a reduced tablet weight of 250 milligrams and a corresponding increase in the Promethazine: Magnesium Stearate percentage to 10% each resulted in a more friable and slower disintegrating tablet. For each sub-lot, one tablet broke during friability testing, and the minimum disintegration time was 30 seconds.

Using MMM Low as the new control, 1.0% Citric Acid, Monohydrate, Granular was added in trial OOO in an attempt to overcome the numbing observed in MMM. These tablets yielded acceptable disintegration results of 21 seconds and 20 seconds and acceptable friability results of 0.51% and 0.43% for OOO and OOO Low respectively. These tablets were less hard and thicker than the MMM tablets which may explain the increase in friability from 0.17% or less. Although acceptable in physical attributes, these tablets were slightly bitter. This is likely due to the addition of Citric Acid without a corresponding addition of sweetener. Some numbness was also still present. A higher level of Citric Acid may be required in this respect.

Although good taste and disintegration had been achieved in MMM, the numbing issue remained unresolved. One method of countering this effect would be to further decrease *in vivo* disintegration time. As previously discussed, Pharmaburst is an off the shelf, ready to use ODT platform from SPI Pharma. This system is intended to be simply mixed with taste-coated or taste-masked drug and sweetener/flavors and directly compressed into orally disintegrating tablets. This system had been evaluated earlier with the Promethazine: Magnesium Stearate pre-blend. However, at that time the tablet weight was much lower (125 mg) and the resulting tablets capped during and after

compression. Trial PPP was undertaken to evaluate this system with the increase in tablet weight to 350 milligrams.

It was readily apparent during press set-up that this blend had a greater bulk volume than the blend from the in-house formulation. The lower die had to be adjusted significantly downward to achieve a tablet weight of 350 milligrams. This reflects the high bulk volume (low bulk density) of this blend. SPI Pharma product literature[16] lists the bulk and tap density ranges for Pharmaburst to be 0.35-0.50 grams/ml and 0.45-0.65 grams/ml respectively. This is much lower than the corresponding values of 0.68 grams/ml and 0.72 grams/ml[26] for Dextrates, our primary diluent. The finished product was a much thicker tablet, with average thickness values almost 1.0 millimeter thicker than values for corresponding tablets produced from the in-house formulation (4.97 mm for PPP Low versus 4.00 mm for MMM Low). Also noted during press set-up was the ability of these tablets to withstand breakage. Although significant edge-wear occurred during this preliminary friability testing, breakage was much less likely.

The Pharmaburst tablets yielded *in vitro* disintegration times of 18 seconds and 22 seconds which were comparable to that observed with the in-house formulation tablets (21 seconds for MMM Low). Informal taste testing appeared to indicate these thicker tablets disintegrated faster *in vivo* than the in-house formulation tablets. However, excessive edge-wear resulted in both sub-lots yielding failing friability results (2.0% and 2.8% for PPP and PPP Low, respectively).

Additional trials were undertaken in an attempt to further decrease the disintegration time of the in-house control (MMM Low). ODT patent literature was reviewed to assess potential ways to improve disintegration. The natural clay Bentonite

may act as a disintegrant by hydrating and swelling[26]. This clay is very different chemically from the cellulose, starch, and polysaccharide disintegrants previously employed. In addition, its adsorbent properties have been used to mask the taste of some drugs. However, Bentonite may also retard drug release[26]. Trial QQQ evaluated the addition of 1.0% Bentonite. Unfortunately, in our trials, Bentonite resulted in longer disintegration times of 55 seconds or more.

Crospovidone is a wicking and swelling disintegrant used successfully in many ODT formulations. Earlier use in lower weight tablets at typical use levels of 5% (lot O) and 10% (lot M) resulted in friability problems. Lot RRR evaluated the addition of 1.0% Crospovidone in this higher weight tablet. Thinner tablets (3.88-3.92 mm as compared to 4.00 mm for MMM Low) required to pass friability testing yielded prolonged disintegration times of 83 seconds and 51 seconds for sub-lots RRR and RRR Low, respectively. Both attempts to add an additional disintegrant were unsuccessful.

The improved *in vivo* disintegration from the Pharmaburst tablets was noted above. It was believed this may be due to the more voluminous (lower bulk density), porous nature of this formulation. Maltodextrin has been used as a binder/diluent in many chewable and ODT formulations. Maltrin QD M500 is an agglomerated form of Maltodextrin, NF with a high bulk volume as reflected by its low bulk and tap density values of 0.26 grams/ml and 0.34 grams/ml respectively[26] It was thought that the combination of the bulking and binding properties of Maltrin QD M500 might yield a thicker, more porous, faster disintegrating tablet. Trial SSS employed adding 20% Maltrin QD M500 to the control (MMM Low). Both sub-lots had higher disintegration

times (greater than one minute) and both had multiple broken tablets when subjected to friability testing.

Other than improved taste and friability from the increase in tablet weight, these trials to further improve disintegration were not successful. It was decided to conduct flavor trials and then proceed with the current 350 milligram tablet control. Citrus Flavors were examined since these would best combine with the Citric Acid used to prevent numbing.

Blind, random taste testing by two researchers of solutions containing drug and individual flavors indicated a Key Lime Flavor to be the best flavor of the choices tested. Further testing was similarly performed. Solutions of Saccharin Sodium, Citric Acid, Promethazine + Citric Acid, Promethazine + Saccharin Sodium, and Promethazine + Saccharin Sodium + Citric Acid + Key Lime Flavor were prepared and tasted. For both persons, the combination of all ingredients tasted best. This mixture resulted in a pleasant tasting solution.

The combination of Drug + Flavor + Citric Acid was further tasted with the addition of Saccharin Sodium, Sucralose, ½ Strength Saccharin Sodium, Saccharin Sodium + Sucralose, and ½ Strength Saccharin Sodium + Sucralose. Each of these solutions had an overall pleasant taste. For all strengths, the combination of Sucralose and Saccharin Sodium tasted better than solutions with only one of the two sweeteners. The combination of ½ Strength Saccharin Sodium and Sucralose was preferred. Based upon these trials, the final flavor/sweetener formula to be further examined was:

Key Lime Flavor	0.40%
Citric Acid	1.50%
Saccharin Sodium	0.25%

Sucralose	0.25%

Calcium Carbonate was also added at a level of 1.1%. Although Calcium Carbonate did not improve disintegration, it yielded a softer tablet. This action combined with the weak effervescence may improve the overall palatability of the formulation. Although 2.0% Calcium Carbonate was used earlier, 1.1% was recommended for the final formulation. This amount will stoichiometrically react the 1.5% Citric Acid while keeping the overall dilution of the tablet base to a minimum. The Calcium Carbonate plus flavor and sweeteners represents 3.5% of the final formulation.

Two, 200 tablet (70 gram), flavored and sweetened trial batches were produced using the materials and methods previously described. Formulation TTT was based upon the in-house formulation whereas formulation UUU utilized Pharmaburst as a base formulation. The individual formulas are shown in Table 4.4g.

As in previous trials, the flavored/sweetened formulation had a slightly increased in vitro disintegration time of 28 seconds versus 21 seconds for MMM Low. MMM Low did not include the Calcium Carbonate, Citric Acid, Flavor, and Sweeteners. Although slightly higher than the 0.17% value for MMM Low, friability was still good for the flavored/sweetened in-house formulation. Values of 0.37% and 0.31% were obtained for in-house formulation tablets TTT and TTT Low, respectively.

As previously observed, informal taste testing indicated *in vivo* disintegration time was from one to two times the *in vitro* disintegration time. Although the flavor trials using Promethazine solutions indicated the opposite, flavor/sweeteners did not improve the tablet taste. Surprisingly, the taste of MMM Low was as good as or better than the

Table 4.4i. Flavored, Sweetened Formulations and Results

	TTT In-House Formulation		UUU Pharmaburst Formulation	
Description	**% W/W**	**Quantity(g)**	**% W/W**	**Quantity(g)**
Promethazine: Magnesium Stearate 1:1 Pre-blend	each 7.14 total 14.29	10.000	each 7.14 total 14.29	10.000
Pharmaburst			83.31	58.320
Dextrates	73.46	51.425		
Sodium Starch Glycolate (SSG)	3.00	2.100		
Croscarmellose Sodium	3.00	2.100		
Calcium Silicate	1.50	1.050		
Soy Polysaccharides	1.25	0.875		
Calcium Carbonate, DC	1.10	0.770		
Citric Acid, Monohydrate, Granular	1.50	1.050	1.50	1.050
Key Lime Flavor	0.40	0.280	0.40	0.280
Saccharin Sodium, USP, Powder	0.25	0.175	0.25	0.175
Sucralose, USP, Micronized	0.25	0.175	0.25	0.175
Totals	100.00	70.000	100.00	70.000

	Average (SD) (%RSD)			Disintegration	Friability (%)
Formula	**Weight (mg)**	**Thickness (mm)**	**Hardness**	**Time**	**(25 rpm, 4 min)**
				(min:sec)	
TTT	**348.1(1.6)(0.5)**	**3.98(0.005)(0.12)**	**5.0(0.6)(11.1)**	**0:28**	**0.31**
TTT Low	**351.0(1.5)(0.4)**	**4.01(0.006)(0.14)**	**5.0(0.7)(14.9)**	**0:28**	**0.37**
UUU	**344.3(3.0)(0.9)**	**4.69(0.020)(0.42)**	**4.1(0.5)(12.6)**	**0:18**	**1.00**
UUU Low	**348.2(3.1)(0.9)**	**4.82(0.007)(0.14)**	**4.4(0.7)(17.2)**	**0:19**	**1.75**

sweetened/flavored product (TTT Low). The *in vivo* disintegration time was still slow enough to yield some numbness.

The flavored, sweetened Pharmaburst formulation (UUU and UUU Low) was made for comparison with the in-house formulation. These tablets were compressed thinner (4.69 mm and 4.89 mm for UUU and UUU Low, respectively) than the previous unflavored, unsweetened Pharmaburst tablets (4.86 mm and 4.97 mm for PPP and PPP Low, respectively) which failed friability. The Low compression force tablets (UUU Low) failed friability (1.75%) whereas the higher compression force tablets (UUU) yielded results at the friability limit (1.00%). Since these tablets suffer from edge-wear rather than breakage, a change from concave tooling to flat-faced beveled edge or similar tooling with less sharp tablet edges would likely improve friability.

The in-house formulation tablets now appear superior to the Pharmaburst tablets in terms of taste. Unflavored, unsweetened (MMM Low) tablets appear to be equal to or better than flavored/sweetened tablets.

As is, this formulation and process yielded a pleasant tasting tablet which disintegrates in less than one minute *in vivo.* However, it was decided that a further reduction in disintegration time would still be needed to completely avoid numbing. Although further increases in Citric Acid might further reduce the numbing, this would result in an unacceptable taste from the Citric Acid itself. Trials were next undertaken with volatile substances in an attempt to further improve disintegration.

The *in vitro* disintegration time of 18 seconds for the flavored, sweetened Pharmaburst tablets which met the friability limit (UUU) was the same as for the unflavored, unsweetened Pharmaburst tablets (PPP). Although both yielded the same

in vitro disintegration time of 18 seconds, the tablets did not appear equivalent *in vivo*. Informal taste testing revealed these tablets to disintegrate slower, taste less favorable, and result in more numbing than the in-house tablets (TTT Low). This is the opposite from what was seen with the thicker Pharmaburst tablets (PPP).

The in-house formulation tablets now appear superior to the Pharmaburst tablets in terms of taste. Unflavored, unsweetened (MMM Low) tablets appear to be equal to or better than flavored/sweetened tablets. The final in-house formulation is shown in table 4.4j. This formulation and process of simple blending followed by direct compression does yield a robust, pleasant tasting tablet which disintegrates *in vitro* in around 21 seconds and *in vivo* in less than one minute. However, in the case of Promethazine HCl, the unpleasant numbing effect is greatly diminished but not eradicated. Separate studies should be undertaken combining this technology with other methods such as sublimation to further improve *in vivo* disintegration and eliminate the unpleasant anesthetic effect.

Table 4.4j. Final In-House Formulation

Ingredient	**Function**	**% W/W**
Promethazine HCl	Active Ingredient	7.1
Magnesium Stearate	Taste-Masking	7.1
Dextrates, NF	Diluent	77.0
Sodium Starch Glycolate	Disintegrant	3.0
Croscarmellose Sodium	Disintegrant	3.0
Calcium Silicate	Disintegrant	1.5
Soy Polysaccharides	Disintegrant	1.3
Total		100.0

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5. SUBLIMATION

Abstract

Orally Disintegrating Tablets (ODTs) have become a very popular dosage form, especially in certain patient populations and disease states. A simple method of producing an ODT was previously reported. This method of simple blending followed by direct compression yielded a rapidly disintegrating tablet which was robust enough to withstand conventional packaging, shipping, and handling. This tablet had a pleasant taste and disintegrated *in vitro* in approximately 21 seconds and *in vivo* in less than one minute. However, in the case of Promethazine HCl, the unpleasant numbing effect of this drug was greatly diminished, but not eradicated.

The current study was undertaken to determine if sublimation further improves the *in vivo* disintegration of the above described formulation. Sublimation has been used to speed disintegration by increasing tablet porosity. Menthol, 3.0% and 6.0%, was incorporated into the tablet blend then sublimed from the compressed tablets at 35°C in a laboratory oven. The sublimation process appeared to follow first or pseudo-first order kinetics. Tablets produced by this method disintegrated faster *in vitro* and *in vivo*. Tablets produced with 6.0% Menthol had no advantage over those produced with 3.0%. This process yielded a pleasant tasting tablet which overcame the previous numbing problem. These tablets passed conventional tablet compendial requirements for friability, dissolution and content uniformity.

5.0 Introduction

Orally Disintegrating Tablets (ODTs) have become a popular dosage form. An ODT may be defined as a tablet which disintegrates and/or dissolves rapidly (< one minute) in the saliva without the need for water or other liquid[1]. These readily transportable dosage forms are intended to be taken anytime or anywhere[1, 2]. Certain patient groups such as children, elderly, and psychiatric patients greatly benefit from this technology[3-5]. This dosage form is especially beneficial in certain medical conditions such as pain, migraine, nausea, panic attack, allergic conditions, cough/cold, and Alzheimer's[3-5].

Market research has shown a significant number of consumers prefer an ODT over a conventional tablet. This research has also shown that taste is a very important factor. Longer disintegration times were acceptable if the taste was good. However, the converse was not true; fast disintegration times were not acceptable if taste was bad[1]. Although some drugs have little taste and a simple addition of flavor will result in an acceptable taste, most drugs to be incorporated into an ODT formulation require taste-masking [1].

A simple method of producing an ODT was previously developed in our lab. This method of simple blending followed by direct compression yielded a pleasant tasting, rapidly disintegrating tablet which was also robust enough to withstand conventional packaging, shipping, and handling. Drug (Promethazine HCl) was blended with Magnesium Stearate in a 1:1 ratio to produce taste-masking. This was combined with a mixture of Dextrates and disintegrates followed by direct compression. This formulation and process of simple blending followed by direct compression yielded a

robust, pleasant tasting tablet which disintegrates *in vitro* in approximately 21 seconds and *in vivo* in less than one minute. However, in the case of Promethazine HCl, the unpleasant numbing effect was greatly diminished, but not eradicated.

The current study was undertaken to determine if sublimation further improves the *in vivo* disintegration time of the above described formulation. Sublimation has been used to speed disintegration by increasing tablet porosity[2, 5]. A volatile substance is used as part of the tablet composition; the tablets are then compressed followed by sublimation of the volatile substance. Substances used include menthol, camphor, thymol, organic and lower fatty acids, urea, ammonium carbonate, ammonium bicarbonate, and hexa methylene tetramine. Both vacuum and/or heat may be used to sublime the volatile material[2, 5].

Menthol was chosen as the volatile agent for these trials. Menthol is easily sublimed[6] and is considered very safe for pharmaceutical use. Menthol is used extensively in the United States in food, candy, cigarettes, cough drops, cold tablets, and topical and inhalation formulations. The United States Food and Drug Administration recognizes Menthol as having GRAS (Generally Recognized as Safe) status[7]. The World Health Organization lists an Allowable Daily Intake (ADI) of up to 4 mg/kg (280 mg/70 kg)[8]. The maximum recommended daily dose of Promethazine is 150 mg (six 25 mg tablets)[9]. For this study, six of these planned tablets contain 63 mg (3.0%) or 126 mg (6.0%) of Menthol before sublimation. The maximum value before sublimation in these planned tablets is less than one-half of the WHO Allowable Daily Intake. The oven sublimation is expected to remove a very large percentage, if not essentially all, of this Menthol.

5.1 Materials

The following materials were used as received:

-Promethazine HCl, USP; Honeywell (Ireland); Lot BPMH119117;

-Magnesium Stearate, NF, Impalpable Powder; Fisher Scientific, Lot 974493;

-Dextrates, NF; EMDEX, JRS Pharma, LP, Lot 04H502X;

-Sodium Starch Glycolate, NF; Explotab, JRS Pharma LP, Lot 4111034021X;

-Croscarmellose Sodium, NF; Ac-Di-Sol, FMC Biopolymer, Type SD-711, Lot T442N;

-Calcium Silicate; RxCipients FM 1000, Huber, Lot 294/102

-Soy Polysaccharides; Emcosoy STS IP, JRS Pharma LP, Lot P660002580X;

-Menthol, USP, Natural, Levorotatory; Amend Drug & Chemical Company, Lot G17985A18.

5.2 Methods

Formulations

Formulations are shown in Table 5.2. These formulations differ from the control (MMM Low) from previous trials in that additions of Menthol are offset by a corresponding decrease in the diluent, Dextrates. Initially, two batches of 200 tablets (70 grams) batch size were made. Lot VVV contained 3.0% Menthol whereas Lot WWW contained 6.0% Menthol. A subsequent larger batch (Lot XXX, 1000 tablets, 350 grams) was made containing 3.0 % Menthol.

Blending

Blending was performed using a Patterson-Kelley Twin Shell (V) Dry Blender, Serial Number LB853S, tabletop unit with interchangeable shells. An approximately two quart (actual volume equals 1820 ml) acrylic shell with a speed of 22 rpm was used. All

Table 5.2 Menthol Formulations

Description	% W/W	Quantity/ Tablet(mg)
Promethazine: Magnesium Stearate 1:1 Pre-blend	each 7.14 total 14.29	each 25.000 total 50.000
Dextrates	73.96 or 70.96	258.860 or 248.360
Sodium Starch Glycolate	3.00	10.500
Croscarmellose Sodium	3.00	10.500
Calcium Silicate	1.50	5.250
Soy Polysaccharides	1.25	4.375
l-Menthol, USP Lots VVV & XXX Lot WWW	 3.00 or 6.00	 10.500 or 21.000
Totals	100.00	349.985

materials other than Menthol were passed through a 20 mesh screen (14 mesh for Dextrates) prior to weighing and blending. Menthol was manually ground using a glass mortar and pestle and passed through a 20 mesh screen prior to weighing. A single 100 gram pre-blend of Magnesium Stearate and Promethazine HCL was prepared by blending for 60 minutes in the V-blender. This pre-blend was discharged and set aside for later use. Portions of this same pre-blend were used for each batch. Visible residue was wiped from the blender using paper towels. For each individual batch, all other materials were add to the V-blender and blended for 4 minutes. The appropriate amount of Promethazine: Magnesium Stearate pre-blend was added and a final blending (80 seconds) was performed. The blend was discharged, weighed, and forwarded to compression.

Sublimation

The finished tablets were immediately and randomly separated into two portions. One portion was immediately tested for friability, weight, thickness, hardness, and disintegration as previously described. The other portion was placed on a 6 mesh sieve in a 35 °C vented standard laboratory oven. At specific time intervals, all tablets were removed and 20 randomly selected tablets were weighed. (Note: For the second batch, Lot WWW, all 100 tablets dried were weighed each time.) All tablets were then returned to the oven. Percent Loss for each time-point was calculated as:

Percent Loss = (Initial Weight – Final Weight)/ (Initial Weight) * 100.

The Theoretical Percent Remaining was calculated by subtracting the Percent Loss from the initial amount of Menthol used in the formulation, either 3.0 or 6.0%.

After sublimation appeared complete, tablets were subjected to the same physical testing described above.

Based upon results from the initial trials, a third, larger batch size (1000 tablets, 350 grams), 3% Menthol batch (lot XXX) was made. Blending and compression were unchanged. Sublimation in the standard vented laboratory oven at 35°C was performed by placing the tablets on five inch square, 16 mesh, steel wire gauzes. At each time-point for sublimation weight sampling, the same wire gauze containing 100 tablets was removed, weighed, and readily returned to the oven. Batch drying was performed for 48 hours. The weight sampling tablets were dried for an additional 48 hours then left exposed to the atmosphere at ambient conditions for 72 hours.

Hardness, Thickness, and Weight Testing

All tablets for testing were randomly selected from each finished lot or sub-lot. Tablet Hardness was determined for ten tablets using a J. H. DeLamar & Son, Inc. Model PT 102, Serial Number 39, Hardness Tester. Although units are not listed on this instrument, one souce[10] gives kg/cm^2 as the units. Thickness was determined by manually measuring the thickest point of ten individual tablets using a Fisher Scientific battery-operated, digital dial caliper. Ten tablets were weighed individually using an analytical balance. Average and Standard Deviation values were determined and reported for each parameter.

Friability

Friability was determined as per USP <1216> Tablet Friability[11] using a Roche-type friabilator rotated at 25 rpm for four minutes for a total of 100 revolutions. Drop-height was 156.0 ± 2.0 mm (6.1 inches). Ten randomly selected tablets were de-dusted,

weighed, and placed in the friabilator. After 100 rotations, the tablets were removed, de-dusted, and re-weighed. Percent Friability was determined as:

((Initial Weight – Final Weight)/ (Initial Weight)) * 100.

A maximum weight loss of not more than 1.0 % was considered acceptable. Broken tablets were noted and considered a test failure. Friability testing was performed on each lot or sub-lot.

Disintegration

Disintegration testing was performed as per USP <701> Disintegration[11] for uncoated tablets. Purified water at 37 ± 2 °C was used as the test media. Six randomly selected tablets were placed into each of the six tubes of the apparatus. The apparatus was operated and the time for the last tablet to disintegrate was recorded as the disintegration time. Notable observations were also recorded.

Dissolution

Three randomly selected final sublimed tablets from the larger batch XXX were subjected to dissolution testing. Dissolution testing was based upon the compendial method[11] for conventional Promethazine HCL tablets with modifications recommended for ODTs[12, 13]. Dissolution test parameters included using a de-aerated 0.2M pH 6.4 Phosphate Buffer, 900 ml, 37 ± 0.5° C, and Apparatus 2 (paddles) at 50 rpm. Samples were taken at 2, 5, 10, 15, and 30 minutes. Five milliliter samples were withdrawn manually with a ten ml plastic syringe. Media was replaced after each sampling. A new 5 micron filter needle was attached to the syringe. The first two ml expressed was discarded and the remaining three ml collected in a glass sample tube. Absorbance was

determined at 249 nm for suitably diluted samples. Percent Dissolved values were determined using a standard curve equation.

Content Uniformity

Ten randomly selected final sublimed tablets from the larger batch XXX were subjected to Content Uniformity testing utilizing the compendial method[11]. This method is performed by dissolving and serially diluting individual tablets or reference sample in 1% W/V Citric Acid Solution and comparing the reference and sample absorbance values at 298 nm using a spectrophotometer. The Promethazine raw material utilized in the tablets was used as a reference.

5.3 Results and Discussion

Overall, no major problems were encountered during blending and compression of the Menthol containing formulations. In the initial trials, the 6% Menthol formulation tablets exhibited a visible surface depression slightly off center on the upper punch side of the tablet. Since this was not observed with the three percent tablets, it was initially believed this was related to the amount of Menthol present and rapid sublimation during the compression process. However, when the same defect was observed with the larger batch size 3% Menthol tablets, further investigation was initiated. At this point, removal and examination of the upper punch revealed a barely visible area of punch erosion or damage corresponding to the area of tablet depression. This resulted in powder adhering to this damaged area which subsequently resulted in a corresponding depressed area in the tablet.

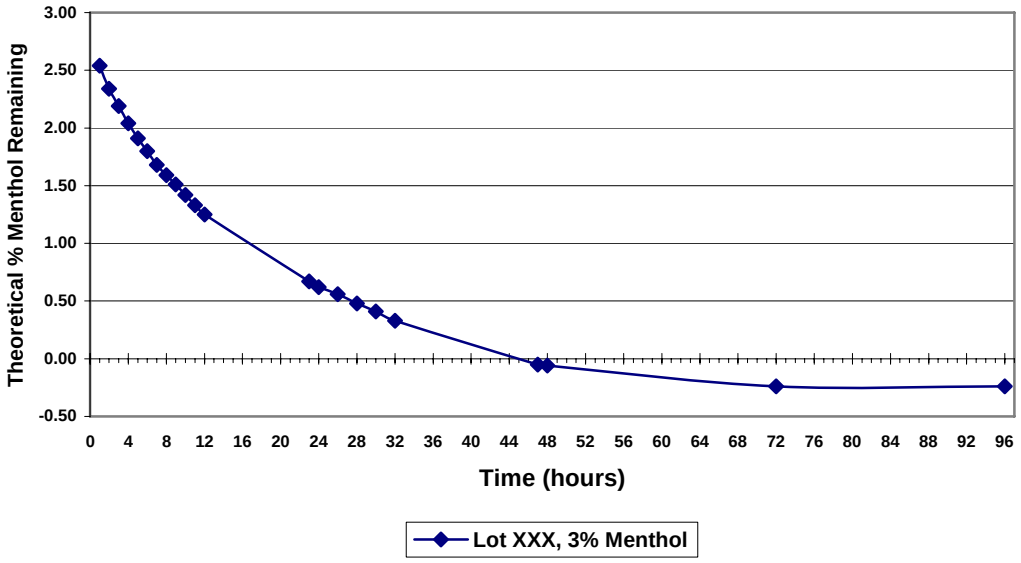
Sublimation of Menthol was performed in a vented standard laboratory oven at 35 °C. This mild temperature is above the temperature (21 °C) at which sublimation begins and below the menthol melting point of 41-42 °C [6]. It should be noted that a forced air oven would likely be more efficient and yield faster sublimation times. Oven sublimation was chosen over vacuum extraction because this method would be more universally available in solid dosage form pharmaceutical manufacturing facilities.

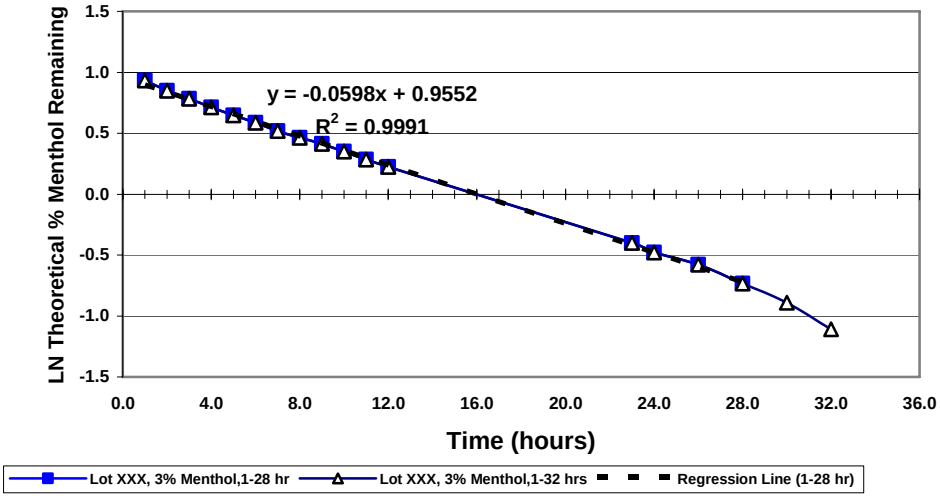
Sublimation data are shown in Table 5.3a. The data are presented graphically in Figure 5.3a. The initial sublimation weight loss determination methods and sampling times were only preliminary in nature and the data were insufficient to describe the sublimation process. The larger batch size yielded more data in this respect as well as provided additional tablets for expanded finished product testing. The larger batch (lot XXX) data were used to more thoroughly evaluate the sublimation process. Batch sublimation was stopped at 48 hours when the Theoretical Percent Remaining was consistently below zero. This was in agreement with the observations from the smaller batch of 6.0% Menthol tablets. The smaller batch of 3.0% Menthol tablets yielded different results but likely utilized too few tablets for accurate weight sampling. The weight sample tablets were sublimed for an additional 48 hours. Further loss had occurred between 48 and 72 hours but detectable loss was not observed between 72 and 96 hours.

A plot of Percent Menthol Remaining versus Time readily indicates the sublimation process is not zero order. The curvature observed readily compares to that typically observed with a first or pseudo-first order process. The negative Percent Remaining values (as low as -0.24) also indicate that not all loss is Menthol.

Table 5.3a. Menthol Tablet Sublimation Data (35°C)			
Lot/ Description	Drying Time (hours)	% Loss	Theoretical % Remaining
VVV	1.0	0.53	2.47
3%	2.0	0.65	2.35
Menthol	4.0	1.05	1.95
	6.0	1.15	1.85
	22.0	3.03	-0.03
	28.0	2.91	0.09
WWW	1.0	0.68	5.32
6%	17.0	3.76	2.24
Menthol	22.0	4.31	1.69
	41.0	5.64	0.36
	46.0	5.89	0.11
	48.0	5.96	0.04
XXX	1.0	0.46	2.54
3%	2.0	0.66	2.34
Menthol	3.0	0.81	2.19
	4.0	0.96	2.04
	5.0	1.09	1.91
	6.0	1.20	1.80
	7.0	1.32	1.68
	8.0	1.41	1.59
	9.0	1.49	1.51
	10.0	1.58	1.42
	11.0	1.67	1.33
	12.0	1.75	1.25
	23.0	2.33	0.67
	24.0	2.38	0.62
	26.0	2.44	0.56
	28.0	2.52	0.48
	30.0	2.59	0.41
	32.0	2.67	0.33
	47.0	3.05	-0.05
	48.0	3.06	-0.06
	72.0	3.24	-0.24
	96.0	3.24	-0.24

Figure 5.3a. Menthol Sublimation Plots (35° C)





When one considers that some sublimation likely occurs during blending and compression (i.e., the intercept is not 3.0) the true Percent Remaining values are likely even more negative than observed. This loss other than Menthol is likely adsorbed water which is commonly present in pharmaceutical excipients. The sublimation temperature of 35°C is too low to remove water of hydration or crystallization. The weight sample tablets quickly gained weight to a level of 0.19 and 0.31 Percent Remaining after exposure to the atmosphere at ambient conditions for one and two hours, respectively. These values rose to approximately 0.5% at both five and seven hours, but had returned to 0.31% after three days. Although this was informal in nature, it readily supports the theory that some of the loss was adsorbed water and varied with humidity.

A plot of LN Percent Remaining versus Time indicates the sublimation process to be first or pseudo-first order. The data from 1 to 28 hours yield a straight line with a R^2 value of 0.9991. This same line yields a y-intercept corresponding to 2.6 Percent Remaining. The equation (LN % Remaining = -0.0598*Time + 0.9552) yields a theoretical amount remaining at 48 hours of 0.15%. This represents removal of 95% of the initial 3.0% Menthol. This would indicate 48 hours to be an appropriate sublimation time for these conditions. It is evident that this linearity drops after 28 hours. Although most of the curve may represent Menthol and adsorbed water loss, it is reasonable to expect the latter points represent more water loss than Menthol loss. Whatever the reason, loss of linearity at the extremes is not uncommon. Removal of the one hour data point would increase the R^2 value from 0.9991 to 0.9995.

A photograph of tablets with and without Menthol is shown in Figure 5.3b. Physical test results are shown in Table 5.3b. Menthol formulation tablets revealed visible pores not observed with the control tablets. Although this was even more evident after sublimation, pores were visible even before oven sublimation.

In the initial Menthol batches, the tablets produced were notably thicker (4.08 mm and 4.07 mm for the 3.0% and 6.0% tablets, respectively) than the control formulation (MMM Low, 4.00 mm). The Menthol appears to have some binding effect. This is not completely surprising considering the adhesive or sticky nature of this substance. After sublimation, the tablets had expanded, yielding an average thickness value of 4.11 mm for both formulations. This is an especially notable increase (2.8%) from the control value of 4.00 mm. This expansion was not anticipated. This could be due to the creation of pores resulting in less bonding within the tablet structure. Another possibility is the tablet expansion being similar to dough rising in the baking process as gases are produced and escape. The larger batch was produced using less compression force and yielded even thicker tablets with a before sublimation average thickness value of 4.15 mm which is 4.8% thicker than the small batch control (MMM Low, 4.00 mm). As observed with the initial batches, thickness was further increased (average = 4.19 mm) when measured after sublimation.

Although tablet hardness is variable, both initial lots of Menthol formulation tablets appear less hard (maximum average hardness of 5.4) than the control tablets (average value of 7.2). There was no absolute trend with regard to hardness decreasing after sublimation. It might be expected that sublimation would lead to decreased hardness

Figure 5.3b. Photograph of Menthol Formulation Tablets

From right to left: 0, 3, and 6 Percent Menthol Formulation Tablets
Magnification: 3.7X

Table 5.3b. Physical Test Results

	Average (SD) (%RSD)				
Formula	Weight (mg)	Thickness (mm)	Hardness	DT*	** % Friability
MMM Low (No Menthol)	356.3(1.3)(0.4)	4.00(0.006)(0.14)	7.2(1.1)(15.1)	0:21	0.17
3% Menthol-Before Sublim.	348.2(1.6)(0.4)	4.08(0.007)(0.17)	5.1(0.8)(15.2)	0:20	0.29
3% Menthol-After Sublim.	341.2(1.5)(0.4)	4.11(0.007)(0.17)	5.4(0.7)(14.0)	0:20	0.38
6% Menthol-Before Sublim.	347.3(1.2)(0.3)	4.07(0.008)(0.21)	4.7(0.7)(14.4)	0:20	0.40
6% Menthol-After Sublim.	329.0(1.6)(0.5)	4.11(0.006)(0.15)	4.4(0.8)(18.4)	0:21	0.92
3%, Larger Batch, Before	343.3(3.0)(0.9)	4.15(0.015)(0.36)	5.5(0.7)(12.1)	0:16	0.25
3%, Larger Batch, After	333.8(1.9)(0.6)	4.19(0.012)(0.29)	4.5(0.6)(12.4)	0:17	0.59
*Disintegration Time (min:sec) ** % Friability (25 rpm, 4 min)					

and increased friability. The overall trend did reflect a tendency for sublimation to lead to an increase in friability. The 3.0% Menthol tablets had satisfactory friability results before and after sublimation (0.29% and 0.38%, respectively). After sublimation, the 6.0% Menthol formulation tablets yielded a friability result (0.92%) near the upper limit. The larger batch size 3.0% Menthol tablets followed the same trend with regard to friability increasing after sublimation. Acceptable results of 0.25% and 0.59% were obtained before and after sublimation of tablets, respectively.

In-vitro disintegration times of 20 to 21 seconds were obtained for the initial Menthol formulation tablets. However, the Menthol formulation tablets were faster disintegrating in-vivo than the control formulation. The 3.0% Menthol formulation yielded an acceptable taste without numbing. It was believed the lack of numbing was a direct result of an improvement in in-vivo disintegration time. However, a small amount of residual Menthol, a phenolic compound, could have some effect. The 6.0% Menthol formulation tablets retained a slightly less pleasant Menthol taste.

The 3.0% Menthol formulation tablets were the best produced to date. The decision to make a larger batch was made based upon these positive results. As noted above, this allowed better characterization of the sublimation curve as well as yielded tablets for expanded finished product testing. As previously discussed, these larger batch tablets were produced with a lower compression force. As might be expected, the in vitro and *in vivo* disintegration times were further improved with the lower compression force. *In vitro* disintegration times of 16 seconds and 17 seconds were observed for the before and after sublimation tablets, respectively. These values are lower than any observed to date.

In vivo disintegration was again much improved over non-Menthol containing formulations. These tablets yielded a pleasant taste without numbing.

These tablets, which met all physical and taste requirements, were now subjected to chemical testing. Final mixing times were kept at a minimum for mixing the Promethazine: Magnesium Stearate pre-blend with the inactive ingredient blend. Therefore, assessment of Content Uniformity was critical. Results are shown in Table 5.3c. The results (n=10) yielded a range of 94.4 – 102.7% Label Claim, an average of 97.4% Label Claim, and a Relative Standard Deviation of 2.8%. These results meet the standard USP requirements (range 85.0 – 115.0%, RSD ≤ 6.0%). Thus, the reduced mixing time employed was sufficient.

Another critical parameter to be assessed was dissolution. The large amount of Magnesium Stearate employed for taste-masking could potentially adversely affect dissolution. Dissolution data are presented numerically in Table 5.3d and graphically in Figure 5.3c. The tablets (n=3) yield an average percent dissolved of 73.0% at five minutes and 85.7% dissolved at thirty minutes. These results meet the USP limits of NLT 75% (Q) in 45 minutes for conventional Promethazine tablets.

In summary, these trials indicate this formulation to meet all requirements of a Promethazine Orally Disintegrating Tablet. More importantly, they were manufactured using only conventional excipients and blending followed by direct compression. While the sublimation of Menthol is an additional step, it only required a common laboratory oven and a time of 48 hours.

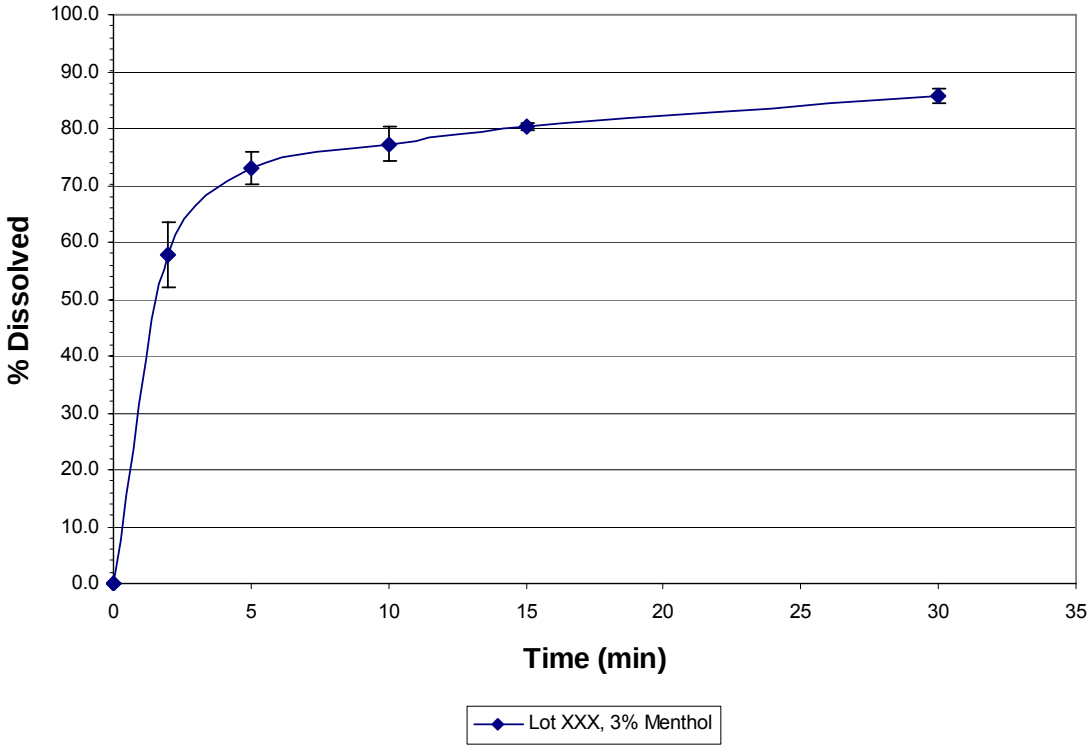
Table 5.3c. Content Uniformity Data

Promethazine 25 mg ODT			
Lot XXX, 3% Menthol, Larger Batch Size			
Content Uniformity Data			
Sample	Abs at 298nm	mg/tablet	% label claim
Standard	0.569	25.2	100.8
Tablet 1	0.540	23.9	95.7
Tablet 2	0.569	25.2	100.8
Tablet 3	0.555	24.6	98.3
Tablet 4	0.553	24.5	98.0
Tablet 5	0.549	24.3	97.3
Tablet 6	0.539	23.9	95.5
Tablet 7	0.546	24.2	96.7
Tablet 8	0.533	23.6	94.4
Tablet 9	0.534	23.6	94.6
Tablet 10	0.580	25.7	102.7
Tablet Avg	0.550	24.3	97.4
SD	0.015	0.7	2.7
%RSD	2.8	2.8	2.8
Min		23.6	94.4
Max		25.7	102.7
USP Limits			
Range: 85.0 - 115.0 %			
RSD: ≤ 6.0 %			

Table 5.3d. Dissolution Data

Dissolution Data (n=3),900 ml 0.2M pH 6.4 Phosphate Buffer, Paddles, 50 rpm						
Promethazine 25 mg ODT Tablets, Lot XXX, 3% Menthol						
Sample Description	Percent Dissolved @ Time (min)					
Time	0	2	5	10	15	30
Flask 1	0.0	63.0	75.8	80.1	80.3	84.3
Flask 2	0.0	51.7	73.3	77.4	80.7	86.8
Flask 3	0.0	59.0	70.0	74.1	79.5	85.9
Average	0.0	57.9	73.0	77.2	80.2	85.7
SD	0.0	5.7	2.9	3.0	0.6	1.3
%RSD	0.0	9.9	4.0	3.9	0.8	1.5
USP Limits (Conventional Tablet): NLT 75% (Q) in 45 minutes						

Figure 5.3c. Dissolution Plot



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6. CONCLUSIONS

The broad hypothesis for this work was that a pleasant tasting, rapidly disintegrating (less than one minute *in vivo*) Orally Disintegrating Tablet could be manufactured through the development of a simple manufacturing method, preferably simple blending followed by direct compression. Promethazine HCl was chosen as a model drug based upon its high degree of water solubility, its bitter taste, and the limitations of current dosage forms of this drug.

The immediate secondary hypothesis was that a material or blend of materials could be used to taste-coat Promethazine HCl via simple blending. Dissolution was primarily used to test this hypothesis and limited taste-testing was also employed. The compendial dissolution test[1] for conventional Promethazine HCL tablets was utilized with modifications recommended for ODT dosage forms[2, 3]. One pharmacokinetic study concluded the compendial dissolution test assures satisfactory bioavailability[4]. The preferred dissolution profile is no Promethazine HCL dissolved at the initial time point followed by a rapid increase in dissolution. The taste testing was limited in that only two people, the researchers involved in the project, performed this screening. However, no decision to accept the hypothesis was made based upon acceptable taste alone.

Initially, newer lubricants (partial glycerides of vegetable origin) and chemically similar materials were evaluated[5, 6]. These materials have been utilized in taste-coating,

but not in the absence of heat or shear[5, 6]. Glyceryl Dipalmitostearate, Hard Fat, and a mixture of Hard Fat and Glyceryl Behenate failed the hypothesis in that they did not retard dissolution or produce taste-masking. The particle size of these materials may be too large to accomplish coating via simple blending since a larger particle size results in less surface area for coating of the drug.

Various other materials were screened for taste-coating and failed. The ability of Promethazine HCL to dissolve in aqueous and non-aqueous environments also makes this material very difficult to taste-coat, especially by simple blending alone. Magnesium Stearate, a hydrophobic tablet lubricant with a very small particle size, and therefore a very large surface area, was found to provide some degree of taste-coating. A 1:1 ratio of Magnesium Stearate with Promethazine HCl was found to be superior to lower amounts of this lubricant. Higher amounts were not evaluated due to the known ability of Magnesium Stearate to retard tablet disintegration and increase tablet friability, both of which are inconsistent with the properties of an ideal ODT.

Magnesium Stearate resulted in a lower amount of drug dissolved at the initial time-point (two minutes). Taste-testing appeared to support this observation. It was accepted that a 1:1 ratio of Magnesium Stearate and Promethazine HCl V-blended for one hour results in taste-coating Promethazine HCl via a simple blending process. The next hypothesis was that this new taste-coating method would withstand further blending with additional excipients and tablet compression. This 1:1 mixture of Magnesium Stearate and Promethazine HCl was blended with Pharmaburst, an off-the-shelf ODT platform, and compressed. These soft, friable tablets had reduced dissolution at the initial time-point followed by an increase in percent dissolved to above the compendial limits at

later time-points. These tablets met the compendial standards for dissolution. Since taste was also graded as acceptable, the hypothesis was accepted.

Although the hypothesis was accepted, limitations were noted. A much lower amount of drug dissolved at the initial time-point would be desired. Use of more modern dissolution test equipment would allow collection of moment by moment dissolution data and would allow a better assessment of this method. Even a brief period of no dissolution may allow improved taste in that the interaction of other ingredients such as flavors and sweeteners with taste and smell receptors will affect the subsequent interpretation of drug taste[7]. This new method of taste-coating should be better for drugs which are less water soluble than Promethazine HCl, which is extremely water soluble (500mg/ml)[8, 9]. Not only would a slower initial dissolution rate be possible but lower levels of Magnesium Stearate could likely be utilized possibly resulting in faster disintegration and lower friability. Also, the anesthetic effect was a big problem with Promethazine HCl. An equally soluble drug which is bitter but does not produce an anesthetic effect might be a better candidate for this method. This method may be of limited value for high dose drugs, especially those which are very water soluble. In this case the amount of Magnesium Stearate required would be prohibitive in terms of tablet size, disintegration time, and friability.

Having accepted the hypothesis that this simple method results in Promethazine HCl being taste-coated and that this coating withstands further blending and tablet compression, the next hypothesis was that this high Magnesium Stearate content formulation could be combined with other materials to produce a tablet which is both non-friable and rapidly disintegrating. Magnesium Stearate is well known to cause

tableting problems, especially in amounts above one or two percent and/or with the use of extended blending times. Magnesium Stearate physically coats the active ingredient and excipients. This hydrophobic coating retards disintegration and dissolution and also decreases bonding between particles during the compression process which leads to increased friability[10]. Initial trials with excipients routinely used in ODTs indicated that, as expected, significant problems with capping and friability occur.

Additional early trials were conducted to evaluate various diluents, diluent/binder combinations, and glidants. Some initial evaluations of disintegrants were also performed. A small particle-size grade of spray-dried Mannitol was initially evaluated as a primary diluent. A suitable tablet could not be obtained due to problems with capping. Although sugars in general undergo brittle fracture to overcome lubricant sensitivity[10], this is less likely with these very small, uniform, spray-dried particles. Dextrates, NF was evaluated next and solved problems with capping. This material consists of large crystalline particles[11] which likely overcome this lubricant sensitivity by undergoing brittle fracture during compression. This brittle fracture results in the creation of new, uncoated surfaces for tablet bonding[10]. In addition, a glidant was not required when using Dextrates. Dextrates particles are large and spherical, both of which promote good flow[11]. This Promethazine HCl/ Magnesium Stearate/ Dextrates system was selected for further evaluation.

It was determined that any notable amount of dilution of this Promethazine HCl/ Magnesium Stearate/ Dextrates combination resulted in friable tablets. In this case, the tablet size was increased initially to 300 milligrams total tablet weight and later to 350 milligrams to incorporate more Dextrates. As discussed earlier, this limits this

technology from being useful for high dose drugs, especially those which are also highly water soluble.

As noted throughout this work, the balancing of friability and disintegration time is critical in the development of an ODT. Now that a formulation resulting in non-friable tablets was developed, trials with various disintegrants were undertaken since the hypothesis was that the tablet could be both non-friable and rapidly disintegrating. Prior to beginning this work, it had been planned to evaluate two disintegrants at a time using a 3^2 randomized full factorial design as utilized by Gohel and coworkers[12]. This approach and its accompanying statistical analysis would have yielded robust results. However, the fragile nature of this high Magnesium Stearate content formulation allowed only small changes in one variable at a time. In this case, a qualitative comparison of friability and disintegration data was used to evaluate formulations. This compromises our ability to generalize these results beyond our current study.

Various concentrations of disintegrants with various mechanisms of action were evaluated. A final combination of Sodium Starch Glycolate, Croscarmellose Sodium, Calcium Silicate, and Soy Polysaccharides was selected. Prior use of Soy Polysaccharides as a disintegrant in ODTs has not been reported. At this stage, the product was a non-friable (0.33%) tablet with an *in vitro* disintegration time of 19 seconds and an *in vivo* disintegration time of less than one minute. The hypothesis was accepted that a non-friable and rapidly disintegrating tablet could be formulated. However, the taste was judged to be unacceptable at this point and the initial broad hypothesis required the product to also be pleasant tasting.

Numerous other trials were undertaken in an attempt to further decrease disintegration time and/or improve taste. Materials evaluated included:

- Materials which promote binding therefore enabling a lower compression force to be utilized;
- Materials which increase the overall hydrophilic or hydrophobic nature of the tablet;
- Surfactants;
- Flavors/Sweeteners.

Formulations were evaluated as before. None of the extensive number of formulations evaluated resulted in any notable improvement. Most of these materials likely undergo plastic or visco-elastic deformation and are more subject to lubricant sensitivity. Only a reduction in final blending time and further dilution with Dextrates to a total tablet weight of 350 milligrams resulted in notable improvement. At this point, the tablets obtained were non-friable (0.17%), had an *in vitro* disintegration time of 21 seconds, and an *in vivo* disintegration time of less than one minute. Although the bitter taste of Promethazine HCl was masked, the unpleasant anesthetic effect in the oral cavity was not completely eliminated.

With regard to the initial broad hypothesis, this formulation and process of simple blending followed by direct compression did yield a robust, rapidly disintegrating, pleasant tasting Orally Disintegrating Tablet. However, in the case of Promethazine HCl, the unpleasant numbing effect was greatly diminished, but not eradicated. As noted earlier, limitations exist with regard to tablet size, scale-up, and overall robustness of the

process and methods. As also noted, the method may be more suited to less soluble drugs and less suited to drugs which are both high dose and/or highly water soluble.

The next hypothesis was that incorporation of Menthol (3.0% or 6.0%) into the tablet blend followed by post-tableting sublimation could be combined with the above described technology to further improve its usefulness as a method to produce ODTs. Obviously the sublimation would have to be complete in a reasonable period of time using mild conditions to be suitable for the large scale manufacturing of ODTs. Sublimation appeared to follow first order or pseudo-first order kinetics and was complete after 48 hours in a standard laboratory oven at 35°C. This sublimation time could be further reduced in industry through the use of a forced air oven.

The 6.0% menthol formulation offered no advantage over the lower 3.0% formulation. The addition of 3.0% Menthol with sublimation post tableting resulted in a visibly more porous tablet with a shorter *in vitro* disintegration time (17 seconds) and a shorter *in vivo* disintegration time (45 seconds or less). These tablets yielded a pleasant taste without numbing and met compendial Dissolution and Content Uniformity requirements for conventional Promethazine HCl tablets. The hypothesis was accepted that incorporation of a volatile substance followed by post-tableting sublimation can improve the original method.

In summary, this study has shown that an ODT can be produced through simple blending followed by direct compression. The use of Magnesium Stearate as a taste-coating agent combined with Dextrates and disintegrants in certain proportions resulted in a non-friable (0.17%), rapidly disintegrating (21 seconds *in vitro*, < one minute *in vivo*) Promethazine HCl Orally Disintegrating Tablet. The tablet was pleasant tasting but the

anesthetic effect in the oral cavity was greatly reduced but not eliminated. The addition of Menthol to the formulation followed by post-tableting sublimation resulted in an even better ODT with acceptable friability (0.59%) and faster disintegration (17 seconds *in vitro*, < 45 seconds *in vivo*). These tablets had a pleasant taste without the anesthetic effect.

These findings have many potential uses. The material will be divided into three serial publications (taste-masking, disintegrant trials, and sublimation). These will be submitted to *AAPS PharmSciTech* or to *Drug Development & Industrial Pharmacy*. It should be noted that the concept of a tablet containing these high levels (7-8%) of Magnesium Stearate yet being non-friable and rapidly disintegrating defies all conventional wisdom in the area of pharmaceutical product formulation. In addition, a Technology Disclosure has been filed with the Auburn University Office of Technology Transfer. This office believes this new, simple method of manufacturing an ODT can be patented and a provisional patent has been filed..

As with any study, one must assess how this work could be improved. As noted, improvements in equipment and methods would make any results more robust and more capable of being applied in a general fashion beyond the current work. As to other methods to consider, the combination of Dextrates and multiple disintegrants with a more robust taste-coating method such as fluid bed coating has unlimited potential in the development of Orally Disintegrating Tablets.

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APPENDIX

Active Ingredient Tablet Trials Individual Physical Test Results

Description	Weight (mg)	Thickness (mm)	Hardness
AA.	303	3.38	9.5
Magnesium	304	3.38	19.5
Stearate (8.3%)	301	3.38	19.5
Promethazine	301	3.37	20.0
HCl (8.3%)	303	3.37	13.5
Dextrates	303	3.37	19.5
(79.3%)	302	3.37	9.5
SSG (4%)	302	3.37	12.5
(Sodium Starch	302	3.37	13.0
Glycolate)	300	3.37	9.0
Average	302.1	3.37	14.6
SD	1.1	0.005	4.6
%RSD	0.4	0.14	31.8
Min	300	3.37	9.0
Max	304	3.38	20.0

Description	Weight (mg)	Thickness (mm)	Hardness
BB.	301	3.42	7.5
Magnesium	299	3.38	9.5
Stearate (8.3%)	298	3.38	4.0
Promethazine	297	3.40	4.0
HCl (8.3%)	299	3.41	5.5
Dextrates	298	3.37	7.5
(75.3%)	301	3.44	5.0
SSG (8%)	298	3.38	4.0
	296	3.36	3.5
	301	3.44	8.0
Average	298.7	3.40	5.9
SD	1.7	0.029	2.1
%RSD	0.6	0.84	36.0
Min	296	3.36	3.5
Max	301	3.44	9.5

Description	Weight (mg)	Thickness (mm)	Hardness
CC.	296	3.40	16.0
Magnesium	294	3.39	12.5
Stearate (8.3%)	298	3.39	18.5
Promethazine	302	3.41	10.0
HCl (8.3%)	294	3.39	16.0
Dextrates	298	3.40	19.0
(79.3%)	297	3.39	12.5
SSG (2%)	298	3.40	16.0
Croscarmellose	299	3.40	15.0
Na (2%)	297	3.40	16.0
Average	297.0	3.40	15.2
SD	2.3	0.007	2.8
%RSD	0.8	0.20	18.3
Min	294	3.39	10.0
Max	302	3.41	19.0

Description	Weight (mg)	Thickness (mm)	Hardness
CC.Low	297	3.48	13.5
Magnesium	296	3.48	13.0
Stearate (8.3%)	295	3.48	15.0
Promethazine	297	3.48	9.0
HCl (8.3%)	298	3.54	13.0
Dextrates	297	3.48	12.0
(79.3%)	297	3.48	9.0
SSG (2%)	298	3.49	15.0
Croscarmellose	297	3.48	13.5
Na (2%)	296	3.48	13.5
Average	296.8	3.49	12.7
SD	0.9	0.019	2.1
%RSD	0.3	0.54	16.8
Min	295	3.48	9.0
Max	298	3.54	15.0

Description	Weight (mg)	Thickness (mm)	Hardness
DD.	301	3.41	9.5
Magnesium	303	3.41	15.0
Stearate (8.3%)	303	3.42	17.0
Promethazine	300	3.40	18.5
HCl (8.3%)	305	3.41	17.5
Dextrates	299	3.39	17.0
(78.3%)	301	3.40	16.0
SSG (2%)	301	3.39	14.0
Croscarmellose	301	3.42	21.0
Na (3%)	301	3.40	15.0
Average	301.5	3.41	16.1
SD	1.6	0.011	3.1
%RSD	0.5	0.32	19.0
Min	299	3.39	9.5
Max	305	3.42	21.0

Description	Weight (mg)	Thickness (mm)	Hardness
DD. Low	301	3.50	14.0
Magnesium	302	3.51	15.0
Stearate (8.3%)	304	3.51	12.5
Promethazine	300	3.50	7.5
HCl (8.3%)	303	3.50	16.0
Dextrates	303	3.51	16.0
(78.3%)	301	3.50	12.0
SSG (2%)	300	3.50	15.0
Croscarmellose	300	3.50	14.5
Na (3%)	304	3.50	15.0
Average	301.8	3.50	13.8
SD	1.5	0.005	2.6
%RSD	0.5	0.14	18.6
Min	300	3.50	7.5
Max	304	3.51	16.0

Description	Weight (mg)	Thickness (mm)	Hardness
EE.	297	3.42	11.0
Magnesium	300	3.43	13.0
Stearate (8.3%)	300	3.44	8.5
Promethazine	301	3.44	14.5
HCl (8.3%)	303	3.44	16.0
Dextrates	300	3.44	17.0
(78.3%)	303	3.44	15.0
SSG (3%)	302	3.43	10.5
Croscarmellose	299	3.42	12.0
Na (2%)	301	3.43	15.0
Average	300.7	3.43	13.3
SD	1.7	0.008	2.7
%RSD	0.6	0.24	20.5
Min	297	3.42	8.5
Max	303	3.44	17.0

Description	Weight (mg)	Thickness (mm)	Hardness
EE. Low	301	3.46	15.0
Magnesium	299	3.47	14.5
Stearate (8.3%)	302	3.47	9.0
Promethazine	304	3.47	15.0
HCl (8.3%)	306	3.48	16.0
Dextrates	302	3.47	14.5
(78.3%)	302	3.48	12.0
SSG (3%)	300	3.47	9.5
Croscarmellose	301	3.48	13.0
Na (2%)	302	3.46	14.5
Average	301.8	3.47	13.3
SD	1.9	0.007	2.4
%RSD	0.6	0.21	18.1
Min	299	3.46	9.0
Max	306	3.48	16.0

Description	Weight (mg)	Thickness (mm)	Hardness
FF.	302	3.44	14.5
Magnesium	304	3.45	17.0
Stearate (8.3%)	303	3.45	12.0
Promethazine	306	3.45	12.5
HCl (8.3%)	303	3.44	15.0
Dextrates	298	3.44	13.5
(77.3%)	303	3.44	13.5
SSG (3%)	303	3.45	15.0
Croscarmellose	307	3.47	15.0
Na (3%)	303	3.45	13.5
Average	303.4	3.45	14.2
SD	2.4	0.009	1.5
%RSD	0.8	0.27	10.3
Min	298	3.44	12.0
Max	307	3.47	17.0

Description	Weight (mg)	Thickness (mm)	Hardness
FF. Low	303	3.56	9.0
Magnesium	306	3.56	9.0
Stearate (8.3%)	306	3.57	7.5
Promethazine	304	3.57	6.0
HCl (8.3%)	303	3.57	12.0
Dextrates	305	3.58	5.5
(77.3%)	305	3.57	10.5
SSG (3%)	304	3.56	10.5
Croscarmellose	303	3.56	8.0
Na (3%)	302	3.56	7.0
Average	303.9	3.57	8.5
SD	1.3	0.007	2.1
%RSD	0.4	0.20	24.6
Min	302	3.56	5.5
Max	306	3.58	12.0

Description	Weight (mg)	Thickness (mm)	Hardness
GG.	299	3.49	7.5
Magnesium	300	3.49	5.5
Stearate (8.3%)	300	3.49	7.5
Promethazine	298	3.49	9.0
HCl (8.3%)	300	3.50	9.0
Dextrates	300	3.49	10.5
(74.3%),SSG(3%)	297	3.49	10.5
Croscarmellose	298	3.49	7.0
Na (3%),Copovi-	298	3.49	7.5
done (3%)	297	3.50	7.5
Average	298.7	3.49	8.2
SD	1.2	0.004	1.6
%RSD	0.4	0.12	19.4
Min	297	3.49	5.5
Max	300	3.50	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
GG. Low	303	3.57	7.5
Magnesium	302	3.57	9.0
Stearate (8.3%)	300	3.58	9.0
Promethazine	297	3.56	7.5
HCl (8.3%)	296	3.56	7.5
Dextrates	298	3.56	6.0
(74.3%),SSG(3%)	295	3.56	6.0
Croscarmellose	300	3.57	7.5
Na (3%),Copovi-	294	3.56	9.0
done (3%)	298	3.56	5.5
Average	298.2	3.57	7.5
SD	3.0	0.007	1.3
%RSD	1.0	0.20	17.5
Min	294	3.56	5.5
Max	303	3.58	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
HH.	301	3.39	7.0
Magnesium	303	3.39	10.5
Stearate (8.3%)	303	3.40	10.5
Promethazine	301	3.39	7.5
HCl (8.3%)	303	3.40	10.5
Dextrates	304	3.40	10.5
(75.3%)	304	3.40	7.5
SSG (4%)	304	3.40	14.5
Croscarmellose	300	3.38	7.5
Na (4%)	303	3.40	7.5
Average	302.6	3.40	9.4
SD	1.4	0.007	2.4
%RSD	0.5	0.21	25.5
Min	300	3.38	7.0
Max	304	3.40	14.5

Description	Weight (mg)	Thickness (mm)	Hardness
HH. Low	301	3.50	9.0
Magnesium	301	3.49	10.5
Stearate (8.3%)	302	3.50	6.0
Promethazine	305	3.50	10.5
HCl (8.3%)	303	3.51	5.0
Dextrates	299	3.50	7.5
(75.3%)	297	3.51	9.0
SSG (4%)	297	3.49	9.0
Croscarmellose	299	3.50	10.5
Na (4%)	298	3.49	9.0
Average	300.2	3.50	8.6
SD	2.4	0.007	1.9
%RSD	0.8	0.21	22.1
Min	297	3.49	5.0
Max	305	3.51	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
II.	302	3.43	8.5
	301	3.41	9.0
	302	3.41	9.5
	302	3.42	8.0
	301	3.42	7.5
	297	3.40	8.5
	301	3.42	9.0
	301	3.41	9.0
	301	3.42	7.5
	303	3.42	9.0
Average	301.0	3.42	8.6
SD	1.5	0.008	0.7
%RSD	0.5	0.25	8.0
Min	297	3.40	7.5
Max	303	3.43	9.5

Description	Weight (mg)	Thickness (mm)	Hardness
II. Low	302	3.61	6.0
	302	3.62	7.5
	300	3.62	5.5
	301	3.61	6.0
	300	3.62	5.5
	301	3.62	5.0
	303	3.62	7.5
	301	3.62	7.5
	304	3.62	7.5
	300	3.62	8.5
Average	301.3	3.62	6.7
SD	1.3	0.004	1.2
%RSD	0.4	0.12	17.7
Min	300	3.61	5.0
Max	304	3.62	8.5

Description	Weight (mg)	Thickness (mm)	Hardness
JJ.	303	3.54	12.0
	301	3.52	12.0
	305	3.55	10.0
	304	3.53	10.5
	302	3.52	8.0
	302	3.52	9.5
	303	3.53	10.5
	303	3.53	12.0
	304	3.53	8.5
	301	3.51	11.0
Average	302.8	3.53	10.4
SD	1.3	0.011	1.4
%RSD	0.4	0.32	13.7
Min	301	3.51	8.0
Max	305	3.55	12.0

Description	Weight (mg)	Thickness (mm)	Hardness
JJ. Low	304	3.58	11.0
	304	3.58	9.0
	308	3.59	6.0
	301	3.59	5.5
	306	3.59	10.0
	303	3.59	10.5
	309	3.60	10.0
	305	3.58	9.0
	303	3.58	7.5
	300	3.58	9.0
Average	304.3	3.59	8.8
SD	2.7	0.007	1.9
%RSD	0.9	0.19	21.3
Min	300	3.58	5.5
Max	309	3.60	11.0

Description	Weight (mg)	Thickness (mm)	Hardness
KK	295	3.50	11.0
	301	3.51	12.0
	298	3.51	7.5
	298	3.51	9.0
	299	3.52	9.0
	300	3.52	9.0
	299	3.52	9.0
	298	3.51	11.0
	297	3.51	7.5
	297	3.52	7.5
Average	298.1	3.51	9.3
SD	1.5	0.007	1.6
%RSD	0.5	0.19	17.3
Min	295	3.50	7.5
Max	301	3.52	12.0

Description	Weight (mg)	Thickness (mm)	Hardness
KK. Low	299	3.59	7.5
	295	3.59	6.0
	300	3.59	7.5
	299	3.60	7.5
	299	3.59	7.5
	299	3.60	6.0
	299	3.59	7.0
	299	3.60	7.5
	297	3.59	6.0
	303	3.60	9.0
Average	298.9	3.59	7.2
SD	1.9	0.005	0.9
%RSD	0.6	0.14	13.2
Min	295	3.59	6.0
Max	303	3.60	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
LL.	307	3.51	10.0
	305	3.51	13.5
	305	3.52	9.0
	307	3.52	7.5
	306	3.52	9.5
	306	3.51	8.0
	306	3.52	10.0
	305	3.51	7.5
	301	3.49	7.5
	303	3.51	7.5
Average	305.0	3.51	9.0
SD	2.0	0.009	1.9
%RSD	0.7	0.26	21.1
Min	301	3.49	7.5
Max	307	3.52	13.5

Description	Weight (mg)	Thickness (mm)	Hardness
LL. Low	304	3.57	10.5
	300	3.56	4.5
	299	3.56	7.5
	306	3.57	9.0
	305	3.57	7.5
	301	3.56	7.5
	304	3.57	4.0
	304	3.57	4.5
	302	3.56	6.0
	307	3.57	6.0
Average	303.2	3.58	6.7
SD	2.6	0.005	2.1
%RSD	0.8	0.14	31.3
Min	299	3.56	4.0
Max	307	3.57	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
MM.	305	3.61	4.5
	304	3.61	5.5
	307	3.61	6.0
	302	3.61	6.0
	302	3.60	4.0
	304	3.61	6.0
	303	3.62	4.0
	303	3.62	4.0
	306	3.61	5.0
	305	3.61	6.0
Average	304.1	3.61	5.1
SD	1.7	0.006	0.9
%RSD	0.5	0.16	17.8
Min	302	3.60	4.0
Max	307	3.62	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
MM. Low	305	3.65	5.0
	301	3.65	5.5
	302	3.64	5.5
	304	3.64	6.0
	304	3.66	4.0
	304	3.63	6.0
	304	3.62	5.5
	302	3.66	4.0
	301	3.65	5.0
	301	3.66	6.0
Average	302.8	3.65	5.3
SD	1.5	0.013	0.8
%RSD	0.5	0.37	14.4
Min	301	3.62	4.0
Max	305	3.66	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
NN.	297	3.60	6.0
	299	3.60	7.5
	297	3.60	5.0
	300	3.62	6.5
	299	3.61	7.0
	297	3.60	7.0
	300	3.60	6.0
	302	3.60	7.5
	300	3.60	7.5
	298	3.60	7.5
Average	298.9	3.60	6.8
SD	1.7	0.007	0.9
%RSD	0.6	0.19	12.7
Min	297	3.60	5.0
Max	302	3.62	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
NN. Low	290	3.66	5.5
	299	3.70	6.0
	301	3.69	5.0
	298	3.68	5.5
	297	3.68	4.0
	299	3.68	4.0
	299	3.69	4.0
	297	3.67	4.0
	302	3.68	5.5
	290	3.65	4.0
Average	297.2	3.68	4.8
SD	4.0	0.015	0.8
%RSD	1.4	0.40	17.4
Min	290	3.65	4.0
Max	302	3.70	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
OO.	303	3.56	5.5
	305	3.57	6.0
	303	3.57	5.5
	303	3.57	5.0
	303	3.56	7.5
	305	3.58	5.5
	304	3.59	5.0
	303	3.57	7.5
	306	3.57	6.0
	307	3.58	7.5
Average	304.2	3.57	6.1
SD	1.5	0.009	1.0
%RSD	0.5	0.26	16.8
Min	303	3.56	5.0
Max	307	3.59	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
OO. Low	304	3.61	4.0
	307	3.64	7.5
	304	3.64	9.0
	310	3.63	9.0
	303	3.64	5.5
	313	3.66	4.5
	307	3.64	4.0
	304	3.63	6.0
	307	3.62	6.0
	307	3.64	6.0
Average	306.6	3.64	6.2
SD	3.1	0.014	1.8
%RSD	1.0	0.37	29.9
Min	303	3.61	4.0
Max	313	3.66	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
PP.	295	3.42	5.5
	296	3.44	7.5
	296	3.44	7.0
	299	3.44	6.0
	298	3.45	6.0
	298	3.44	9.0
	296	3.45	6.0
	298	3.45	7.5
	297	3.44	6.0
	298	3.44	6.0
Average	297.1	3.44	6.7
SD	1.3	0.009	1.1
%RSD	0.4	0.25	16.3
Min	295	3.42	5.5
Max	299	3.45	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
PP. Low	294	3.51	4.0
	296	3.52	6.0
	295	3.52	6.0
	297	3.52	5.5
	299	3.52	4.5
	293	3.52	4.0
	299	3.50	6.0
	300	3.53	6.0
	296	3.53	5.0
	298	3.53	6.0
Average	296.7	3.52	5.3
SD	2.3	0.009	0.9
%RSD	0.8	0.27	16.2
Min	293	3.50	4.0
Max	300	3.53	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
QQ.	301	3.53	7.5
	301	3.51	8.5
	300	3.52	6.0
	304	3.54	5.0
	303	3.53	6.5
	304	3.53	7.5
	304	3.53	8.0
	302	3.53	9.0
	304	3.54	5.0
	302	3.53	5.5
Average	302.5	3.53	6.9
SD	1.5	0.009	1.5
%RSD	0.5	0.25	21.2
Min	300	3.51	5.0
Max	304	3.54	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
QQ. Low	308	3.60	6.0
	303	3.58	6.0
	306	3.59	7.5
	300	3.55	6.0
	299	3.57	6.0
	300	3.58	6.0
	304	3.58	4.5
	300	3.57	4.0
	307	3.59	6.0
	303	3.58	6.0
Average	303.0	3.58	5.8
SD	3.2	0.014	0.9
%RSD	1.1	0.38	16.4
Min	299	3.55	4.0
Max	308	3.60	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
RR	306	3.49	9.0
	302	3.49	6.5
	307	3.49	8.5
	304	3.49	6.0
	303	3.49	7.5
	304	3.48	11.0
	301	3.47	9.0
	301	3.47	7.5
	303	3.48	7.5
	303	3.49	11.0
Average	303.4	3.48	8.4
SD	1.9	0.008	1.7
%RSD	0.6	0.24	20.4
Min	301	3.47	6.0
Max	307	3.49	11.0

Description	Weight (mg)	Thickness (mm)	Hardness
RR Low	307	3.58	5.5
	312	3.58	7.0
	304	3.56	7.5
	304	3.59	7.5
	308	3.57	7.5
	305	3.58	9.0
	304	3.57	6.0
	304	3.60	7.0
	305	3.57	6.0
	308	3.59	6.0
Average	306.1	3.58	6.9
SD	2.6	0.012	1.0
%RSD	0.9	0.33	15.2
Min	304	3.56	5.5
Max	312	3.60	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
SS	302	3.49	7.5
	303	3.51	11.0
	303	3.51	6.0
	301	3.51	7.0
	302	3.50	7.0
	302	3.50	7.5
	304	3.51	7.5
	301	3.51	5.0
	303	3.51	5.5
	303	3.51	6.0
Average	302.4	3.51	7.0
SD	1.0	0.007	1.7
%RSD	0.3	0.20	23.8
Min	301	3.49	5.0
Max	304	3.51	11.0

Description	Weight (mg)	Thickness (mm)	Hardness
SS Low	303	3.54	7.5
	304	3.54	5.5
	301	3.54	5.5
	306	3.53	7.5
	309	3.55	7.5
	303	3.54	7.0
	306	3.54	5.0
	302	3.54	6.0
	304	3.56	6.5
	302	3.53	6.0
Average	304.0	3.54	6.4
SD	2.4	0.009	0.9
%RSD	0.8	0.25	14.6
Min	301	3.53	5.0
Max	309	3.56	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
TT	298	3.54	7.5
	298	3.55	6.0
	300	3.55	6.0
	302	3.54	7.5
	301	3.55	6.0
	301	3.55	7.5
	300	3.55	10.5
	299	3.54	6.0
	299	3.54	9.0
	299	3.54	6.5
Average	299.7	3.55	7.3
SD	1.3	0.005	1.5
%RSD	0.4	0.15	20.9
Min	298	3.54	6.0
Max	302	3.55	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
TT Low	299	3.60	5.5
	304	3.60	7.5
	300	3.59	7.5
	306	3.59	6.0
	303	3.59	7.5
	303	3.59	7.5
	303	3.59	7.0
	303	3.59	6.0
	303	3.60	8.0
	303	3.60	5.5
Average	302.7	3.59	6.8
SD	1.9	0.005	0.9
%RSD	0.6	0.14	14.0
Min	299	3.59	5.5
Max	306	3.60	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
UU	295	3.36	9.0
	295	3.37	10.5
	298	3.37	7.0
	297	3.37	7.0
	294	3.36	8.0
	297	3.38	9.0
	296	3.38	7.5
	295	3.37	7.0
	296	3.37	7.0
	298	3.38	7.0
Average	296.1	3.37	7.9
SD	1.4	0.007	1.2
%RSD	0.5	0.22	15.4
Min	294	3.36	7.0
Max	298	3.38	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
UU Low	295	3.41	9.0
	299	3.42	10.0
	296	3.42	6.5
	297	3.40	5.0
	293	3.41	11.0
	296	3.42	9.0
	304	3.43	7.0
	297	3.41	8.0
	300	3.42	5.5
	296	3.41	7.5
Average	297.3	3.42	7.9
SD	3.1	0.008	1.9
%RSD	1.0	0.25	24.6
Min	293	3.40	5.0
Max	304	3.43	11.0

Description	Weight (mg)	Thickness (mm)	Hardness
VV	300	3.41	9.0
	303	3.42	8.0
	300	3.45	6.5
	302	3.44	10.0
	302	3.45	7.0
	301	3.44	8.0
	298	3.44	5.5
	301	3.43	8.0
	294	3.43	5.5
	301	3.45	9.0
Average	300.2	3.44	7.7
SD	2.6	0.013	1.5
%RSD	0.9	0.39	19.7
Min	294	3.41	5.5
Max	303	3.45	10.0

Description	Weight (mg)	Thickness (mm)	Hardness
VV Low	298	3.51	6.0
	298	3.51	8.0
	304	3.52	6.0
	301	3.52	10.5
	301	3.52	8.0
	302	3.51	7.5
	300	3.51	7.0
	298	3.51	8.0
	298	3.53	9.0
	299	3.52	7.5
Average	299.9	3.52	7.8
SD	2.1	0.007	1.3
%RSD	0.7	0.20	17.3
Min	298	3.51	6.0
Max	304	3.53	10.5

Description	Weight (mg)	Thickness (mm)	Hardness
WW	301	3.61	6.0
	301	3.60	6.0
	304	3.60	5.0
	301	3.60	6.0
	300	3.60	6.0
	300	3.60	7.5
	306	3.62	6.0
	302	3.63	5.5
	302	3.60	7.5
	304	3.62	7.5
Average	302.0	3.61	6.3
SD	1.7	0.011	0.9
%RSD	0.6	0.31	14.1
Min	300	3.60	5.0
Max	306	3.63	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
WW Low	302	3.65	6.0
	304	3.68	6.0
	303	3.67	6.0
	306	3.69	6.0
	308	3.69	6.0
	306	3.69	6.0
	303	3.67	6.0
	306	3.68	4.5
	304	3.67	6.0
	303	3.66	5.0
Average	304.5	3.68	5.8
SD	1.9	0.014	0.5
%RSD	0.6	0.37	9.4
Min	302	3.65	4.5
Max	308	3.69	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
XX	303	3.61	4.0
	302	3.62	4.0
	302	3.61	5.5
	302	3.62	4.0
	303	3.61	4.0
	302	3.63	6.0
	305	3.64	4.5
	306	3.63	5.0
	304	3.63	6.0
	302	3.61	4.0
Average	303.1	3.62	4.7
SD	1.4	0.011	0.9
%RSD	0.5	0.30	18.2
Min	302	3.61	4.0
Max	306	3.64	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
XX Low	299	3.60	2.5
	305	3.67	4.0
	304	3.66	6.0
	305	3.68	4.0
	305	3.67	6.0
	302	3.66	5.5
	300	3.66	4.0
	303	3.67	4.5
	300	3.68	4.0
	302	3.66	4.0
Average	302.5	3.66	4.5
SD	2.3	0.023	1.1
%RSD	0.8	0.62	24.5
Min	299	3.60	2.5
Max	305	3.68	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
YY	302	3.60	6.5
	304	3.60	4.0
	302	3.60	6.0
	307	3.61	5.0
	302	3.61	6.0
	303	3.60	7.5
	305	3.62	6.0
	304	3.61	6.0
	302	3.61	4.0
	303	3.60	5.5
Average	303.4	3.61	5.7
SD	1.6	0.007	1.1
%RSD	0.5	0.19	19.1
Min	302	3.60	4.0
Max	307	3.62	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
YY Low	304	3.64	6.0
	309	3.66	6.0
	300	3.65	4.0
	302	3.64	4.0
	302	3.64	5.0
	301	3.65	5.0
	303	3.64	4.0
	302	3.67	5.0
	302	3.65	5.5
	299	3.64	5.0
Average	302.4	3.65	5.0
SD	2.7	0.010	0.8
%RSD	0.9	0.28	15.4
Min	299	3.64	4.0
Max	309	3.67	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
ZZ	304	3.55	5.0
	304	3.58	5.5
	306	3.57	5.0
	304	3.57	5.0
	303	3.56	4.0
	306	3.57	5.0
	305	3.58	6.0
	305	3.57	4.5
	306	3.58	6.0
	307	3.57	6.0
Average	305.0	3.57	5.2
SD	1.2	0.009	0.7
%RSD	0.4	0.26	13.0
Min	303	3.55	4.0
Max	307	3.58	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
ZZ Low	308	3.63	6.0
	308	3.63	7.5
	305	3.63	5.5
	307	3.64	6.0
	310	3.63	6.5
	308	3.64	6.0
	308	3.64	4.5
	307	3.64	4.0
	309	3.65	6.0
	306	3.64	5.0
Average	307.6	3.64	5.7
SD	1.4	0.007	1.0
%RSD	0.5	0.19	17.6
Min	305	3.63	4.0
Max	310	3.65	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
AAA	299	3.42	6.5
	302	3.43	7.0
	302	3.44	7.0
	301	3.43	5.5
	301	3.44	5.5
	300	3.43	5.5
	299	3.44	5.5
	301	3.43	7.0
	298	3.42	7.0
	299	3.42	6.0
Average	300.2	3.43	6.3
SD	1.4	0.008	0.7
%RSD	0.5	0.24	11.5
Min	298	3.42	5.5
Max	302	3.44	7.0

Description	Weight (mg)	Thickness (mm)	Hardness
AAA Low	300	3.49	5.0
	301	3.47	6.0
	302	3.47	4.0
	303	3.47	5.5
	301	3.49	6.0
	303	3.49	6.0
	301	3.48	5.0
	300	3.48	5.0
	302	3.49	5.0
	301	3.50	7.5
Average	301.4	3.48	5.5
SD	1.1	0.011	0.9
%RSD	0.4	0.30	17.1
Min	300	3.47	4.0
Max	303	3.50	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
BBB Low	302	3.49	4.0
	298	3.48	5.5
	296	3.47	4.0
	295	3.48	4.0
	301	3.49	5.5
	298	3.48	5.5
	300	3.49	6.0
	296	3.49	5.5
	297	3.48	5.5
	299	3.48	6.0
Average	298.2	3.48	5.2
SD	2.3	0.007	0.8
%RSD	0.8	0.19	15.9
Min	295	3.47	4.0
Max	302	3.49	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
BBB	303	3.42	5.5
	299	3.41	6.0
	298	3.41	6.0
	302	3.42	6.0
	297	3.42	6.0
	302	3.42	7.0
	301	3.42	6.0
	300	3.42	6.0
	300	3.43	6.0
	299	3.42	5.5
Average	300.1	3.42	6.0
SD	1.9	0.006	0.4
%RSD	0.6	0.17	6.8
Min	297	3.41	5.5
Max	303	3.43	7.0

Description	Weight (mg)	Thickness (mm)	Hardness
CCC Low	298	3.59	4.0
	299	3.60	6.0
	300	3.63	4.0
	299	3.62	4.0
	297	3.57	4.0
	301	3.60	4.0
	298	3.58	4.5
	298	3.59	6.0
	304	3.60	5.0
	306	3.63	7.5
Average	300.0	3.60	4.9
SD	2.9	0.020	1.2
%RSD	1.0	0.56	24.9
Min	297	3.57	4.0
Max	306	3.63	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
CCC	297	3.58	5.5
	301	3.59	6.0
	302	3.60	7.5
	304	3.62	6.0
	303	3.60	4.5
	301	3.61	4.5
	300	3.58	6.0
	302	3.62	4.0
	301	3.62	5.0
	301	3.62	4.0
Average	301.2	3.60	5.3
SD	1.9	0.016	1.1
%RSD	0.6	0.46	21.0
Min	297	3.58	4.0
Max	304	3.62	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
DDD Low	299	3.53	4.5
	293	3.52	6.0
	299	3.53	7.5
	304	3.53	8.5
	299	3.53	6.0
	294	3.50	4.0
	299	3.54	4.0
	299	3.54	5.5
	296	3.54	4.0
	301	3.55	5.0
Average	298.3	3.53	5.5
SD	3.2	0.014	1.5
%RSD	1.1	0.39	28.1
Min	293	3.50	4.0
Max	304	3.55	8.5

Description	Weight (mg)	Thickness (mm)	Hardness
DDD	297	3.48	6.5
	300	3.50	6.0
	302	3.50	6.0
	302	3.50	6.0
	301	3.50	9.0
	302	3.50	7.5
	298	3.50	9.5
	301	3.50	7.5
	300	3.50	9.0
	300	3.50	7.5
Average	300.3	3.50	7.5
SD	1.7	0.006	1.3
%RSD	0.6	0.18	18.0
Min	297	3.48	6.0
Max	302	3.50	9.5

Description	Weight (mg)	Thickness (mm)	Hardness
EEE Low	295	3.52	5.0
	302	3.54	5.5
	297	3.53	5.0
	297	3.53	4.0
	295	3.53	4.5
	297	3.53	5.0
	296	3.52	4.0
	295	3.53	4.0
	294	3.54	4.0
	296	3.54	4.0
Average	296.4	3.53	4.5
SD	2.2	0.007	0.6
%RSD	0.7	0.21	12.8
Min	294	3.52	4.0
Max	302	3.54	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
EEE	296	3.52	6.0
	298	3.51	6.0
	300	3.50	5.5
	299	3.52	6.0
	297	3.50	7.5
	296	3.49	6.0
	298	3.51	5.5
	296	3.50	7.0
	299	3.52	6.0
	296	3.50	6.0
Average	297.5	3.51	6.2
SD	1.5	0.011	0.6
%RSD	0.5	0.30	10.2
Min	296	3.49	5.5
Max	300	3.52	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
FFF Low	306	3.56	4.0
	305	3.55	6.0
	305	3.55	6.0
	302	3.56	7.5
	300	3.56	5.5
	304	3.57	7.5
	303	3.58	4.5
	307	3.58	7.5
	304	3.58	5.5
	303	3.58	5.0
Average	303.9	3.57	5.9
SD	2.0	0.013	1.3
%RSD	0.7	0.35	21.4
Min	300	3.55	4.0
Max	307	3.58	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
FFF	303	3.53	7.5
	303	3.53	6.0
	302	3.55	6.0
	302	3.52	5.5
	301	3.51	6.5
	301	3.53	5.5
	303	3.50	7.5
	301	3.52	7.5
	301	3.51	5.5
	302	3.50	6.0
Average	301.9	3.52	6.4
SD	0.9	0.016	0.9
%RSD	0.3	0.44	13.4
Min	301	3.50	5.5
Max	303	3.55	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
GGG Low	292	5.33	4.0
	297	5.34	4.0
	297	5.34	5.5
	291	5.36	4.0
	287	5.34	4.0
	291	5.38	4.0
	287	5.35	4.0
	288	5.34	4.0
	288	5.32	4.0
	290	5.32	4.5
Average	290.8	5.34	4.2
SD	3.7	0.018	0.5
%RSD	1.3	0.34	11.5
Min	287	5.32	4.0
Max	297	5.38	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
GGG	296	5.32	4.0
	291	5.36	4.0
	294	5.34	4.0
	294	5.31	5.0
	294	5.35	4.0
	296	5.36	4.0
	292	5.33	4.0
	293	5.33	4.0
	294	5.31	4.0
	292	5.32	4.0
Average	293.6	5.33	4.1
SD	1.6	0.019	0.3
%RSD	0.6	0.35	7.7
Min	291	5.31	4.0
Max	296	5.36	5.0

Description	Weight (mg)	Thickness (mm)	Hardness
HHH Low	304	3.54	8.5
	305	3.55	8.0
	307	3.56	9.0
	308	3.55	9.0
	308	3.56	7.5
	305	3.54	7.5
	308	3.56	7.5
	308	3.56	7.5
	305	3.56	7.0
	303	3.54	6.0
Average	306.1	3.55	7.8
SD	1.9	0.009	0.9
%RSD	0.6	0.26	11.9
Min	303	3.54	6.0
Max	308	3.56	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
HHH	305	3.53	7.5
	291	3.47	7.5
	291	3.47	6.0
	291	3.47	6.0
	299	3.51	7.5
	300	3.50	8.5
	299	3.49	6.5
	293	3.47	7.5
	293	3.49	7.0
	294	3.49	6.5
Average	295.6	3.49	7.1
SD	4.8	0.020	0.8
%RSD	1.6	0.58	11.3
Min	291	3.47	6.0
Max	305	3.53	8.5

Description	Weight (mg)	Thickness (mm)	Hardness
III Low	304	3.62	4.0
	304	3.62	6.0
	305	3.62	6.0
	304	3.62	6.5
	305	3.62	4.0
	304	3.62	7.0
	303	3.61	6.0
	305	3.62	7.0
	308	3.62	6.0
	306	3.63	4.0
Average	304.8	3.62	5.7
SD	1.4	0.005	1.2
%RSD	0.5	0.13	21.3
Min	303	3.61	4.0
Max	308	3.63	7.0

Description	Weight (mg)	Thickness (mm)	Hardness
III	303	3.58	4.0
	303	3.58	6.0
	303	3.59	6.0
	304	3.59	6.5
	305	3.59	4.0
	307	3.59	7.0
	304	3.59	6.0
	305	3.60	7.0
	303	3.59	6.0
	305	3.61	4.0
Average	304.2	3.59	5.7
SD	1.3	0.009	1.2
%RSD	0.4	0.24	21.3
Min	303	3.58	4.0
Max	307	3.61	7.0

Description	Weight (mg)	Thickness (mm)	Hardness
JJJ Low	303	3.54	9.0
	301	3.56	7.5
	303	3.55	7.5
	302	3.55	7.5
	306	3.55	8.5
	301	3.55	6.0
	301	3.56	9.0
	303	3.56	9.0
	302	3.55	5.5
	302	3.57	8.0
Average	302.4	3.55	7.8
SD	1.5	0.008	1.2
%RSD	0.5	0.24	15.9
Min	301	3.54	5.5
Max	306	3.57	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
JJJ	302	3.53	7.5
	302	3.55	7.5
	301	3.55	8.0
	302	3.56	7.5
	301	3.54	8.5
	301	3.56	8.5
	302	3.56	8.5
	304	3.54	7.5
	301	3.54	9.0
	305	3.57	7.5
Average	302.1	3.55	8.0
SD	1.4	0.012	0.6
%RSD	0.5	0.35	7.2
Min	301	3.53	7.5
Max	305	3.57	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
KKK Low	300	3.57	5.0
	307	3.60	8.5
	295	3.56	4.0
	306	3.61	7.5
	301	3.59	6.0
	309	3.60	8.5
	308	3.61	7.5
	295	3.57	4.5
	297	3.57	5.0
	306	3.59	7.5
Average	302.4	3.59	6.4
SD	5.5	0.018	1.7
%RSD	1.8	0.51	26.5
Min	295	3.56	4.0
Max	309	3.61	8.5

Description	Weight (mg)	Thickness (mm)	Hardness
KKK	298	3.54	4.0
	288	3.52	4.0
	289	3.53	5.0
	287	3.51	4.0
	289	3.52	5.5
	286	3.51	4.0
	288	3.52	5.0
	288	3.53	4.0
	289	3.53	4.0
	287	3.51	3.5
Average	288.9	3.52	4.3
SD	3.3	0.010	0.6
%RSD	1.2	0.29	14.7
Min	286	3.51	3.5
Max	298	3.54	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
LLL Low	303	3.60	4.0
	306	3.60	6.0
	304	3.60	6.0
	302	3.60	4.0
	307	3.60	6.0
	308	3.61	5.5
	301	3.60	4.0
	304	3.60	5.0
	301	3.60	6.0
	310	3.62	6.0
Average	304.6	3.60	5.3
SD	3.1	0.007	0.9
%RSD	1.0	0.19	17.5
Min	301	3.60	4.0
Max	310	3.62	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
LLL	304	3.59	5.5
	305	3.59	7.5
	303	3.56	6.5
	301	3.58	4.5
	300	3.58	4.0
	305	3.60	6.0
	305	3.59	6.0
	305	3.59	4.5
	304	3.61	4.5
	301	3.58	5.0
Average	303.3	3.59	5.4
SD	1.9	0.013	1.1
%RSD	0.6	0.37	20.4
Min	300	3.56	4.0
Max	305	3.61	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
MMM Low	356	4.00	7.5
	357	4.00	6.0
	359	4.00	7.5
	357	4.00	7.0
	355	4.00	5.0
	357	4.00	9.0
	357	4.00	8.0
	355	3.99	7.5
	357	4.01	7.5
	355	3.99	7.0
Average	356.3	4.00	7.2
SD	1.3	0.006	1.1
%RSD	0.4	0.14	15.1
Min	355	3.99	5.0
Max	359	4.01	9.0

Description	Weight (mg)	Thickness (mm)	Hardness
MMM	355	3.96	8.0
	354	3.97	7.5
	355	3.96	7.0
	356	3.97	7.5
	354	3.97	5.5
	354	3.96	6.0
	355	3.96	5.5
	354	3.97	7.5
	355	3.98	7.5
	354	3.98	7.5
Average	354.6	3.97	7.0
SD	0.6	0.008	0.9
%RSD	0.2	0.20	13.3
Min	354	3.96	5.5
Max	356	3.98	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
NNN Low	254	3.15	6.0
	262	3.16	5.5
	254	3.16	6.0
	256	3.15	4.5
	252	3.15	5.5
	254	3.15	6.0
	255	3.16	5.5
	251	3.15	6.0
	257	3.16	6.5
	252	3.15	6.0
Average	254.6	3.15	6.5
SD	3.1	0.005	0.5
%RSD	1.2	0.16	8.3
Min	251	3.15	4.5
Max	262	3.16	6.5

Description	Weight (mg)	Thickness (mm)	Hardness
NNN	253	3.13	7.5
	253	3.12	7.5
	256	3.14	6.0
	252	3.14	7.5
	252	3.13	6.0
	251	3.13	7.5
	254	3.13	7.5
	252	3.12	7.5
	251	3.12	7.5
	253	3.12	7.0
Average	252.8	3.13	7.2
SD	1.3	0.008	0.6
%RSD	0.5	0.25	8.8
Min	251	3.12	6.0
Max	256	3.14	7.5

Description	Weight (mg)	Thickness (mm)	Hardness
OOO Low	352	4.03	5.5
	353	4.03	8.0
	352	4.03	6.5
	352	4.03	6.0
	352	4.03	7.5
	352	4.03	5.5
	352	4.03	7.5
	352	4.04	7.5
	353	4.04	7.5
	353	4.04	7.5
Average	352.2	4.03	6.9
SD	0.5	0.005	0.9
%RSD	0.1	0.12	13.6
Min	352	4.03	5.5
Max	353	4.04	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
OOO	349	4.00	7.0
	351	4.00	7.0
	355	4.01	6.0
	352	4.01	8.0
	352	4.01	6.0
	350	4.01	6.0
	350	4.01	6.0
	353	4.01	6.0
	352	4.01	5.5
	351	4.02	7.0
Average	351.5	4.01	6.5
SD	1.7	0.006	0.8
%RSD	0.5	0.14	11.8
Min	349	4.00	5.5
Max	355	4.02	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
PPP Low	347	4.98	5.0
	346	4.97	4.0
	354	4.98	5.0
	345	4.97	5.5
	347	4.96	4.5
	346	4.96	5.0
	348	4.97	4.0
	349	4.97	5.0
	346	4.96	4.0
	347	4.96	5.5
Average	347.4	4.97	4.8
SD	2.4	0.008	0.6
%RSD	0.7	0.16	12.4
Min	345	4.96	4.0
Max	354	4.98	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
PPP	346	4.85	4.0
	344	4.85	5.5
	344	4.87	6.0
	346	4.86	5.5
	347	4.87	5.5
	347	4.87	5.0
	346	4.86	5.5
	345	4.86	5.0
	347	4.87	6.0
	348	4.87	6.0
Average	346.0	4.86	5.4
SD	1.2	0.008	0.6
%RSD	0.4	0.17	11.4
Min	344	4.85	4.0
Max	348	4.87	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
QQQ Low	355	3.93	5.0
	353	3.93	6.0
	354	3.93	6.0
	351	3.93	8.5
	352	3.93	6.0
	352	3.91	5.5
	353	3.92	6.0
	355	3.93	7.5
	354	3.92	7.5
	357	3.94	5.5
Average	353.7	3.93	6.4
SD	1.7	0.008	1.1
%RSD	0.5	0.21	17.4
Min	351	3.91	5.0
Max	357	3.94	8.5

Description	Weight (mg)	Thickness (mm)	Hardness
QQQ	354	3.88	7.0
	353	3.87	7.0
	351	3.88	6.0
	350	3.88	5.5
	353	3.87	5.5
	351	3.87	7.0
	352	3.87	7.0
	352	3.86	8.0
	352	3.88	7.5
	353	3.88	7.0
Average	352.0	3.87	6.8
SD	1.1	0.007	0.8
%RSD	0.3	0.18	12.2
Min	350	3.86	5.5
Max	354	3.88	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
RRR Low	354	3.92	6.0
	355	3.91	5.5
	360	3.93	5.5
	354	3.93	6.0
	355	3.92	5.5
	356	3.92	6.0
	350	3.92	6.0
	354	3.92	7.0
	354	3.92	5.5
	352	3.92	5.0
Average	354.3	3.92	5.8
SD	2.5	0.006	0.5
%RSD	0.7	0.14	9.3
Min	350	3.91	5.0
Max	360	3.93	7.0

Description	Weight (mg)	Thickness (mm)	Hardness
RRR	357	3.88	8.0
	354	3.88	7.0
	353	3.88	7.0
	355	3.89	7.0
	356	3.89	7.0
	353	3.89	7.0
	356	3.88	7.5
	355	3.88	7.0
	354	3.88	6.0
	356	3.88	8.0
Average	355.0	3.88	7.2
SD	1.5	0.005	0.6
%RSD	0.4	0.12	8.1
Min	353	3.88	6.0
Max	357	3.89	8.0

Description	Weight (mg)	Thickness (mm)	Hardness
SSS Low	355	4.09	5.0
	358	4.10	5.5
	356	4.09	4.0
	355	4.09	4.0
	358	4.10	4.5
	355	4.08	5.5
	355	4.09	6.0
	354	4.10	4.0
	356	4.10	5.0
	357	4.09	5.0
Average	355.7	4.09	4.9
SD	1.5	0.007	0.7
%RSD	0.4	0.16	14.6
Min	354	4.08	4.0
Max	358	4.10	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
SSS	352	4.06	4.0
	349	4.06	5.5
	349	4.07	6.5
	347	4.06	5.5
	348	4.07	4.5
	352	4.07	4.0
	350	4.06	5.0
	345	4.05	6.0
	349	4.06	6.0
	351	4.06	4.5
Average	348.9	4.06	5.2
SD	2.2	0.006	0.9
%RSD	0.6	0.16	17.2
Min	345	4.05	4.0
Max	352	4.07	6.5

Description	Weight (mg)	Thickness (mm)	Hardness
TTT Low	351	4.00	5.0
	351	4.01	6.0
	351	4.01	6.0
	352	4.01	5.5
	351	4.01	5.5
	348	4.02	4.0
	352	4.01	4.5
	351	4.01	4.0
	350	4.00	5.0
	354	4.01	4.5
Average	351.0	4.01	5.0
SD	1.5	0.006	0.7
%RSD	0.4	0.14	14.9
Min	348	4.00	4.0
Max	354	4.02	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
TTT	349	3.98	4.0
	349	3.98	5.5
	348	3.98	5.5
	346	3.97	5.5
	348	3.98	4.0
	348	3.98	5.0
	352	3.99	5.0
	348	3.98	5.0
	346	3.98	5.0
	347	3.98	5.0
Average	348.1	3.98	5.0
SD	1.6	0.005	0.6
%RSD	0.5	0.12	11.1
Min	346	3.97	4.0
Max	352	3.99	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
UUU Low	350	4.82	6.0
	349	4.81	4.0
	343	4.83	4.0
	351	4.81	5.5
	345	4.82	4.0
	351	4.82	4.0
	347	4.81	4.0
	347	4.81	4.0
	353	4.82	4.0
	347	4.82	4.0
Average	348.2	4.82	4.4
SD	3.1	0.007	0.7
%RSD	0.9	0.14	17.2
Min	343	4.81	4.0
Max	353	4.83	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
UUU	340	4.70	5.5
	345	4.71	4.0
	341	4.68	4.0
	342	4.71	4.0
	346	4.71	4.0
	344	4.66	4.0
	348	4.66	4.0
	341	4.68	4.0
	346	4.68	4.0
	348	4.70	3.5
Average	344.3	4.69	4.1
SD	3.0	0.020	0.5
%RSD	0.9	0.42	12.6
Min	340	4.66	3.5
Max	348	4.71	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
VVV (Before Drying)	347	4.08	6.0
	347	4.08	6.0
	351	4.08	4.0
	349	4.08	6.0
	349	4.07	5.0
	349	4.07	5.0
	346	4.09	5.5
	346	4.07	4.0
	348	4.08	5.0
	349	4.07	4.5
Average	348.2	4.08	5.1
SD	1.6	0.007	0.8
%RSD	0.4	0.17	15.2
Min	346	4.07	4.0
Max	351	4.09	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
VVV (After Drying)	341	4.10	5.5
	342	4.10	5.5
	340	4.11	6.0
	341	4.11	4.0
	343	4.11	5.5
	343	4.11	5.5
	340	4.09	5.5
	344	4.11	6.0
	341	4.11	6.0
	339	4.11	4.0
Average	341.4	4.11	5.4
SD	1.5	0.007	0.7
%RSD	0.4	0.17	14.0
Min	339	4.09	4.0
Max	344	4.11	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
WWW	347	4.07	4.5
(Before Drying)	349	4.06	4.5
	345	4.09	5.5
	348	4.07	5.5
	346	4.07	5.5
	347	4.07	4.0
	347	4.08	5.0
	349	4.08	4.0
	348	4.07	4.0
	347	4.08	4.0
Average	347.3	4.07	4.7
SD	1.2	0.008	0.7
%RSD	0.3	0.21	14.4
Min	345	4.06	4.0
Max	349	4.09	5.5

Description	Weight (mg)	Thickness (mm)	Hardness
WWW (After Drying)	331	4.12	6.0
	332	4.10	4.5
	327	4.11	4.0
	329	4.11	5.0
	329	4.11	4.5
	328	4.12	3.0
	330	4.12	4.0
	326	4.11	4.0
	330	4.11	4.0
	329	4.11	5.0
Average	329.0	4.11	4.4
SD	1.6	0.006	0.8
%RSD	0.5	0.15	18.4
Min	326	4.10	3.0
Max	332	4.12	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
XXX	343	4.16	6.0
Before Drying	341	4.14	6.0
	346	4.15	6.0
	345	4.13	5.5
	346	4.18	6.0
	340	4.15	4.0
	346	4.16	6.0
	341	4.17	5.0
	347	4.14	5.0
	340	4.15	5.5
Average	343.5	4.15	5.5
SD	3.0	0.015	0.7
%RSD	0.9	0.36	12.1
Min	340	4.13	4.0
Max	347	4.18	6.0

Description	Weight (mg)	Thickness (mm)	Hardness
XXX	334	4.19	4.0
After Drying	335	4.19	5.5
	332	4.21	5.0
	335	4.20	4.0
	334	4.20	4.0
	335	4.20	5.0
	332	4.17	4.0
	330	4.20	4.0
	336	4.18	4.5
	334	4.18	4.5
Average	333.8	4.19	4.5
SD	1.9	0.012	0.6
%RSD	0.6	0.29	12.4
Min	330	4.17	4.0
Max	336	4.21	5.5