COMPARATIVE STABILITY OF ASPIRIN IN CSP TECHNOLOGIES ACTIV-VIAL™

AND OWENS- ILLINOIS L-8 PRESCRIPTION VIALS

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# COMPARATIVE STABILITY OF ASPIRIN IN CSP TECHNOLOGIES ACTIV-VIAL™ AND OWENS- ILLINOIS L-8 PRESCRIPTION VIALS

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COMPARATIVE STABILITY OF ASPIRIN IN CSP TECHNOLOGIES ACTIV-VIAL™

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Date: May 10, 2007

# VITA

Atresh Tata, son of Satyanarayana Tata and Subba Rama Lakshmi Tata, was born on August 21st, 1982 in Warangal, Andhra Pradesh, India. He did his schooling at Venkateshwara Convent High School, Hyderabad, India in March 1997 subsequent to which he joined Gangadhar Junior College, Visakhapatnam, to pursue his intermediate education. He then attended Shri Vishnu college of Pharmacy, Andhra University, Bhimavaram, India in 1999 and graduated with a Bachelor of Pharmacy in May 2003. He then entered the graduate program in Pharmaceutics at Auburn University in August 2003. During his studies in the Graduate school he served as a Graduate Teaching and Graduate Research Assistant in the School of Pharmacy.

THESIS ABSTRACT

COMPARATIVE STABILITY OF ASPIRIN IN CSP TECHNOLOGIES ACTIV-VIAL™ AND OWENS- ILLINOIS L-8 PRESCRIPTION VIALS

Atresh Tata

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The traditional way of drug packaging includes a desiccant pouch along with the drug. The desiccant in the vial helps in preventing the drug degradation due to moisture in surrounding environment. This traditional packaging often proves to be ineffective especially in large vials due to uneven distribution of desiccant. Currently pharmaceutical companies are developing new vials that are made of desiccant embedded polymers to achieve effective drug storage. So it is of utmost importance to study the efficacy of such improved methods.

This study presents the results of a comparative study on aspirin stability in CSP Technologies Activ-vial (desiccant embedded polymer vial) with standard Owens-Illinois vials (control). A analytical methods were established and validated to quantify aspirin

and its primary degradation products using automated high-pressure liquid chromatographic (HPLC) analysis on a silica column. The degradation kinetics of aspirin were evaluated with respect to loss of potency of acetylsalicylic acid and the appearance of three oxidative degradation products of acetylsalicylic acid; salicylic acid, salicylsalicylic acid, and acetylsalicylsalicylic acid under simulated use conditions in a humid environment.

The results of this study showed the extent of aspirin degradation was minimal in the time frame studied, although differences were observed in the formation of salicylic acid. Significant suppression of salicylic acid formation was observed in the CSP Technologies Activ-vial when compared to ordinary PET prescription vials. The CSP Technologies Activ-vial is expected to therefore provide an advantage under typical consumer use conditions, particularly in humid geographical regions, for the protection of moisture sensitive pharmaceutical products.

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Finally, the author would like to dedicate this dissertation to the lotus feet of his beloved Lord Vinayaka, Dr. Suryanarayana Somyaji Tata and to his parents (Mrs. Subba Rama Lakshmi Tata and Mr. Satyanaraya Tata), without whose grace, love and forbearance it would not have been possible to learn many things in science as well as in general aspects of life in the course of these years and throughout my life.

Style manual or journal used International Journal of Pharmaceutics

Computer software used Microsoft Office XP for Windows XP

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# 1 INTRODUCTION

The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The self life is the time lapse from initial preparation to the specified expiration date. The stability parameters of a drug dosage form can be influenced by environmental conditions like temperature, light, air and humidity. Pharmacopoeial articles should include required storage conditions on their labeling under which the expiration date shall apply. Stability studies on active substances and packaged dosage forms are conducted by means of "real time," long-term tests at specific temperatures and relative humidity. Labeling and packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air and light on its stability[1]. Each ingredient, whether therapeutically active or pharmaceutically necessary, can affect the stability of drug substances and dosage forms. The primary environmental factors that may reduce the stability include exposure to adverse temperature, light, humidity, oxygen and carbon dioxide. Major factors that influence drug stability include particle size, solvent system composition, compatibility of anions and cations, solution ionic strength, primary container, specific chemical additives, molecular binding temperature, relative humidity and diffusion of drugs and excipients. In dosage forms these reactions usually cause loss of active drug content and

do not provide obvious visual and olfactory evidence of their occurrence. The reactions are hydrolysis, epimerization, decarboxylation, dehydration, oxidation and photochemical decomposition. Many pharmacopoeial articles which undergo the above mentioned reactions require the greatest attention to the containers in which they are stored or maintained even for short periods of time. The stability of drug products needs to be evaluated over time in the same container-closure system in which the drug product is marketed. In some cases, accelerated stability studies can be used to support tentative expiration dates in the event that full shelf life studies are not available. When a drug manufacturer changes the packaging of a drug product (e.g., from a bottle to unit-dose), stability testing must be performed on the product in its new packaging, and expiration dating must reflect the results of the new stability testing. Specific light resistant containers meet the requirements for light transmission.

**Criteria for Acceptable Levels of Stability**

| Type of stability | Conditions maintained throughout the shelf-life of the drug product. |
|---|---|
| Chemical | Each active ingredient retains its chemical integrity and labeled potency, within specified limits. |

| | |
|---|---|
| Physical | The original physical properties, including appearance, palatability, uniformity, dissolution, and suspendability are retained. |
| Microbiological | Sterility or resistance to microbial growth is retained according to specified requirements. Antimicrobial agents that are present retain effectiveness within specified limits. |
| Therapeutic | The therapeutic effect remains unchanged. |
| Toxicological | No significant increase in toxicity occurs. |

The design of a stability study varies from product to product. First formulators determine the effects of temperature, light, air, pH, moisture, trace metals, and commonly used excipients or solvents on the active ingredient. At appropriate time intervals, samples of the product are assayed for potency by use of a stability indicating method, observed physical changes, and where applicable, tested for sterility and/or for resistance to microbial growth and for toxicity and bioavailability[2].

## 1.1 Container Moisture Permeation

Tests are provided to determine the moisture permeability of containers utilized for drugs being dispensed on prescription. The term "container" refers to the entire system comprising, usually, the container itself, the liner (if used), the closure in the case of multiple unit containers, and the lidding and blister in case of single unit and multiple unit containers. If the containers are lined with desiccants then permeation of moisture or any extraneous material will be difficult. The desiccant material can be seamlessly integrated into primary packaging. This eliminates the costly step of inserting secondary components into a package and eliminates the risk that the consumer will discard the desiccant material. The rate of moisture permeability is usually calculated in mg per day per liter for multiple unit containers for capsules and tablets[3].

## 1.2 Repackaging of Bulk Drugs

Unit dose packaging systems are currently widespread in health care. Some unit dose containers are available directly from manufacturers and repackagers and some drugs are packaged into unit dose by hospital/community pharmacies or shared service establishments.

A unit dose package makes the administration of drugs more convenient and less susceptible to errors (such as administering too much or too little of the drug at one time). Repackaging previously dispensed drugs into unit dose containers may be inappropriate under the FDA's compliance policy guide for repackaging and return of used

medications, as well as state laws that regulate the practice of pharmacy. Moreover, such repackaging raises liability concerns for pharmacies. In order to repackage a prescription drug, a repackaging entity, including a pharmacy, must have specific information, and such information must appear on the label of the unit dose container. Without the specific information, a unit dose package of a prescription drug is considered to be misbranded under CPG 7132b.10 (FDA, Office of regulatory affairs):

The information required by law is,

1. Name of the drug and quantity of the active ingredient per dosage unit;
2. Expiration date;
3. Lot or control Number;
4. Name and place of business of the manufacturer, packer, or distributor; and
5. Required statements regarding refrigeration or bearing on the special characteristics of the drug.

CPG 7132.13 clarifies that repackagers are not required to separately undertake testing procedures associated with good manufacturing practices, but only if the following is true:

1. The incoming bulk containers of finished dosage form drug products are received intact, in undamaged container which are completely and properly labeled as received, and there is no reason to suspect that they have been subjected to improper storage or transit conditions prior to receipt; and

2. The repackaged containers are labeled with the same substantive labeling declarations (e.g., identity, strength, and directions for use) concerning the properties and use of the drug product which are consistent with the labeling on the incoming bulk containers.

No action will be initiated against any unit dose repackaging firm, including shared services, or drug product in a unit dose container meeting all other conditions of FDA's repackaging requirements solely on the basis of the failure of the repackaging firm to have stability studies supporting the expiration dates used, provided:

1. The unit dose container complies with the class A or class B standard described in the twentieth edition of the United States Pharmacopoeia, general tests, single-unit containers and unit-dose containers for capsules and tablets (page 955).
2. The expiration date does not exceed six months; and
3. The six month expiration period does not exceed 25 percent of the remaining time between the date of repackaging and expiration date shown on the original manufacture's bulk container of the drug repackaged, and the bulk container has not been previously opened.

This policy only applies to solid and liquid oral dosage forms in unit dose containers. This policy does not apply to antibiotics or to nitroglycerin sublingual tablets which are

known to have stability problems that preclude them from being repackaged. The question remains whether this policy applies to other moisture sensitive drugs[4, 5].

## 1.3 Pharmaceutically Used Desiccants

A desiccant is a substance with very hygroscopic properties, meaning it will adsorb water vapor from the air surrounding it. A number of different substances are capable of doing this, but only a relative few are of practical use and fewer still are going to be readily available. Before elaborating on the different types that might be useful for any given purposes it's necessary to explain how to choose a desiccant.

The U.S. military has done much of the best research on the use of desiccants in packaging and have largely set the standards by which they are judged. Each type of desiccant has temperature and humidity ranges where it performs best and particular physical and chemical characteristics that may need to be considered in relation to what you propose to do with them. The most applicable standard for home food storage defines a unit of desiccant as the amount of desiccant that will adsorb at least 6 grams of water vapor at 40% relative humidity at 77º F (25º C).

The following table provides the adsorptive capacity of some commonly used desiccants (Table 1) [6].

**Table 1**: Amount of desiccant needed to absorb at least 6 grams of water vapor at 40% relative humidity at 77º F (25º C).

| Desiccant | Mass (grams) |
|---|---|
| | |
| Silica Gel | 15 |
| Indicating Silica Gel | 75 |
| Montmorillonite Clay | 24 |
| Calcium Oxide (quicklime) | 22 |
| Calcium Sulfate (gypsum, Drierite) | 60 |
| Wood | 43 |

### 1.3.1 Silica Gel

The most commonly known and used desiccant is silica gel which is a form of silica dioxide ($SiO_2$), a naturally occurring mineral. It will work from below freezing to past the boiling point of water, but performs best at room temperatures (70-90 ºF) and high humidity (60-90%). Its performance begins to drop off over 100º F, but retains activity until approximately 220º F. It will lower the relative humidity in a container to around 40% at any temperature in its range until it is saturated. Silica gel will absorb up to 40% of its weight in moisture. Some forms are approved by the Food and Drug Administration (FDA) for direct food use. It recharges easily and does not swell in size as it adsorbs moisture[6].

### 1.3.2 Clay Desiccant

Clay desiccant is fairly common in commercial and industrial use. The primary reason for this seems to be that it is inexpensive compared to any other form of desiccant. The material is montmorillonite clay, composed primarily of magnesium aluminum silicate, a naturally occurring mineral. After mining it is purified, reduced to granules and subjected to a controlled dehydration process to increase its sorbent porosity. It recharges easily and does not swell as it adsorbs water vapor. It works well at low and room temperatures, but has a rather low ceiling temperature. At 120º F it will begin to desorbs or shed the moisture it has adsorbed. This is an important consideration for storage in hot areas. Subject to a degree of variability for being a natural material, clay desiccant will adsorb approximately 25% of its weight in water vapor at 77º F and 40% relative humidity[6].

### 1.3.3 Calcium Sulfate

Also known as the mineral gypsum and commercially as Drierite, calcium sulfate is another naturally occurring mineral. It is produced by the controlled dehydration of gypsum ($CaSO_4$). It is chemically stable and does not readily release its adsorbed moisture. It has a low adsorbency capacity, only approximately 10% of it weight. It can be regenerated, but not easily[6].

### 1.3.4 Calcium Oxide

Also known as "quicklime" or "unslaked lime", calcium oxide is a slow, but strong adsorbent. It is efficient at low humidity's and can drop moisture vapor to below 10% relative humidity. Quicklime is caustic and must be carefully handled, particularly with regards to dust inhalation and exposure to skin and eyes. It expands as it soaks up water vapor and this must be taken into account when packaging it. It will adsorb up to about 28% of its weight in moisture, but does it slowly over a period of several days rather than a matter of hours like other desiccants. It is most effective when used in high humidity environment where a very low humidity level is desired. It will release a fair amount of heat if exposed to directly to moisture or extreme humidity's [6].

## 1.4 Moisture Sensitive Drugs

The pharmacopoeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph. Moisture sensitive drugs are to be stored in tight containers. Tight containers protect the contents from extraneous liquid, solids, or vapors, from the loss of the article and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage and distribution, the containers must be capable of tight re-closure. Pharmacopoeial standards, however, do not address typical consumer use conditions.

The following table represents some of the moisture sensitive drugs[7]

**Table 2**: List of moisture sensitive drugs

| | | |
|---|---|---|
| Albendazole | Guanadrel | Oxytetracycline |
| Alprazolam | Guanfacine | Penicillamine |
| Aminophylline | Haloperidol | Phenytoin Sodium |
| Amoxicillin | Hydralazine Hydrochloride | Piroxicam |
| Aspirin | Hydrocodone Bitartrate | Phensuximide |
| Bendroflumethiazide | Hydroflumethiazide | Promethazine Hydrochloride |
| Bethanechol Hydrochloride | Hydromorphone Hydrochloride | Pyridostigmine Bromide |
| Biperidine Hydrochloride | Imipramine Hydrochloride | Quinidine Sulfate |
| Bromocriptine Mesylate | Iopanoic Acid | Quinine Sulfate |
| Buspirone Hydrochloride | Ipodate Sodium | Ranitidine |
| Captopril | Isotretinion | Reserpine |
| Chloramphenicol | Isoxsuprine Hydrochloride | Riboflavin |
| Carbamazepine | Kanamycin | Rifampin |
| Cyclosporine | Labetalol Hydrochloride | Ritodrine Hydrochloride |
| Cyclophosphamide | Levodopa | Scopolamine Hydrochloride |
| Desipramine Hydrochloride | Lincomycin Hydrochloride | Secobarbital Sodium |
| Diazepam | Liothyronin Sodium | Simvastatin |
| Diclefenac Sodium | Lorazepam | Spironolactone |
| Digitalis | Mazindol | Stanozolol |
| Disulfuram | Mesalamine | Tetracycline Hydrochloride |
| Ephedrine Sulfate | Methsuximide | Thiabendazole |
| Ergocalciferol | Minoxidil | Trimethoprim |
| Ethosuximide | Mitotane | Trichlormethiazide |
| Ethotoin | Neostigmine Bromide | Thiamine Hydrochloride |
| Flucytosine | Niacinamide | Valporic Acid |
| Fluoxetine | Nifedipine | Vancomycin Hydrochloride |
| Fluphenazine Hydrochloride | Nitroglycerin | Verapamil Hydrochloride |
| Flurazepam Hydrochloride | Nystatin | Vitamin A |
| Furazolidone | Oxandrolone | Vitamin E |
| Glipizide | Oxtriphylline | Warfarin Sodium |
| Greseofulvin | Oxybutynin Chloride | Zalcitabine |
| Guanabenz | Oxycodone Hydrochloride | Zidovudine |

# 2 EVALUATION OF THE CSP TECHNOLOGIES ACTIV-VIAL ASSOCIATED WITH ASPIRIN STABILITY

## 2.1 Description of CSP Technologies Activ-Vial

CSP Technologies (Auburn AL) M-3006-47 Activ-Vial [TM.] The Activ-Vial is a two-shot flip top vial. The outer vial is molded polypropylene using a process which allows closure of the vial with a polypropylene cap in the mold. The body and cap are cooled together creating a tight seal. The vial body contains an over-molded inner sleeve containing 8.0 grams of porous (4Å) alumina silicate and manufactured using a patented process incorporating a base polymer and channeling agent. Both vials have a volume of approximately 31 cc.

The Activ-Pak polymer blend is made up of three components – the polymer, a channeling agent, and an active component such as desiccant – that allows for the creation of stable, co-continuous, interpenetrating – or "web-like" – channels. These channels facilitate transport, via diffusion, of substances throughout the polymer. The resulting polymer blend responds to external signals and stimuli in a pre-programmed fashion, activating the desired environmental control, whether it is absorption, release, transport or activation of substances through the channels. This process

removes the barrier characteristic associated with plastic, while retaining the characteristic of structure.

Activ-Pak offers functionality and flexibility in plastics. Many different materials can be incorporated into these polymer blends, enabling you to provide a controlled environment within product packaging. Formulators can reproducibly and predictably control the rate and duration of the desired activity[8].

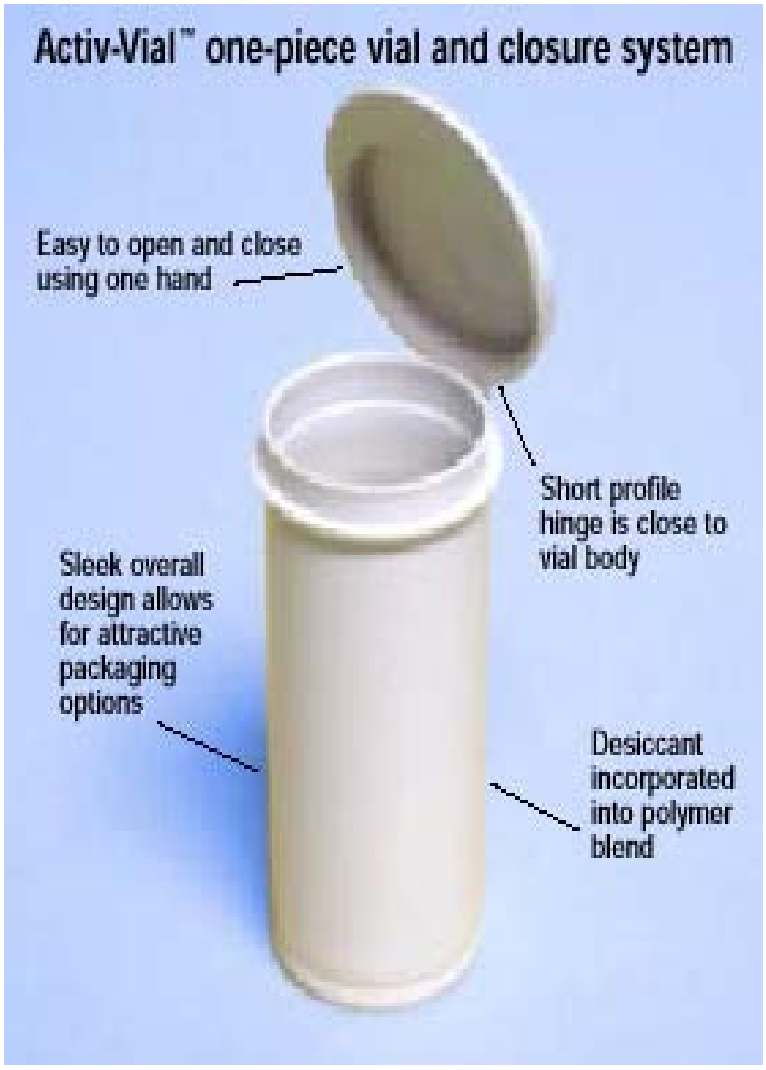


**Figure 1**: Activ- Vial

**Applications for Activ- Pak Technology**

| | |
|---|---|
| Moisture absorption | $CO_2/O_2$/ethylene/formaldehyde absorption |
| Biocide release | Flavor/odor/fragrance |
| Dry sterilization | Absorption or release |

## 2.2 Proposed Advantages of Activ- Vial

These are some of the advantages of Activ- Vial

1. The Activ-Vial offers control and reproducibility of the rate and duration of humidity control required to optimize the performance of the products.
2. It offers an air-tight and leak-proof environment to maintain product integrity and prolong shelf-life.
3. The unique single-mold vial and closure system vial allows the user to open and close with one hand and requires minimal pressure to seal.
4. The cost-effective one-piece design enhances the inventory control and production efficiencies, eliminates mismatches between bottles and caps, and removes cross contamination issues.
5. It provides greater moisture adsorptive capacity than ordinary silica gel[8].

**Figure 2**: Vials and containers, desiccant sheets and desiccant films.

## 2.3 Potential Market for Use Stability of Moisture Sensitive Drugs

It is an industry axiom that the number one threat to pharmaceutical stability is moisture and its effect on increasing molecular mobility. As such, incorporating desiccants into packaging for moisture control has been a long-established practice. An array of new solid-dose drug formulations, however, can reasonably be described as unstable, and therefore require special protection beyond the "traditional" moisture-controlling desiccant or oxygen scavenger. A number of molecules that are particularly moisture-sensitive or highly-oxidative have been shelved by drug manufacturers over the past 10 to 20 years because they could not be stabilized through reformulation and/or traditional

packaging protection options. Thus, many promising drugs have been stopped in the pipeline for years.

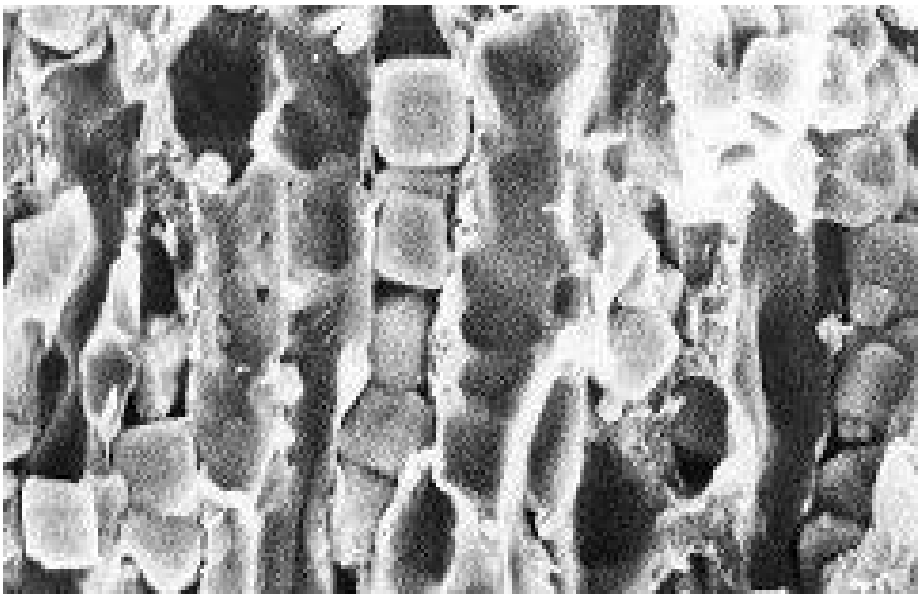

**Figure 3**: Water-extracted cross-section of a film illustrating a Polymer / Channel Agent / Molecular Sieve desiccants (cube-shaped particles). The desiccants are entrained within interconnecting pathways within a polymer.

## 2.4 Aspirin as a Prototypical Moisture Sensitive Drug

Aspirin, the prototype of the salicylates, is a nonsteroidal anti-inflammatory agent. Aspirin is the salicylate ester of acetic acid. In vivo, the drug rapidly hydrolyzes to salicylate and acetate. Aspirin occurs as white crystals, which are usually tabular or needle-like, or as a white, crystalline powder. Aspirin is stable in dry air. However, in moist air or in aqueous or hydro alcoholic solutions, the drug hydrolyzes to salicylate and acetate and emits a strong vinegar-like odor; the rate of hydrolysis is increased by heat and is pH dependent. In aqueous solutions, aspirin is most stable at a pH of 2–3, less

stable at a pH of 4–8, and least stable at a pH less than 2 or greater than 8. In a saturated aqueous solution at a pH of 5–7, aspirin is almost completely hydrolyzed within 1 week at 25°C. Manufacturers labeling suggests that aspirin extra-strength (Anacin®) tablets should be stored at 20–25°C and protected from moisture. Aspirin (Bayer products, excluding Alka-Seltzer® products) tablets or caplets should be stored at room temperature; high humidity and excessive heat (40°C) should be avoided.

## 2.5 Objectives of this Study

The purpose of this study is to compare the stability of aspirin in CSP Technologies Acitv- vials containing an over- molded desiccant polymer and in standard Owens-Illinois polyethylene prescription vials when exposed to simulated consumer use conditions in a high humidity environment. The degradation kinetics of aspirin was evaluated with respect to loss of potency of acetylsalicylic acid and formation of salicylic acid, salicylsalicylic acid, and acetylsalicylsalicylic acid. A stability- indicating assay for the analyses of aspirin and its degradation products, salicylic acid and salicylsalicylic acid was established and validated[9].

# 3 EXPERIMENTAL

## 3.1 Reagents and sources

Chloroform (A.C.S. grade), n-heptane (HPLC grade), and acetic acid (glacial, A.C.S. PLUS grade) are used as chromatographic solvents (Fisher Scientific/Acros Organics, Pittsburgh, PA). Chloroform and n-heptane are kept dry by the addition of sodium calcium aluminosilicate hydrate dessicant sponges (Fisher). Analytical standards are prepared from acetylsalicylic acid (ASA), purity 99% (Acros), salicylic acid (SA), purity >99% (Acros), salicylsalicylic acid (SSA), purity 99% (Acros), and benzoic acid (BA), purity >99% (J. T. Baker Chemical Co., Phillipsburg, NJ).

Disintegrated tablets are filtered using disposable solvent-resistant PTFE filter units (Fisher) and standard polypropylene syringes.

## 3.2 Materials

Owen-Illinois (Toledo OH) L-8 polyethylene prescription vials with SL-26 Screw-Loc closures designated as USP 671 tightly closed (T) and light resistant (LR).

Commercial Bayer Aspirin (Bayer Healthcare LLC, Consumer care division, Morristown NJ) 325 mg coated tablets (lot no. 294414K, expiration date 7/06). Inert ingredients are corn starch, hypromellose, powdered cellulose and triacetin.

## 3.3 Procedures

Bayer Aspirin 325 mg tablets were placed in Owens-Illinois PET prescription vials or CSP Technologies M-3006-47 Activ-Vials. Owens-Illinois vials were closed with Screw-Loc child resistant caps when appropriate. Five treatments were tested as follows:

Treatment 1: Owens-Illinois vial containing aspirin tablets and closed with a Screw-Loc cap. The prescription vial system remained closed throughout the duration of the study with the exception of the time required to remove tablets for sample collection. This treatment was a negative control for the Owens-Illinois vial system.

Treatment 2: CSP Technologies M-3006-47 Activ-Vial containing aspirin tablets and closed with its attached cap. The vial system remained closed throughout the duration of the study with the exception of the time required to remove tablets for sample collection. This treatment was a negative control for the CSP technologies vial system.

Treatment 3: Owens-Illinois vial containing aspirin tablets and closed with a Screw-Loc cap. The prescription vial system was periodically opened three times-a-

day for duration of 1.0 minute each exposure and 3.0 minutes per day total exposure to environmental conditions. This treatment was designed to mimic typical consumer use conditions.

Treatment 4: CSP Technologies M-3006-47 Activ-Vial containing aspirin tablets and closed with its attached cap. The vial system was periodically opened three times-a-day for duration of 1.0 minute each exposure and 3.0 minutes per day total exposure to environmental conditions. This treatment was designed to mimic typical consumer use conditions.

Treatment 5: Owens-Illinois vial containing aspirin tablets without a closure. This vial represented a positive control with 100% exposure to environmental conditions.

Each treatment was exposed to controlled environmental conditions in a stability (temperature/humidity) chamber at 30°C and 80% relative humidity. All vials remained in the chamber throughout the duration of study. The total duration of exposure of the aspirin tablets subject to cyclic opening and closing was 360 min or 0.208% of the total study period. Treatments 1, 2, and 5 were exposed to environmental conditions of 40°C and 75% relative humidity for an additional 30 days following completion of the initial treatment protocol for 120 days.

Six tablets were sampled from each treatment vial at 0, 30, 60, 90, and 120 days. For treatments 1, 2, and 5 only three tablets were removed for sampling at 120 days and the remaining tablets retained for further exposure to 40°C and 75% relative humidity for an additional 30 days. Sampled tablets were sealed in moisture retardant metallized polyester barrier pouches until analyzed.

## 3.4 Preparation of stock solutions and calibration standards

ASA and SSA stock solutions were freshly prepared on the day of use. A stock solution of aspirin was prepared by accurately weighing 400 mg of ASA and adding it to a 100-mL volumetric flask. The ASA was dissolved in solvent containing 5% acetic acid, 47.5% chloroform and 47.5% n-heptane (v/v/v) resulting in a final concentration of 4.0 mg/mL. Stock solutions of salicylic acid and salicylsalicylic acid are separately prepared by accurately weighing 200 mg of SA and 100 mg of SSA, respectively, and adding to 100-mL volumetric flasks. The SA and SSA are dissolved in solvent containing 5% acetic acid, 47.5% chloroform and 47.5% n-heptane (v/v/v) resulting in a final concentration of 2.0 mg/mL and 1.0 mg/mL, respectively. For SA, serial dilutions were prepared by diluting 10.0 ml of the 2.0 mg/mL primary stock solution to 100 mL with 5% acetic acid, 47.5% chloroform and 47.5% n-heptane in a 100-mL volumetric flask, and diluting 1.0 mL of this solution to 10.0 mL with the same solvents resulting in a final concentration of 2.0 µg/mL. For SSA, secondary serial dilutions are prepared by diluting 10.0 mL of the 1.0 mg/mL primary stock solution to 100 mL with 5% acetic acid, 47.5% chloroform and 47.5% n-heptane in a 100-mL volumetric flask, and diluting 1.0 mL of

this solution to 10.0 mL with the same solvents resulting in a final concentration of 10.0 µg/mL. A stock solution of benzoic acid was prepared by accurately weighing 400 mg BA, adding to a 100-mL volumetric flask, and dissolving in 5% acetic acid, 47.5% chloroform and 47.5% n-heptane (v/v/v) resulting in a final concentration of 4.0 mg/mL. Benzoic acid was used as a competitive inhibitor of SA and SSA adsorption on glass[10-13].

Calibration standards of ASA are prepared by diluting 500 µL, 406 µL, 313 µL, and 188 µL of the 4.0 mg/mL ASA stock solution to 10.0 mL, respectively, with 50% chloroform and 50% n-heptane in 10-mL volumetric flasks. The final concentrations of the ASA calibration standards are 200, 163, 125 and 75 µg/mL, respectively.

Calibration standards for SA and SSA containing the internal standard are prepared by adding 7.5 mL of the 2.0 µg/mL SA stock solution, 5.0 mL of the 10.0 µg/mL SSA stock solution, and 500 µL of the 4.0 mg/mL BA stock solution to a 10-mL volumetric flask and diluting with 50% chloroform and 50% n-heptane. Similarly standards containing, 5 mL of SA stock, 2.0 mL of SSA stock, and 500 µL of BA stock; 2.5 mL of SA stock, 1.0 mL of SSA stock, and 500 µL of BA stock; and, 1 mL of SA stock, 0.5 mL of SSA stock, and 500 µL of BA stock and 500 µL of SA stock and 500 µL of BA stock are prepared. The resulting final concentrations for these calibration standards are 1.5 µg/mL SA and 5 µg/mL SSA, 1.0 µg/mL SA and 2 µg/mL SSA, 0.5 µg/mL SA and 1 µg/mL SSA, and 0.2 µg/mL SA and 0.5 µg/mL SSA and 0.1 µg/mL of SA respectively. The final BA concentration 200 µg/mL for all calibration standards.

## 3.5 Preparation of tablet samples

One (1) tablet of aspirin with an initial labeled content of 325 mg aspirin was added to a 100-mL volumetric flask. Solvent containing 5% acetic acid, 47.5% chloroform and 47.5% n-heptane (v/v/v) was added to the flask and brought to volume. The sample was sonicated for 10 min to aid in disintegration of the tablet. An aliquot of the resulting solution containing particulate matter was filtered through an inert PTFE filter membrane using a polypropylene syringe, and 0.5 mL transferred to a 10-mL volumetric flask. An aliquot of 500 µL of the 4.0 mg/mL BA stock solution was added to the flask and diluted with solvent containing 50% chloroform and 50% n-heptane[14, 15].

## 3.6 Chromatographic conditions and instrumentation

The chromatographic system consists of Varian (Walnut Creek, CA) ProStar 210 solvent delivery pumps, a ProStar 320 variable-wavelength UV/Vis detector, and ProStar 400 auto sample. Data collection and processing use Star Chromatography Data Acquisition v5 software and a PC computer.

Chromatography was carried out in the normal-phase mode. The stationary phase was Microsorb-MV 5 µm silica, 25 cm x 4.6 mm i.d. column (Varian). The mobile phase was 4.4% acetic acid (glacial), 76.3% n-heptane and 19.3% chloroform delivered at a flow rate of 1.0 mL/min. Column temperature was ambient. The detector wavelength for all analytes was 292 nm. The injection volume was 40 µL.

# 4 RESULTS

## 4.1 Chromatography and selectivity

Typical chromatograms obtained from spiked standards are illustrated in Figures 4 and 5. Figure 4 shows SA with a retention time of 6.0 min and SSA with a retention time of 7.1 min. Salicylic acid and salicylsalicylic acid can be quantified using a single calibration curve. A separate calibration curve is required to quantify aspirin since both analytical standards and aspirin tablets contain trace levels of salicylic acid (Figure 5). The retention time of ASA was 10.6 min and SA was 5.8 min. Small variations in retention times were observed. Blank samples (injected mobile phase) showed no detectable levels of any analyte. The retention time of benzoic acid was 4.9 min. Shifting the detection absorbance wavelength to 292 nm results in a large increase in BA absorbance and detector response.

## 4.2 Linearity, accuracy and precision

Calibration curves were fit by linear least-squares regression. The calibration curve for ASA, SA, and SSA were based on peak area. ASA concentrations were linear in the calibration range of 75 to 200 μg/mL (Fig. 6). The corresponding *r* value was 0.9942. SA concentrations were linear in the calibration range 0.1 to 2.0 μg/mL (Fig. 7). The corresponding *r* value was 0.9980. SSA concentrations were linear in the calibration

range of 0.50 to 5.0 μg/mL (Fig. 8) the corresponding *r* value was 0.9948. Extended concentration ranges for all analytes exhibited nonlinear trends, which were determined to result from adsorption of analytes to glassware and probably nonlinear on-column silica adsorption as well. Salicylic acid was found to be the most severely adsorbing analyte. The addition of 5% acetic acid to stock solutions and benzoic acid with a concentration of 200 μg/mL minimized glassware adsorption by competitive binding but did not eliminate all nonlinear trends. In all cases, the linear ranges of analytes were limited. Extreme caution was required when changing analyte concentration ranges as well as revalidation for the modified ranges.

The accuracy and precision of ASA, SA and SSA are provided in Table 3. The accuracy of ASA analyses was within 2% of the nominal values for all concentration levels. Reproducibility was < 6% relative standard deviation (RSD) for all levels. The accuracy of SA analyses was within 7% of the nominal values for levels of 0.2 to 1.5 μg/mL and 110% at the lowest calibration level of 0.1 μg/mL. Reproducibility was <12% RSD for concentration levels of 0.2 to 1.5 μg/mL, and 40% at the lowest calibration level of 0.1 μg/mL. The accuracy of SSA analyses was within 3% of the nominal values for levels of 0.5, 1, 5 μg/mL and <13% for calibration level of 2 μg/mL. Reproducibility was <8% RSD for all levels.

## 4.3 Stability of calibration standards

The stability of solutions of ASA in 5% acetic acid, 47.5% chloroform and 47.5% n-heptane (v/v/v) were evaluated for quantifiable loss of ASA and generation of SA.

Freshly prepared solutions at initial concentrations of 150, 250 and 400 μg/mL ASA were analyzed at timed intervals. Solutions were left undisturbed at ambient temperature (20-23°C) on the bench top.

No detectable degradation in ASA peak area was observed at all concentration levels (Fig. 9), however, increased levels of SA were detectable and quantified over a 6-hour period (Fig. 10). At an initial (C0) ASA concentration of 150 μg/mL, SA showed stable kinetics. SA peak areas were uncorrelated with time, and no detectable slope in the curve was determined. At an initial ASA concentration of 250 μg/mL a significant time-correlation was observed. At 6 hr, a relative increase of 41% in SA peak area was observed. At an initial ASA concentration of 400 μg/mL, SA peak areas were correlated with time and showed 114% increase in peak area at 6 hr. These results indicate that stock solutions of ASA and extracted tablet solutions must be prepared at the time of analysis and diluted to appropriate concentrations as rapidly as feasible. To insure accurate calibration of SA concentration levels, separate calibration curves are required for SA and ASA. The highest level ASA calibration standard was specified in this method at 200 μg/mL. Based on the methodology presented in this report, a 325 mg aspirin tablet would result in a 162.5 μg/mL solution of ASA after sample processing at time 0 hr. Although the relative increases in SA levels at 6 hr represent the conversion of ASA to SA, initial SA levels in raw material, analytical standards or tablets, are present as trace quantities. Nevertheless, strict control of processing time and dilution levels was required to insure that artifactual degradation of ASA is minimized, and that assayed values are actually representative of test conditions.

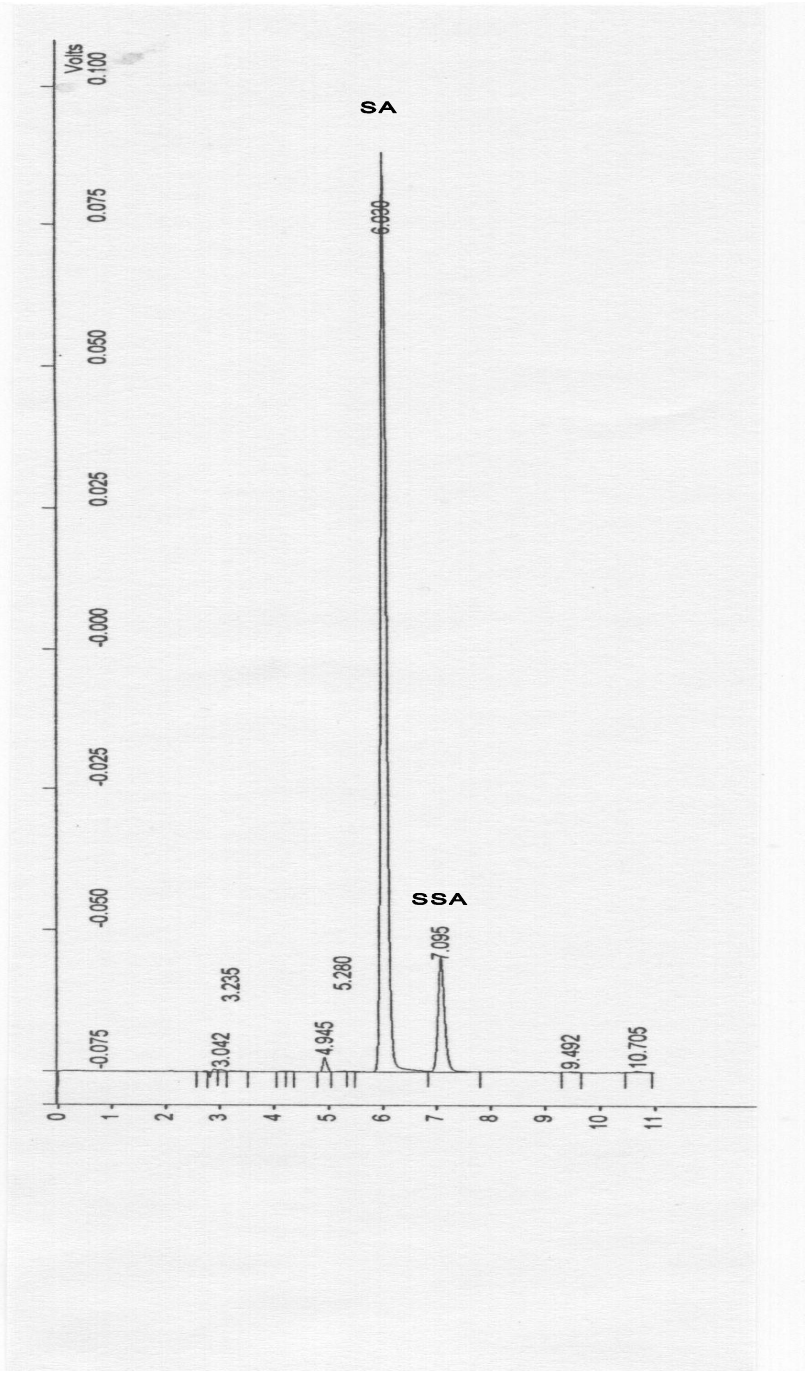
Volts
0.100
0.075
0.050
0.025
-0.000
-0.025
-0.050
-0.075
SA
6.999
SSA
7.095
5.280
3.235
3.042
4.945
9.492
10.705
0
1
2
3
4
5
6
7
8
9
10
11

**Figure 4**: Chromatogram of salicylic acid (SA), RT 6.0 min and salicylsalicylic Acid (SSA), RT 7.1 min.

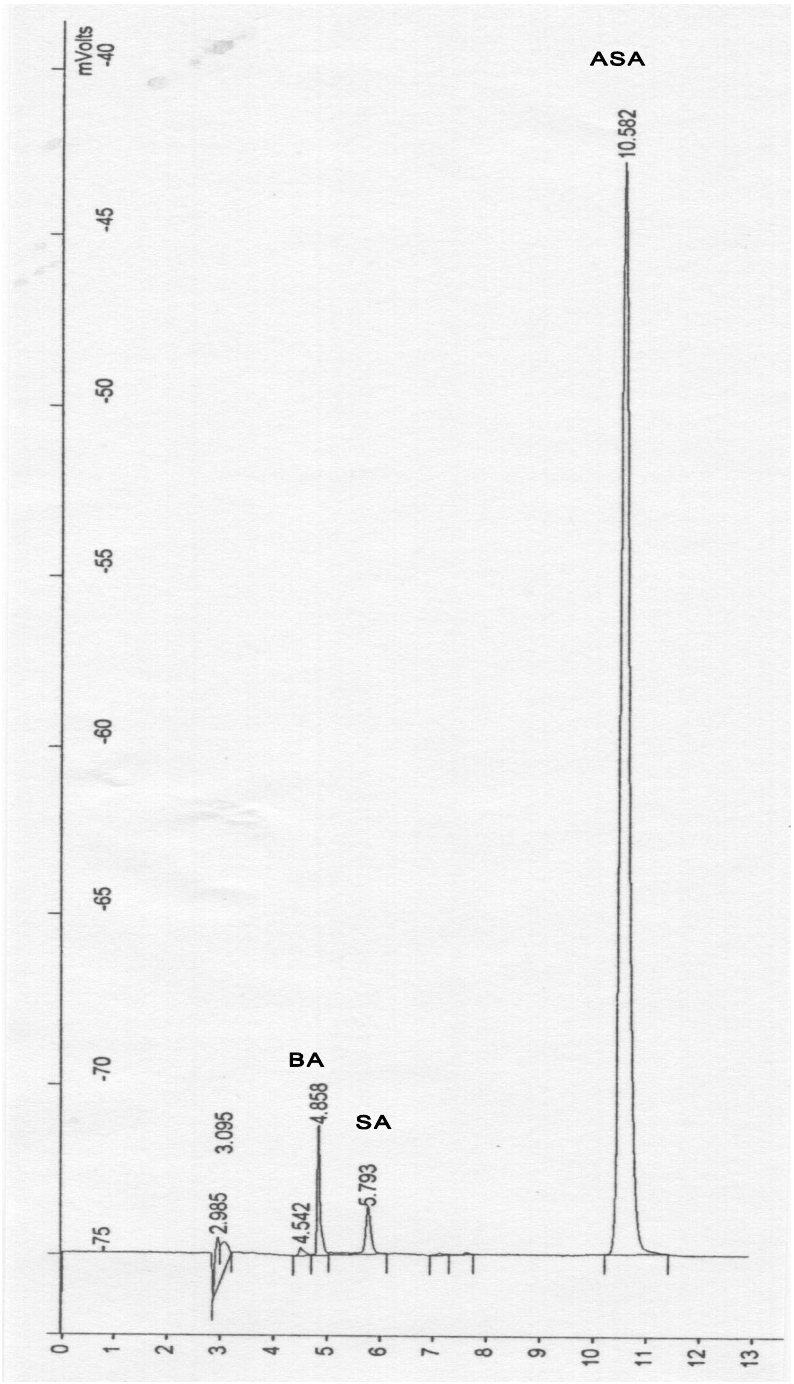


**Figure 5**: Chromatogram of SA, RT 5.8 min and acetylsalicylsalicylic acid (ASA), RT 10.6 min; aspirin standard BA, RT 4.9 min.

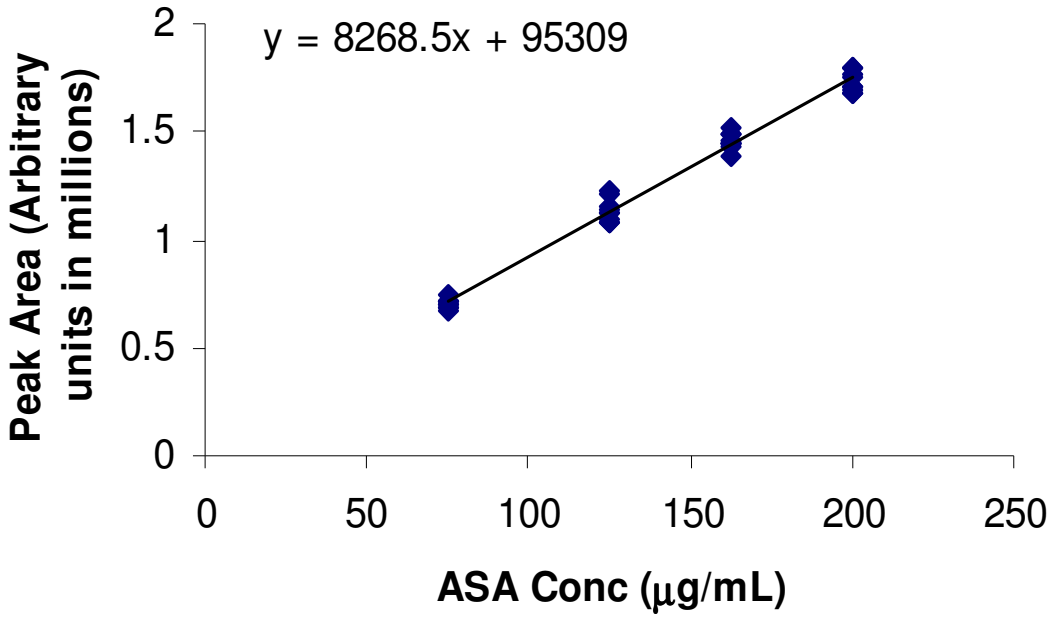


**Figure 6**: Acetyl salicylic acid calibration curve.

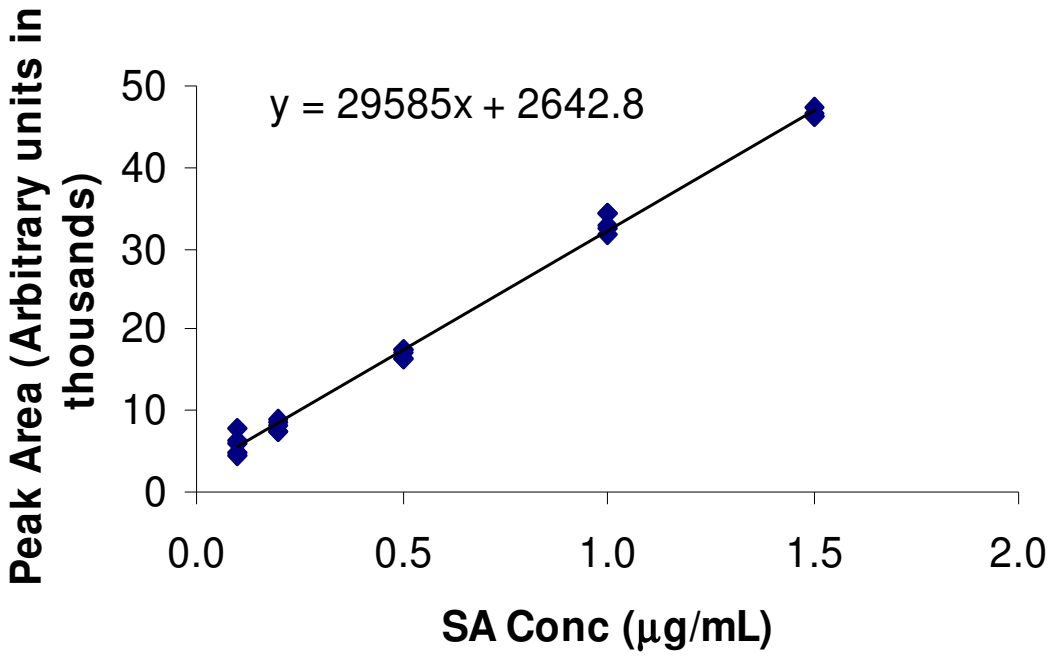


**Figure 7**: Salicylic acid calibration curve.

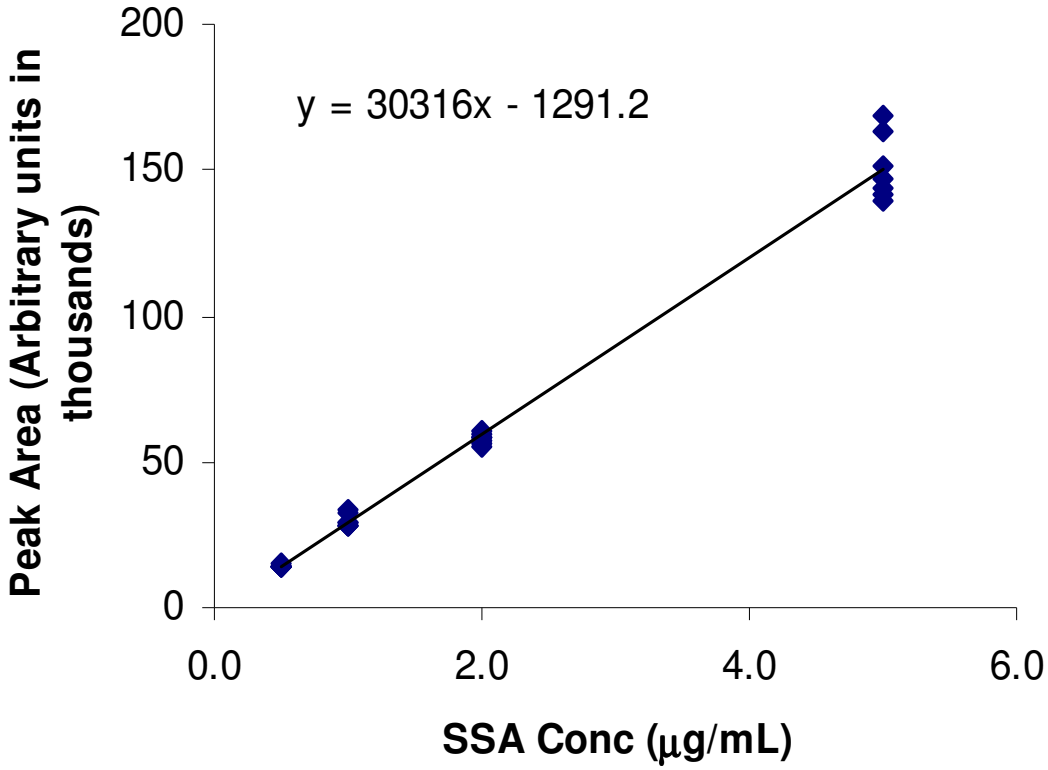


**Figure 8**: Salicylsalicylic acid calibration curve.

**Table 3**: Accuracy and precision for the determination of aspirin, salicylic acid and salicylsalicylic acid.

| Analyte | Calibration Level (ug/mL) | N | Assay Mean (ug/mL) | Accuracy % | RSD % |
|---|---|---|---|---|---|
| Aspirin | 75 | 9 | 73.7 | 98.3 | 2.82 |
| | 125 | 9 | 126.1 | 100.9 | 5.19 |
| | 162.5 | 9 | 164.6 | 101.3 | 2.75 |
| | 200 | 9 | 198.1 | 99.1 | 2.87 |
| Salicylic acid | 0.1 | 5 | 0.11 | 110.0 | 39.74 |
| | 0.2 | 5 | 0.19 | 93.4 | 11.47 |
| | 0.5 | 5 | 0.49 | 97.5 | 3.38 |
| | 1 | 5 | 1.03 | 103.1 | 3.96 |
| | 1.5 | 5 | 1.48 | 99.0 | 1.32 |
| Salicylsalicylic acid | 0.5 | 7 | 0.51 | 101.2 | 2.49 |
| | 1 | 7 | 1.03 | 102.9 | 7.48 |
| | 2 | 7 | 1.95 | 97.6 | 3.39 |
| | 5 | 7 | 5.01 | 100.3 | 7.24 |

RSD, relative standard deviation

N, number of replicates

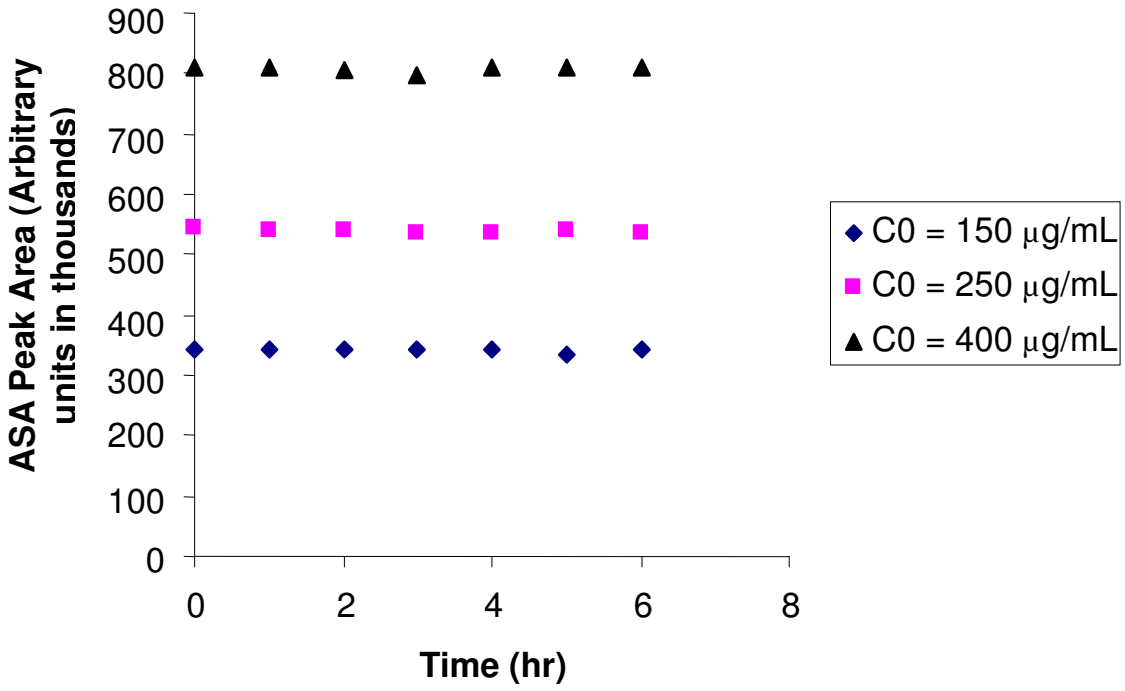


**Figure 9**: Calibration standards stability of acetyl salicylic acid for a period of 6 hours at the initial concentration, C0, for 150 µg/mL, 250 µg/mL and 400 µg/mL.

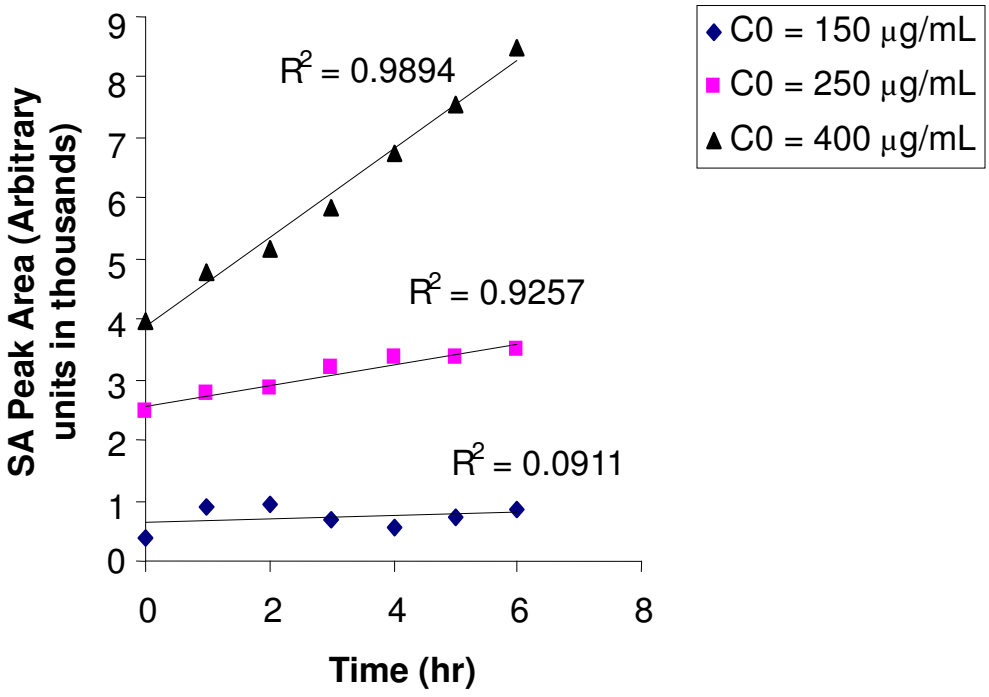


**Figure 10**: Calibration standards stability of salicylic acid from acetylsalicylic acid for a period of 6 hours at the initial concentration, C0 for 150 µg/mL, 250 µg/mL and 400 µg/mL.

## 4.4 Statistical Analysis

Comparative statistics were analyzed by one-way ANOVA with treatment or treatment within time period used as factors. In some cases, Treatments 1 and 2 (negative controls) were considered reference standards for relative comparisons of time-related trends. These tests used a minimum 5% level of significance to determine comparative differences, and all reported P values are two sided. Other statistical analyses include least-squares regression analysis and correlation analysis. Nominal statistics include the average and standard deviation (SD).

## 4.5 Aspirin Analyses

No time related trends were observed associated with the degradation of ASA for treatments utilizing Owens-Illinois PET prescription vials (Fig.11) or CSP Technologies Activ-Vial (Fig. 12). There was no statistical distinction ($p = 0.51$) between any of the three treatments employing the Owens-Illinois vials. The correlation coefficient ($R^2$) corresponding to the relationship between ASA content per tablet and duration of exposure was 0.0004 which was not statistical distinguishable ($p = 0.87$) from 0, that is, no correlation. In addition, there was no statistical distinction ($p = 0.24$) between the two treatments employing the CSP Technologies Activ-Vial. The $R^2$ value corresponding to the relationship between ASA content per tablet and duration of exposure was 0.0018 which was not significant ($p = 0.77$). The mean (SD) aspirin content corresponding to Treatments 1, 3 and 5 was 312.9 (12.97) mg per tablet, or 96.3% of the labeled content. The mean (SD) aspirin content corresponding to Treatments 2 and 4 was 313.8 (17.10)

mg per tablet, or 96.5% of the labeled content. Both of these values are within FDA regulatory specifications of ± 5% for labeled content of manufactured pharmaceuticals tablets.

## 4.6 Salicylic Acid Analyses

There was no significant time-related trend associated with Treatment 1 (Fig. 13). The $R^2$ value corresponding to the relationship between SA content per tablet and duration of exposure was 0.0010 which was not significant ($p = 0.88$). For treatment 2 (Fig. 14), the SA content per tablet was negatively correlated ($R^2$=0.2719) with the duration of exposure to environmental conditions. This relationship was statistically significant ($p< 0.01$). Bayer aspirin tablets contained as average 0.25 mg of SA per tablet on day 0, prior to exposure to any of the test conditions. This initial level of SA reflects unavoidable contamination of aspirin raw material at the time of manufacturing and is well within compendial tolerance of 3.0% for coated tablets or 0.1% for aspirin raw material relative to ASA content. Although quantitative analysis of SA concentrations corresponding with Treatments 1 and 2 resulted in levels of 0.1 to 0.2 µg/mL at all sampling times, levels near the quantifiable limit of the assay, the significant reduction in initial SA content per tablet resulting from Treatment 2 may indicate some leaching by the vial. The lack of a significant time-related trend for Treatment 1 does not necessarily preclude leaching by the Owens-Illinois vials since accumulation of SA by degradation due to moisture ingress may offset any observable difference in SA levels relative to the

initial (Day 0) SA content. In either case, however, aspirin is stable for at least 120 days to significant degradation which may result from moisture ingress in the closed Owens-Illinois or CSP technologies vial systems.

Treatment 3, 4, and 5 all showed time-related accumulation of SA. Each of these treatments was associated with either continuous exposure to moisture or exposure to trapped moisture due to intermittent opening and closing of vials. No tablet showed accumulation of SA in excess 1 mg or 0.4% of labeled SA equivalents within 120 days for any of these treatments. This level of degradation is consistent with ASA content findings since $\leq 0.4\%$ degradation is well within distinguishable statistical limits of ASA content variability. Statistically distinguishable ($p < 0.05$) accumulation of SA was observed beginning at 60 days for the open Owens-Illinois vial (Treatment 5) and at 90 days for the periodically open CSP Technologies Activ-Vial (Treatment 4).

Comparative analysis of the Owens-Illinois PET prescription vials (Treatment 3) and CSP Technologies Activ-Vial (Treatment 4) showed significant ($p < 0.001$) suppression of SA formation beginning at 60 days (Fig. 15). The relative suppression of SA formation was 58% at 60 days, 60% at 90 days, and 41% at 120 days. Although neither vial system completely eliminated the formation of SA when exposed to simulated use conditions at 30°C and 80% RH and compared to ingress moisture degradation only, the extent of protection provided by the Activ-Vial system was substantial. These results demonstrate the utility of the CSP Technologies Activ-Vial to reduce humidity within the vial under simulated conditions for a period of 120 days.

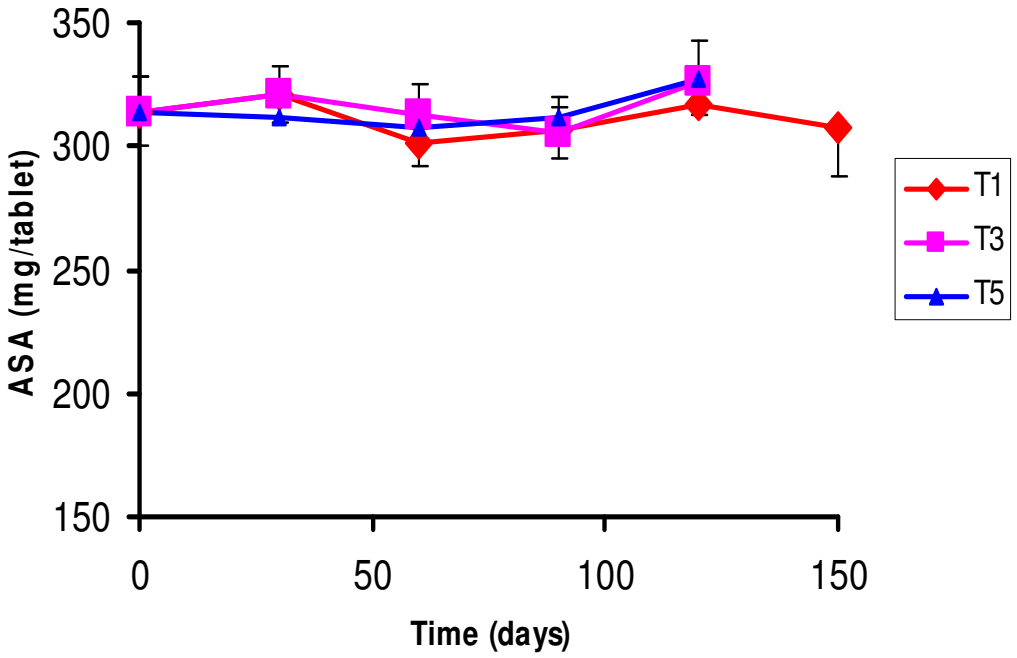


**Figure 11**: Comparison of treatment 1 (T1), 3 (T3) and 5 (T5) for Owen- Illinois PET vials for acetyl salicylic acid. No statistically significant differences were detected between any of the three treatments.

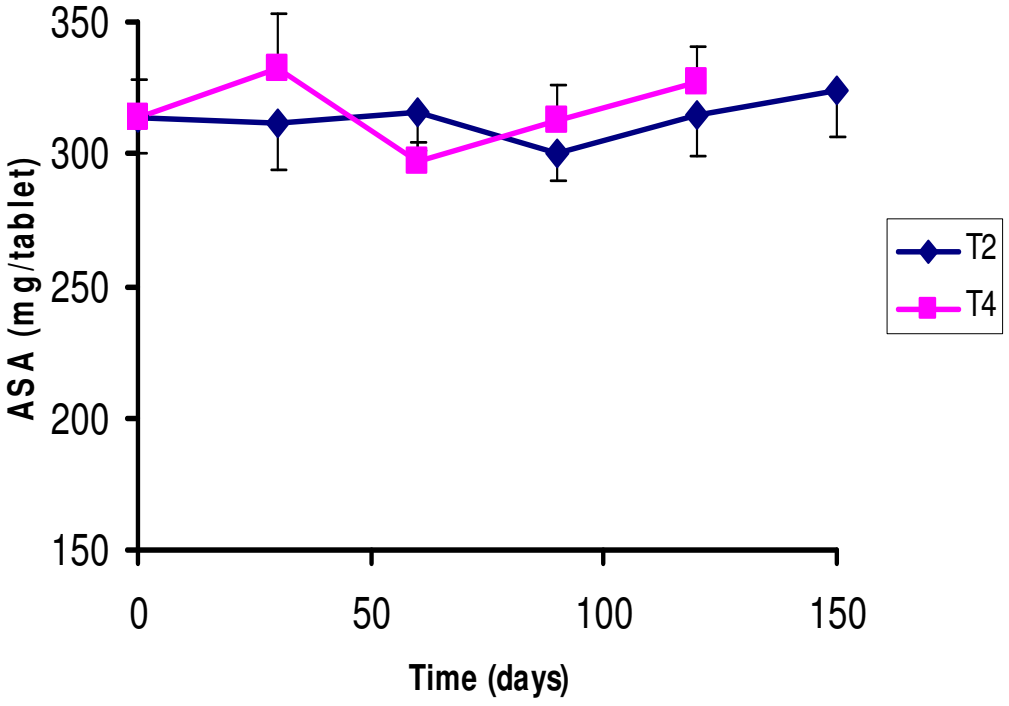


**Figure 12**: Comparison of treatments 2 (T2) and 4 (T4) for CSP technologies activ-vials for acetyl salicylic acid. No statistically significant differences were detected between the two treatments.

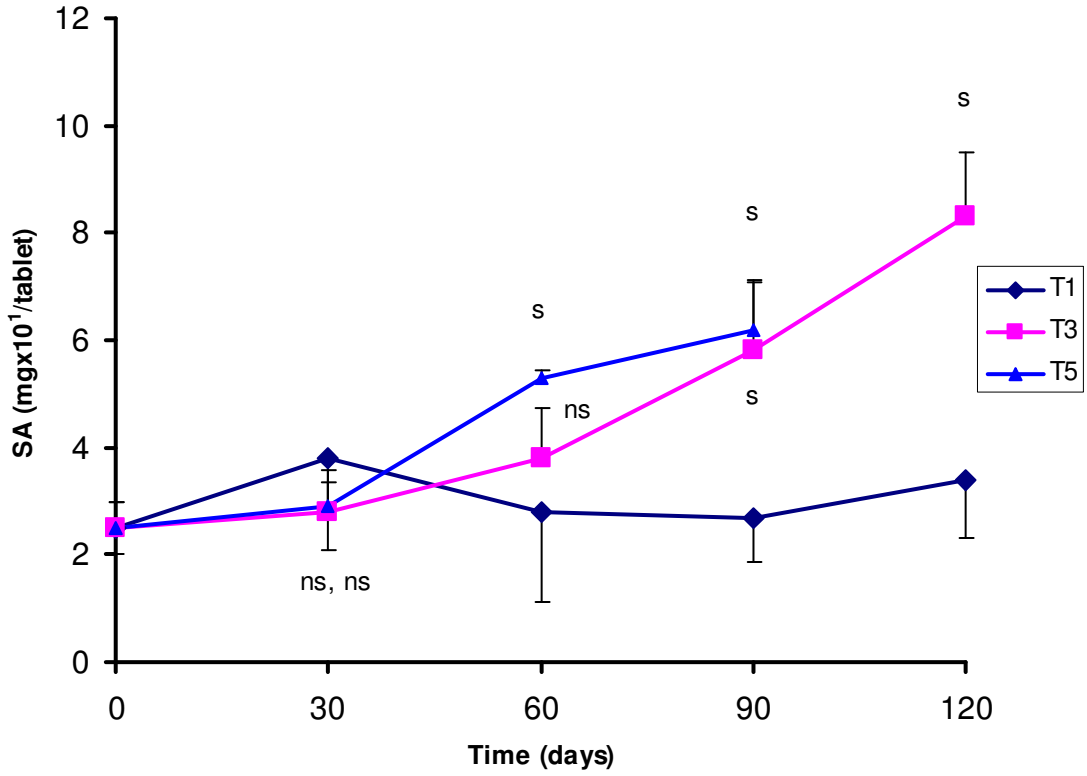


**Figure 13**: Comparison of treatments 1 (T1), 3 (T3) and 5 (T5) for Owens-Illinois PET vials for salicylic acid. *S* denotes a statistically significant ($p < 0.05$) difference from T1, the negative control, and *ns* denotes no significant difference.

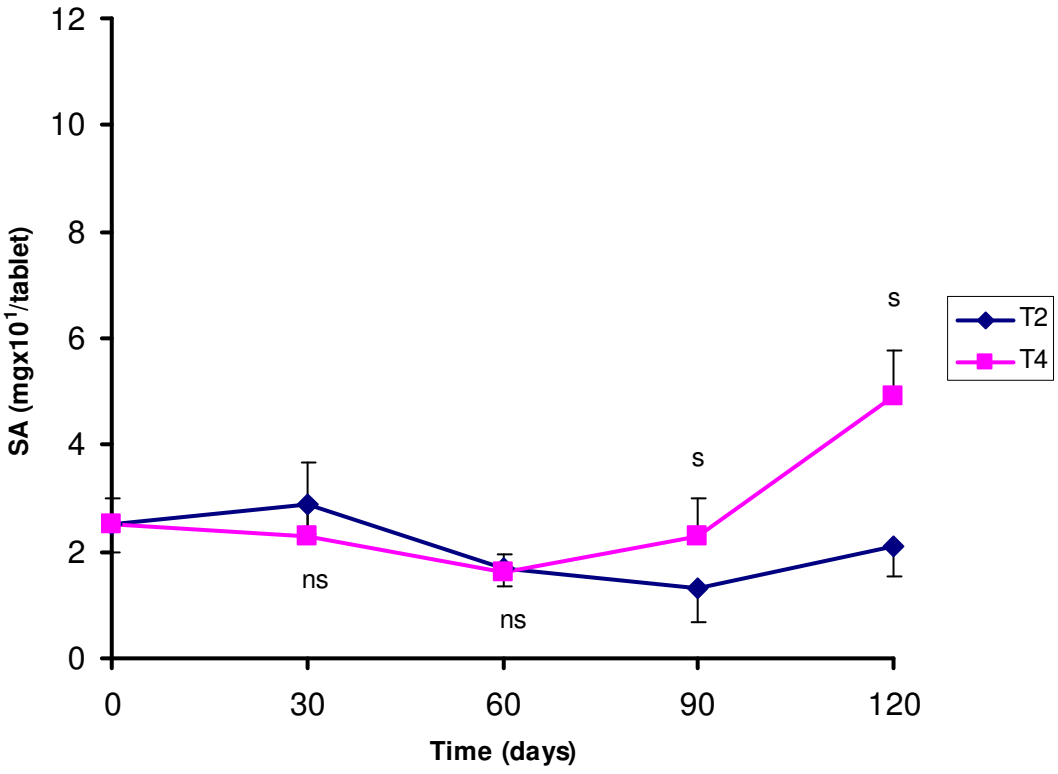


**Figure 14**: Comparison of treatments 2 (T2) and 4 (T4) for CSP technologies activ-vials for salicylic acid. *S* denotes a statistically significant ($p < 0.05$) difference from T2, the negative control, and *ns* denotes no significant difference.

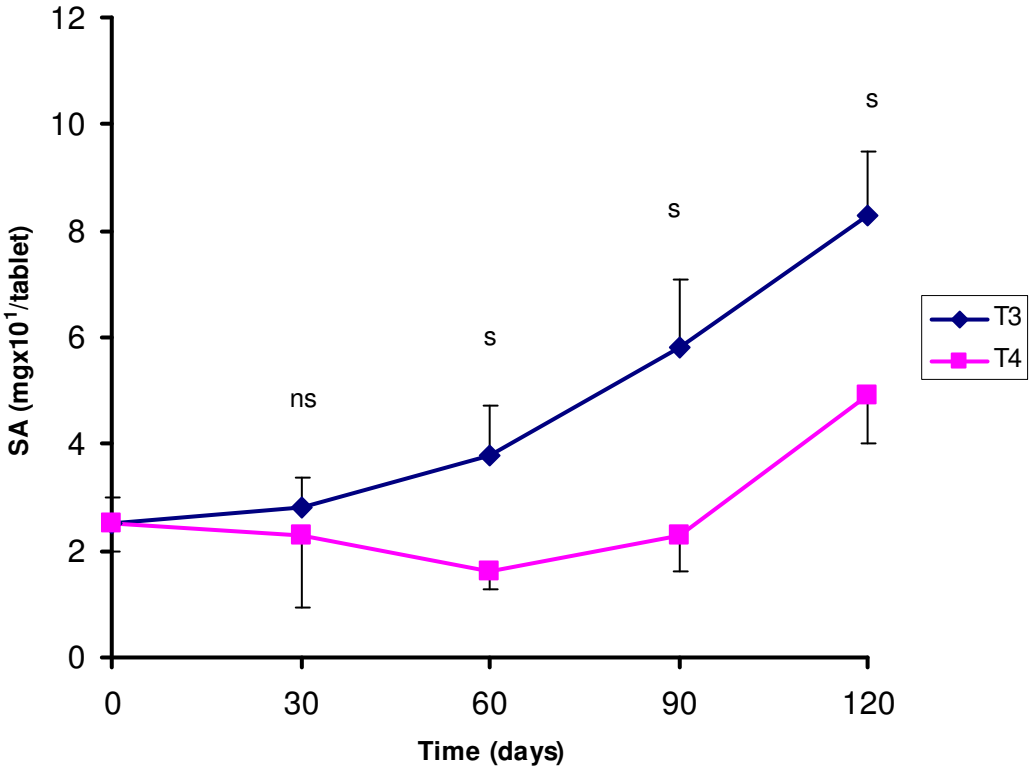


**Figure 15**: Comparison of treatments 3 (T3) and 4 (T4) for salicylic acid in a simulated use conditions. A relative 40-60% suppression of SA formation was observed for the CSP technologies Activ-Vial.

# 5 CONCLUSIONS

A stability-indicating assay was established and validated suitable for analyses of aspirin and its degradation products in appropriate concentration ranges corresponding to levels expected from one (1) aspirin tablet containing 325 mg of aspirin. Formation of salicylic acid as the result of aspirin degradation was observed within the 120 days period studied under simulated use conditions of 30°C and 80% relative humidity with a total exposure rate of 3 minutes per day (three one minute periodic exposures). The extent of aspirin degradation was minimal in this time frame. Never-the-less, significant suppression of salicylic acid formation was demonstrated by the CSP Technologies Activ-Vial system when compared to ordinary PET prescription vials. Although minimal moisture ingress is a necessary characteristic of pharmaceutical product packaging and repackaging for use, additional properties are required to minimize relative humidity within vials when subjected to typical use conditions. The CSP technologies Activ-Vial is expected to therefore provided an advantage under typical consumer use conditions, particularly in humid geographical regions, for the protection of moisture sensitive pharmaceutical products. In retrospect, current regulatory guidelines offer little assurance of the integrity and stability of moisture sensitive drugs under typical use conditions due to trapped moisture once the vials are opened.

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# APPENDICES

Appendix I – Representative Study sample chromatograms

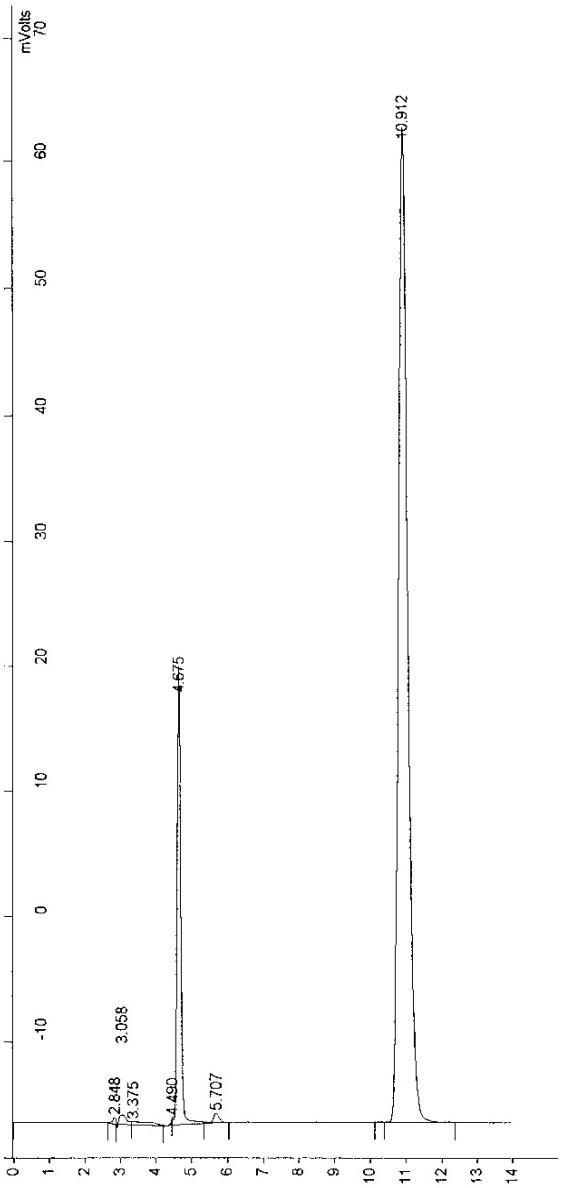


**Figure 16:** Chromatogram of Owen- Illinois closed, at day 30, salicylic acid (SA), RT 5.7 min and acetylsalicylsalicylic acid (ASA), RT 10.9 min; aspirin standard BA, RT 4.6 min.

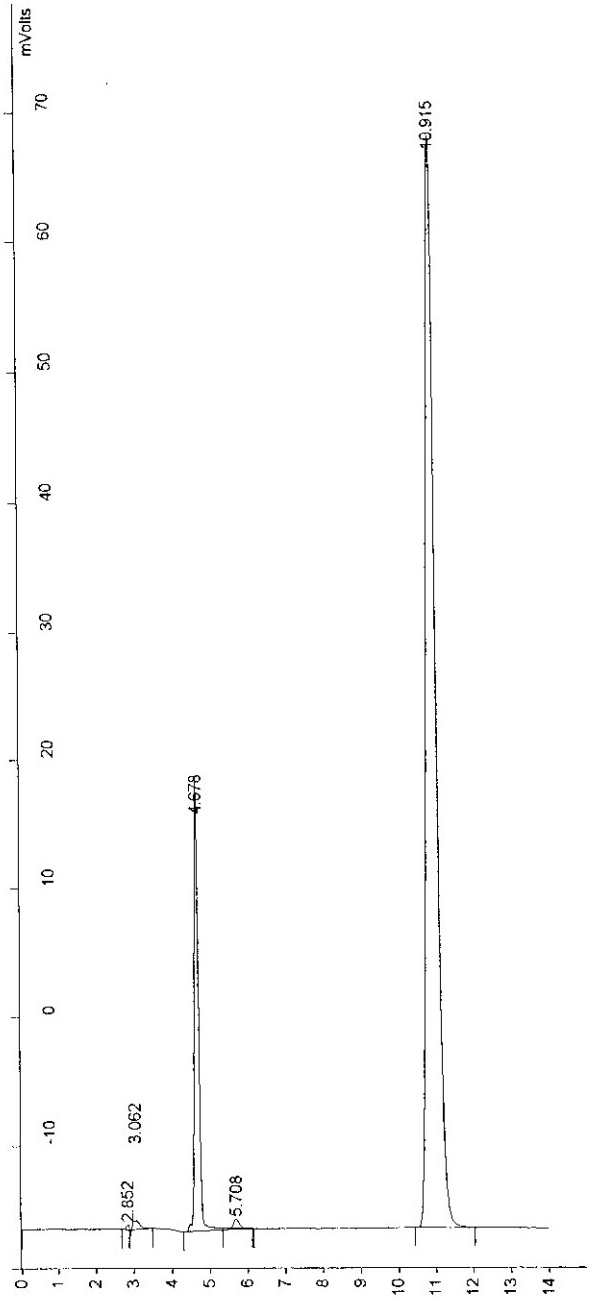


**Figure 17:** Chromatogram of Owen- Illinois closed, at day 30, salicylic acid (SA), RT 5.7 min and acetylsalicylsalicylic acid (ASA), RT 10.9 min; aspirin standard BA, RT 4.6 min.

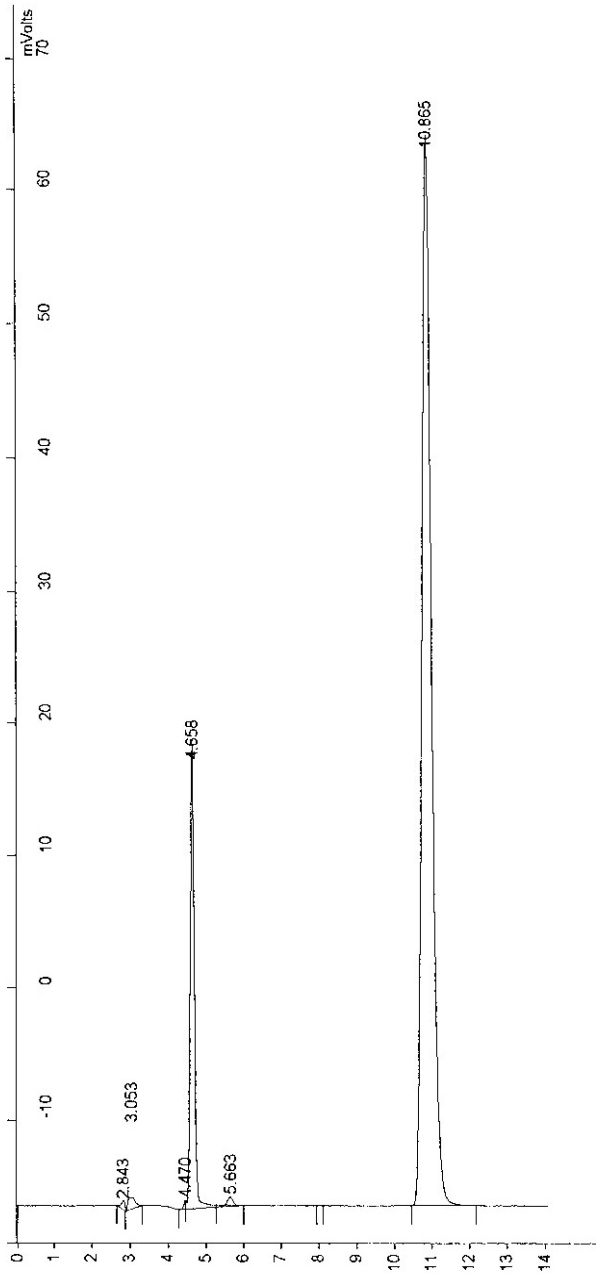


**Figure 18:** Chromatogram of CSP Technologies vial closed, at day 30, salicylic acid (SA), RT 5.6 min and acetylsalicylsalicylic acid (ASA), RT 10.8 min; aspirin standard BA, RT 4.6 min.

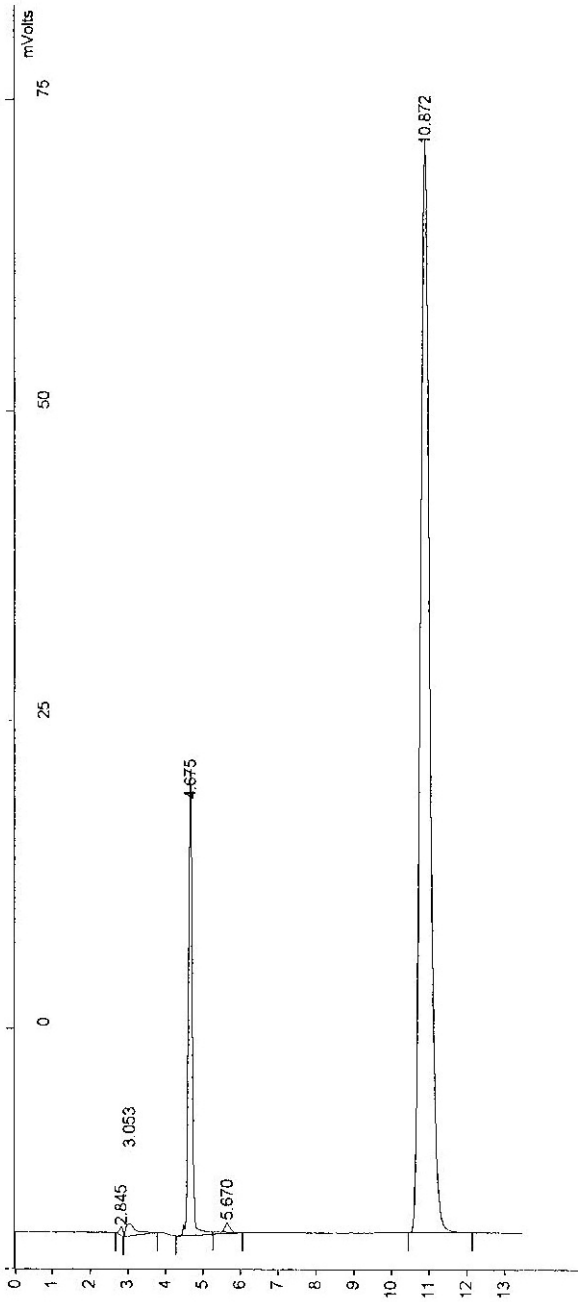


**Figure 19:** Chromatogram of CSP Technologies vial closed, at day 30, salicylic acid (SA), RT 5.6 min and acetylsalicylsalicylic acid (ASA), RT 10.8 min; aspirin standard BA, RT 4.6 min.

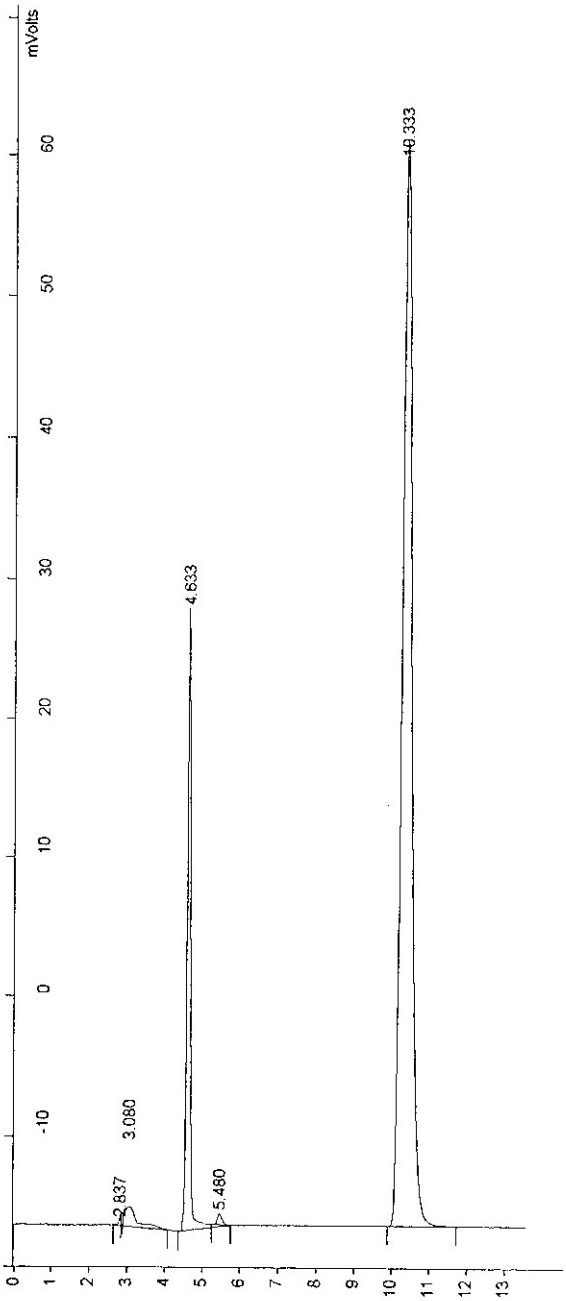


**Figure 20:** Chromatogram of Owen- Illinois vial periodically opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.3 min; aspirin standard BA, RT 4.6 min.

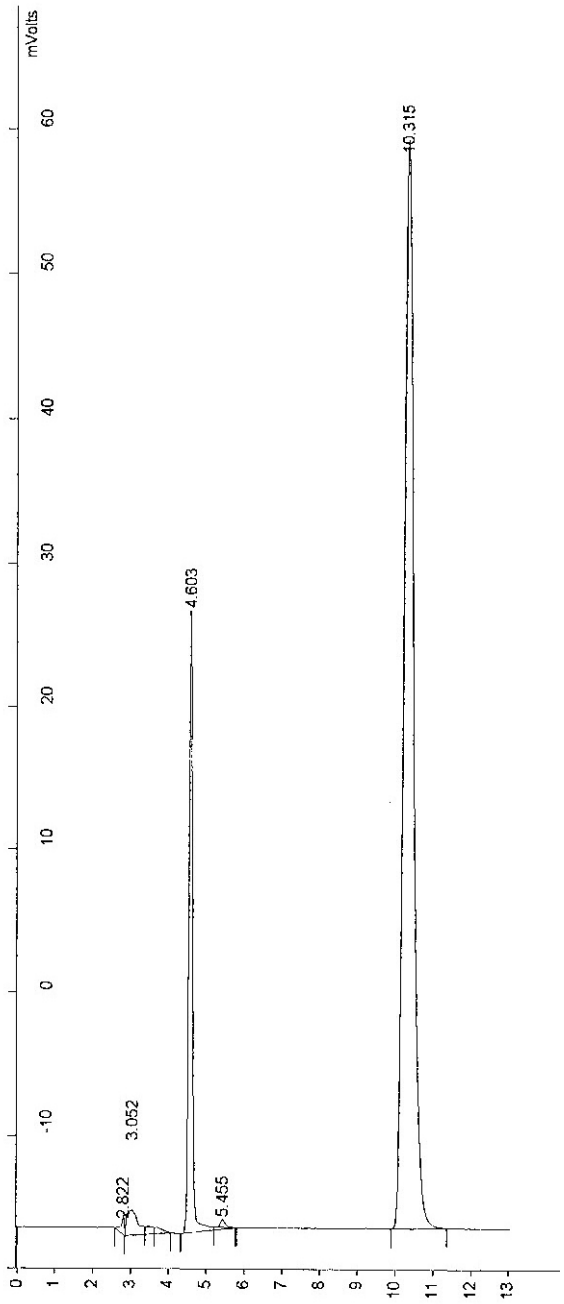


**Figure 21:** Chromatogram of Owen- Illinois vial periodically opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.3 min; aspirin standard BA, RT 4.6 min.

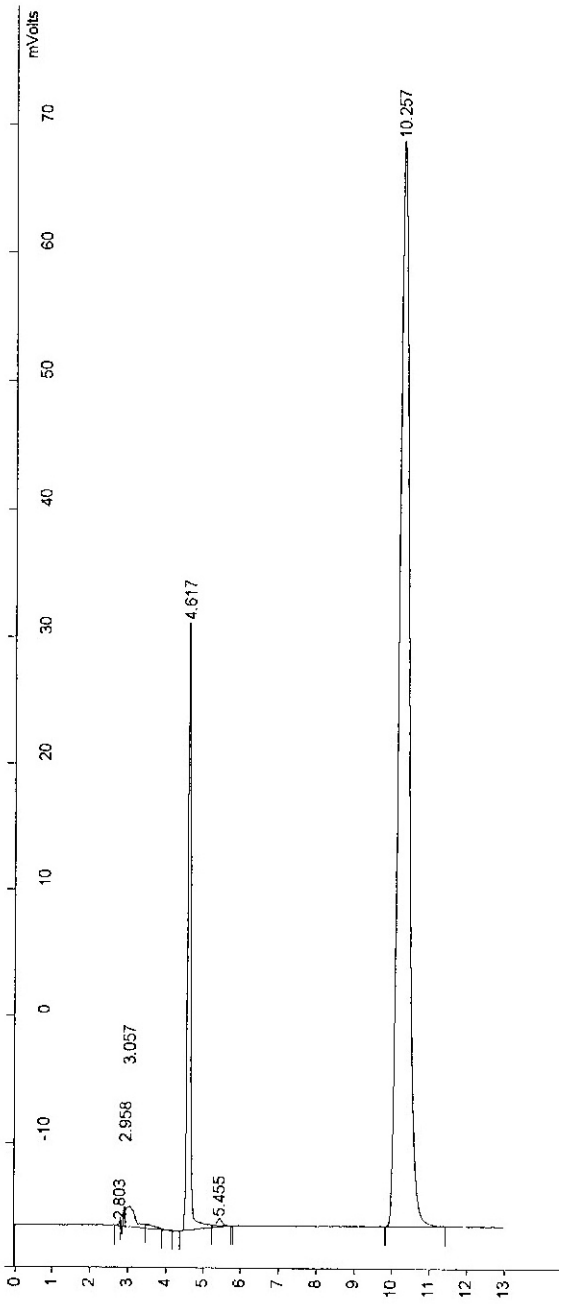


**Figure 22:** Chromatogram of CSP Technologies vial periodically opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.2 min; aspirin standard BA, RT 4.6 min.

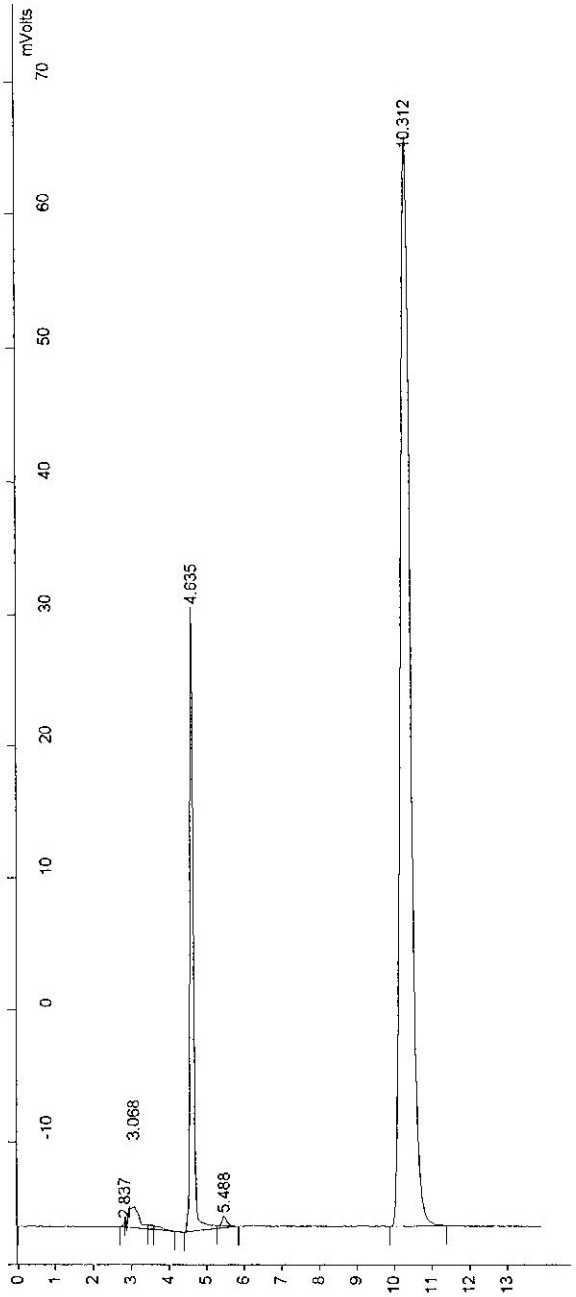


**Figure 23:** Chromatogram of CSP Technologies vial periodically opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.3 min; aspirin standard BA, RT 4.6 min.

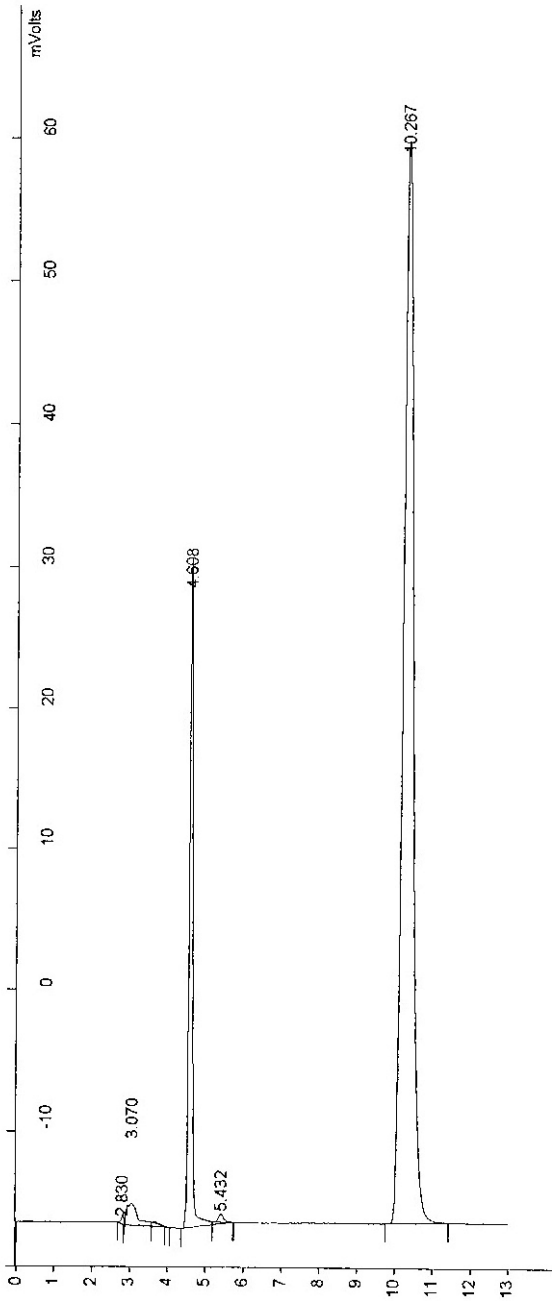


**Figure 24:** Chromatogram of Owen- Illinois vial continuously opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.2 min; aspirin standard BA, RT 4.6 min.

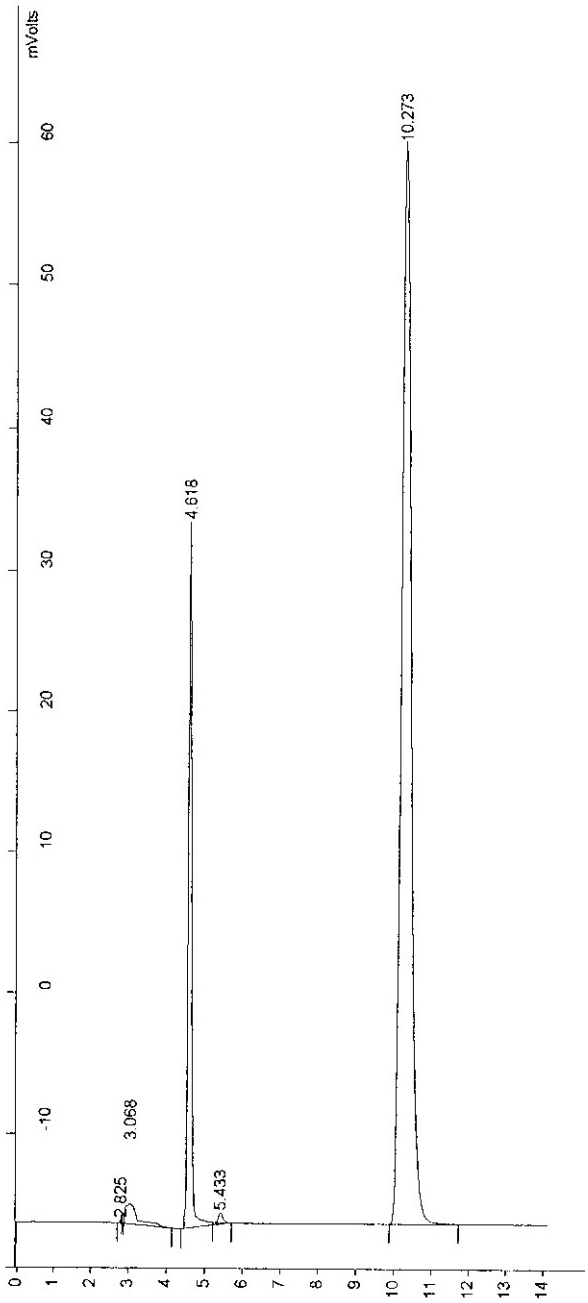


**Figure25:** Chromatogram of Owen- Illinois vial continuously opened, at day 30, salicylic acid (SA), RT 5.4 min and acetylsalicylsalicylic acid (ASA), RT 10.2 min; aspirin standard BA, RT 4.6 min.

# Appendix II – Tabulated Results

**Table 4**

**Owens-Illinois PET prescription vial**
**Treatment 1 Closed Vial**
**Environmental conditions: 30°C and 80% RH**

| Sample | ASA conc (µg/mL) | SA Conc (µg/mL) | ASA per tablet (mg) | SA per tablet (mg) | ASA (% label) | SA equivalent* (% label) |
|---|---|---|---|---|---|---|
| *Time: 0 days* | | | | | | |
| Tablet 1 | 156.0 | 0.085 | 312.0 | 0.17 | 96.0 | 0.068 |
| Tablet 2 | 170.8 | 0.154 | 341.7 | 0.31 | 105.1 | 0.124 |
| Tablet 3 | 151.0 | 0.123 | 302.1 | 0.25 | 92.9 | 0.098 |
| Tablet 4 | 157.5 | 0.522 | 315.0 | 1.05** | 96.9 | 0.421** |
| Tablet 5 | 153.2 | 0.134 | 306.3 | 0.27 | 94.3 | 0.107 |
| Tablet 6 | 153.6 | 0.124 | 307.3 | 0.25 | 94.5 | 0.099 |
| AVG | | | 314.1 | 0.25 | 96.6 | 0.099 |
| SD | | | 14.27 | 0.050 | 4.39 | 0.0202 |
| *Time: 30 days* | | | | | | |
| Tablet 1 | 155.0 | 0.139 | 310.1 | 0.28 | 95.4 | 0.112 |
| Tablet 2 | 166.2 | 0.145 | 332.5 | 0.29 | 102.3 | 0.116 |
| Tablet 3 | 165.5 | 0.145 | 331.1 | 0.29 | 101.9 | 0.117 |
| Tablet 4 | 164.9 | 0.286 | 329.7 | 0.57 | 101.4 | 0.230 |
| Tablet 5 | 158.5 | 0.115 | 317.0 | 0.23 | 97.5 | 0.092 |
| Tablet 6 | 152.6 | 0.312 | 305.2 | 0.62 | 93.9 | 0.251 |
| AVG | | | 320.9 | 0.38 | 98.7 | 0.153 |
| SD | | | 11.77 | 0.171 | 3.62 | 0.0686 |
| *Time: 60 days* | | | | | | |
| Tablet 1 | 150.7 | 0.080 | 301.5 | 0.16 | 92.8 | 0.064 |
| Tablet 2 | 150.2 | 0.074 | 300.5 | 0.15 | 92.5 | 0.060 |
| Tablet 3 | 152.8 | 0.128 | 305.6 | 0.26 | 94.0 | 0.102 |
| Tablet 4 | 141.8 | 0.130 | 283.5 | 0.26 | 87.2 | 0.104 |
| Tablet 5 | 153.0 | 0.128 | 306.0 | 0.26 | 94.2 | 0.102 |
| Tablet 6 | 155.3 | 0.303 | 310.6 | 0.61 | 95.6 | 0.243 |
| AVG | | | 301.3 | 0.28 | 92.7 | 0.113 |
| SD | | | 9.42 | 0.167 | 2.90 | 0.0669 |
| *Time: 90 days* | | | | | | |
| Tablet 1 | 153.2 | 0.164 | 306.5 | 0.33 | 94.3 | 0.132 |
| Tablet 2 | 148.2 | 0.093 | 296.4 | 0.19 | 91.2 | 0.075 |
| Tablet 3 | 164.6 | 0.179 | 329.2 | 0.36 | 101.3 | 0.144 |
| Tablet 4 | 153.4 | 0.078 | 306.8 | 0.16 | 94.4 | 0.062 |
| Tablet 5 | 148.0 | 0.153 | 295.9 | 0.31 | 91.1 | 0.122 |
| Tablet 6 | 153.1 | 0.147 | 306.2 | 0.29 | 94.2 | 0.118 |
| AVG | | | 306.8 | 0.27 | 94.4 | 0.109 |
| SD | | | 12.09 | 0.082 | 3.72 | 0.0328 |
| *Time: 120 days* | | | | | | |
| Tablet 1 | 156.2 | 0.124 | 312.4 | 0.25 | 96.1 | 0.099 |
| Tablet 2 | 158.5 | 0.231 | 317.1 | 0.46 | 97.6 | 0.185 |
| Tablet 3 | 161.2 | 0.159 | 322.3 | 0.32 | 99.2 | 0.127 |
| AVG | | | 317.3 | 0.34 | 97.6 | 0.137 |
| SD | | | 4.94 | 0.110 | 1.52 | 0.0440 |
| *Time: 150 days**** | | | | | | |
| Tablet 1 | 146.4 | 0.129 | 292.9 | 0.26 | 90.1 | 0.104 |
| Tablet 2 | 150.2 | 0.218 | 300.5 | 0.44 | 92.5 | 0.175 |
| Tablet 3 | 165.2 | 0.343 | 330.4 | 0.69 | 101.7 | 0.275 |
| AVG | | | 307.9 | 0.46 | 94.7 | 0.185 |
| SD | | | 19.87 | 0.215 | 6.11 | 0.0862 |

*325 mg aspirin = 249.2 mg salicylic acid

** outlier, omitted from statistics

*** 40°C and 75% RH

## Table 5

## CSP Technologies activ-vial
## Treatment 2 Closed vial

## Environmental Conditions: 30°C and 80% RH

| Sample | ASA conc (µg/mL) | SA Conc (µg/mL) | ASA per tablet (mg) | SA per tablet (mg) | ASA (% label) | SA equivalent* (% label) |
|---|---|---|---|---|---|---|
| *Time: 0 days* | | | | | | |
| Tablet 1 | 156.0 | 0.085 | 312.0 | 0.17 | 96.0 | 0.068 |
| Tablet 2 | 170.8 | 0.154 | 341.7 | 0.31 | 105.1 | 0.124 |
| Tablet 3 | 151.0 | 0.123 | 302.1 | 0.25 | 92.9 | 0.098 |
| Tablet 4 | 157.5 | 0.522 | 315.0 | 1.05** | 96.9 | 0.421** |
| Tablet 5 | 153.2 | 0.134 | 306.3 | 0.27 | 94.3 | 0.107 |
| Tablet 6 | 153.6 | 0.124 | 307.3 | 0.25 | 94.5 | 0.099 |
| AVG | | | 314.1 | 0.25 | 96.6 | 0.099 |
| SD | | | 14.27 | 0.050 | 4.39 | 0.0202 |
| *Time: 30 days* | | | | | | |
| Tablet 1 | 158.1 | 0.107 | 316.2 | 0.21 | 97.3 | 0.086 |
| Tablet 2 | 169.0 | 0.143 | 338.0 | 0.29 | 104.0 | 0.115 |
| Tablet 3 | 146.2 | 0.127 | 292.5 | 0.25 | 90.0 | 0.102 |
| Tablet 4 | 159.8 | 0.152 | 319.7 | 0.30 | 98.4 | 0.122 |
| Tablet 5 | 147.0 | 0.156 | 294.0 | 0.31 | 90.4 | 0.125 |
| Tablet 6 | 154.7 | 0.195 | 309.5 | 0.39 | 95.2 | 0.156 |
| AVG | | | 311.6 | 0.29 | 95.9 | 0.118 |
| SD | | | 17.11 | 0.059 | 5.26 | 0.0237 |
| *Time: 60 days* | | | | | | |
| Tablet 1 | 164.4 | 0.060 | 328.7 | 0.12 | 101.1 | 0.048 |
| Tablet 2 | 160.8 | 0.082 | 321.5 | 0.16 | 98.9 | 0.066 |
| Tablet 3 | 158.2 | 0.07 | 316.3 | 0.14 | 97.3 | 0.056 |
| Tablet 4 | 165.9 | 0.110 | 331.8 | 0.22 | 102.1 | 0.088 |
| Tablet 5 | 147.4 | 0.091 | 294.7 | 0.18 | 90.7 | 0.073 |
| Tablet 6 | 151.3 | 0.091 | 302.7 | 0.18 | 93.1 | 0.073 |
| AVG | | | 316.0 | 0.17 | 97.2 | 0.067 |
| SD | | | 14.64 | 0.035 | 4.50 | 0.0141 |
| *Time: 90 days* | | | | | | |
| Tablet 1 | 152.6 | 0.069 | 305.3 | 0.14 | 93.9 | 0.056 |
| Tablet 2 | 152.6 | 0.046 | 305.2 | 0.09 | 93.9 | 0.037 |
| Tablet 3 | 154.1 | 0.053 | 308.1 | 0.11 | 94.8 | 0.043 |
| Tablet 4 | 154.3 | 0.128 | 308.5 | 0.26 | 94.9 | 0.103 |
| Tablet 5 | 146.8 | 0.053 | 293.6 | 0.11 | 90.3 | 0.042 |
| Tablet 6 | 141.3 | 0.049 | 282.7 | 0.10 | 87.0 | 0.040 |
| AVG | | | 300.6 | 0.13 | 92.5 | 0.053 |
| SD | | | 10.32 | 0.063 | 3.17 | 0.0251 |
| *Time: 120 days* | | | | | | |
| Tablet 1 | 162.1 | 0.130 | 324.2 | 0.26 | 99.8 | 0.104 |
| Tablet 2 | 162.2 | 0.076 | 324.3 | 0.15 | 99.8 | 0.061 |
| Tablet 3 | 148.6 | 0.108 | 297.2 | 0.22 | 91.4 | 0.086 |
| AVG | | | 315.2 | 0.21 | 97.0 | 0.084 |
| SD | | | 15.63 | 0.055 | 4.81 | 0.0220 |
| *Time: 150 days**** | | | | | | |
| Tablet 1 | 157.0 | 0.017 | 313.9 | 0.03 | 96.6 | 0.013 |
| Tablet 2 | 157.0 | 0.027 | 314.0 | 0.05 | 96.6 | 0.022 |
| Tablet 3 | 171.8 | 0.032 | 343.6 | 0.06 | 105.7 | 0.026 |
| AVG | | | 323.8 | 0.05 | 99.6 | 0.020 |
| SD | | | 17.11 | 0.015 | 5.27 | 0.0062 |

*325 mg aspirin = 249.2 mg salicylic acid

** outlier, omitted from statistics

*** 40°C and 75% RH

**Table 6**

**Owens-Illinois PET prescription vial**
**Treatment 3 periodically opened vial**

**Environmental conditions: 30°C and 80% RH**

| Sample | ASA conc (µg/mL) | SA Conc (µg/mL) | ASA per tablet (mg) | SA per tablet (mg) | ASA (% label) | SA equivalent* (% label) |
|---|---|---|---|---|---|---|
| *Time: 0 days* | | | | | | |
| Tablet 1 | 156.0 | 0.085 | 312.0 | 0.17 | 96.0 | 0.068 |
| Tablet 2 | 170.8 | 0.154 | 341.7 | 0.31 | 105.1 | 0.124 |
| Tablet 3 | 151.0 | 0.123 | 302.1 | 0.25 | 92.9 | 0.098 |
| Tablet 4 | 157.5 | 0.522 | 315.0 | 1.05** | 96.9 | 0.421** |
| Tablet 5 | 153.2 | 0.134 | 306.3 | 0.27 | 94.3 | 0.107 |
| Tablet 6 | 153.6 | 0.124 | 307.3 | 0.25 | 94.5 | 0.099 |
| AVG | | | 314.1 | 0.25 | 96.6 | 0.099 |
| SD | | | 14.27 | 0.050 | 4.39 | 0.0202 |
| *Time: 30 days* | | | | | | |
| Tablet 1 | 162.0 | 0.179 | 323.9 | 0.36 | 99.7 | 0.143 |
| Tablet 2 | 155.2 | 0.098 | 310.4 | 0.2 | 95.5 | 0.079 |
| Tablet 3 | 169.9 | 0.163 | 339.7 | 0.33 | 104.5 | 0.131 |
| Tablet 4 | 152.7 | 0.136 | 305.5 | 0.27 | 94 | 0.109 |
| Tablet 5 | 160.1 | 0.147 | 320.1 | 0.29 | 98.5 | 0.118 |
| Tablet 6 | 161.9 | 0.126 | 323.8 | 0.25 | 99.6 | 0.101 |
| AVG | | | 320.6 | 0.28 | 98.6 | 0.114 |
| SD | | | 12.02 | 0.057 | 3.7 | 0.0227 |
| *Time: 60 days* | | | | | | |
| Tablet 1 | 156.7 | 0.189 | 313.4 | 0.38 | 96.4 | 0.152 |
| Tablet 2 | 148.1 | 0.138 | 296.3 | 0.28 | 91.2 | 0.111 |
| Tablet 3 | 162.5 | 0.186 | 324.9 | 0.37 | 100.0 | 0.15 |
| Tablet 4 | 164.9 | 0.146 | 329.8 | 0.29 | 101.5 | 0.117 |
| Tablet 5 | 152.5 | 0.217 | 305.1 | 0.43 | 93.9 | 0.174 |
| Tablet 6 | 153.9 | 0.263 | 307.9 | 0.53 | 94.7 | 0.211 |
| AVG | | | 312.9 | 0.38 | 96.3 | 0.152 |
| SD | | | 12.6 | 0.093 | 3.88 | 0.0373 |
| *Time: 90 days* | | | | | | |
| Tablet 1 | 152.1 | 0.255 | 304.2 | 0.51 | 93.6 | 0.204 |
| Tablet 2 | 148.9 | 0.194 | 297.9 | 0.39 | 91.7 | 0.156 |
| Tablet 3 | 143.7 | 0.284 | 287.3 | 0.57 | 88.4 | 0.228 |
| Tablet 4 | 148 | 0.295 | 295.9 | 0.59 | 91 | 0.236 |
| Tablet 5 | 161.8 | 0.334 | 323.6 | 0.67 | 99.6 | 0.268 |
| Tablet 6 | 161.4 | 0.379 | 322.7 | 0.76 | 99.3 | 0.304 |
| AVG | | | 305.3 | 0.58 | 93.9 | 0.233 |
| SD | | | 14.88 | 0.128 | 4.58 | 0.0513 |
| *Time: 120 days* | | | | | | |
| Tablet 1 | 161.7 | 0.359 | 323.3 | 0.72 | 99.5 | 0.288 |
| Tablet 2 | 156.6 | 0.407 | 313.2 | 0.81 | 96.4 | 0.327 |
| Tablet 3 | 161.3 | 0.362 | 322.6 | 0.72 | 99.3 | 0.29 |
| Tablet 4 | 177.9 | 0.497 | 355.8 | 0.99 | 109.5 | 0.399 |
| Tablet 5 | 156.8 | 0.45 | 313.6 | 0.9 | 96.5 | 0.361 |
| Tablet 6 | | | | | | |
| AVG | | | 325.7 | 0.83 | 100.2 | 0.333 |
| SD | | | 17.47 | 0.119 | 5.38 | 0.0476 |

*325 mg aspirin = 249.2 mg salicylic acid

** outlier, omitted from statistics

**Table 7**

**CSP Technologies activ-vial**
**Treatment 4 periodically opened vial**

**Environmental conditions: 30°C and 80% RH**

| Sample | ASA conc (µg/mL) | SA Conc (µg/mL) | ASA per tablet (mg) | SA per tablet (mg) | ASA (% label) | SA equivalent* (% label) |
|---|---|---|---|---|---|---|
| *Time: 0 days* | | | | | | |
| Tablet 1 | 156.0 | 0.085 | 312.0 | 0.17 | 96.0 | 0.068 |
| Tablet 2 | 170.8 | 0.154 | 341.7 | 0.31 | 105.1 | 0.124 |
| Tablet 3 | 151.0 | 0.123 | 302.1 | 0.25 | 92.9 | 0.098 |
| Tablet 4 | 157.5 | 0.522 | 315.0 | 1.05** | 96.9 | 0.421** |
| Tablet 5 | 153.2 | 0.134 | 306.3 | 0.27 | 94.3 | 0.107 |
| Tablet 6 | 153.6 | 0.124 | 307.3 | 0.25 | 94.5 | 0.099 |
| AVG | | | 314.1 | 0.25 | 96.6 | 0.099 |
| SD | | | 14.27 | 0.050 | 4.39 | 0.0202 |
| *Time: 30 days* | | | | | | |
| Tablet 1 | 180.2 | 0.082 | 360.4 | 0.16 | 110.9 | 0.066 |
| Tablet 2 | 174.3 | 0.149 | 348.5 | 0.3 | 107.2 | 0.12 |
| Tablet 3 | 159 | 0.06 | 317.9 | 0.12 | 97.8 | 0.048 |
| Tablet 4 | 162.7 | 0.234 | 325.4 | 0.47 | 100.1 | 0.188 |
| Tablet 5 | 169.3 | 0.103 | 338.7 | 0.21 | 104.2 | 0.083 |
| Tablet 6 | 152.7 | 0.051 | 305.4 | 0.1 | 94 | 0.041 |
| AVG | | | 332.7 | 0.23 | 102.4 | 0.091 |
| SD | | | 20.35 | 0.138 | 6.26 | 0.0553 |
| *Time: 60 days* | | | | | | |
| Tablet 1 | 152.8 | 0.085 | 305.6 | 0.17 | 94 | 0.068 |
| Tablet 2 | 146.7 | 0.09 | 293.4 | 0.18 | 90.3 | 0.073 |
| Tablet 3 | 145.6 | 0.081 | 291.2 | 0.16 | 89.6 | 0.065 |
| Tablet 4 | 148.6 | 0.086 | 297.2 | 0.17 | 91.4 | 0.069 |
| Tablet 5 | 144.1 | 0.045 | 288.3 | 0.09 | 88.7 | 0.036 |
| Tablet 6 | 152.6 | 0.087 | 305.3 | 0.17 | 93.9 | 0.07 |
| AVG | | | 296.8 | 0.16 | 91.3 | 0.063 |
| SD | | | 7.29 | 0.034 | 2.24 | 0.0136 |
| *Time: 90 days* | | | | | | |
| Tablet 1 | 157.8 | 0.127 | 315.7 | 0.25 | 97.1 | 0.102 |
| Tablet 2 | 156.3 | 0.074 | 312.7 | 0.15 | 96.2 | 0.06 |
| Tablet 3 | 155.3 | 0.072 | 310.6 | 0.14 | 95.6 | 0.058 |
| Tablet 4 | 157.5 | 0.134 | 315 | 0.27 | 96.9 | 0.107 |
| Tablet 5 | 144.8 | 0.159 | 289.7 | 0.32 | 89.1 | 0.128 |
| Tablet 6 | 166.5 | 0.119 | 333 | 0.24 | 102.5 | 0.095 |
| AVG | | | 312.8 | 0.23 | 96.2 | 0.092 |
| SD | | | 13.88 | 0.069 | 4.27 | 0.0277 |
| *Time: 120 days* | | | | | | |
| Tablet 1 | 158.4 | 0.248 | 316.9 | 0.5 | 97.5 | 0.199 |
| Tablet 2 | 164.1 | 0.184 | 328.3 | 0.37 | 101 | 0.147 |
| Tablet 3 | 173.7 | 0.307 | 347.4 | 0.61 | 106.9 | 0.246 |
| Tablet 4 | 165 | 0.256 | 330.1 | 0.51 | 101.6 | 0.206 |
| Tablet 5 | 156.5 | 0.233 | 313 | 0.47 | 96.3 | 0.187 |
| Tablet 6 | | | | | | |
| AVG | | | 327.1 | 0.49 | 100.6 | 0.197 |
| SD | | | 13.46 | 0.089 | 4.14 | 0.0356 |

*325 mg aspirin = 249.2 mg salicylic acid

** outlier, omitted from statistics

## Table 8

### Owens-Illinois PET prescription vial
### Treatment 5 Continuously open vial

### Environmental conditions: 30°C and 80% RH

| Sample | ASA conc (µg/mL) | SA Conc (µg/mL) | ASA per tablet (mg) | SA per tablet (mg) | ASA (% label) | SA equivalent* (% label) |
|---|---|---|---|---|---|---|
| *Time: 0 days* | | | | | | |
| Tablet 1 | 156.0 | 0.085 | 312.0 | 0.17 | 96.0 | 0.068 |
| Tablet 2 | 170.8 | 0.154 | 341.7 | 0.31 | 105.1 | 0.124 |
| Tablet 3 | 151.0 | 0.123 | 302.1 | 0.25 | 92.9 | 0.098 |
| Tablet 4 | 157.5 | 0.522 | 315.0 | 1.05** | 96.9 | 0.421** |
| Tablet 5 | 153.2 | 0.134 | 306.3 | 0.27 | 94.3 | 0.107 |
| Tablet 6 | 153.6 | 0.124 | 307.3 | 0.25 | 94.5 | 0.099 |
| AVG | | | 314.1 | 0.25 | 96.6 | 0.099 |
| SD | | | 14.27 | 0.050 | 4.39 | 0.0202 |
| *Time: 30 days* | | | | | | |
| Tablet 1 | 158.7 | 0.091 | 317.4 | 0.18 | 97.7 | 0.073 |
| Tablet 2 | 153.8 | 0.128 | 307.6 | 0.26 | 94.6 | 0.103 |
| Tablet 3 | 157.7 | 0.164 | 315.3 | 0.33 | 97.0 | 0.131 |
| Tablet 4 | 157.4 | 0.159 | 314.7 | 0.32 | 96.8 | 0.127 |
| Tablet 5 | 155.9 | 0.143 | 311.7 | 0.29 | 95.9 | 0.115 |
| Tablet 6 | 153 | 0.187 | 306.0 | 0.37 | 94.1 | 0.150 |
| AVG | | | 312.1 | 0.29 | 96.0 | 0.117 |
| SD | | | 4.55 | 0.066 | 1.4 | 0.0267 |
| *Time: 60 days* | | | | | | |
| Tablet 1 | 161.4 | 0.317 | 322.9 | 0.63 | 99.3 | 0.254 |
| Tablet 2 | 150.5 | 0.187 | 301.0 | 0.37 | 92.6 | 0.150 |
| Tablet 3 | 156.9 | 0.287 | 313.8 | 0.57 | 96.6 | 0.231 |
| Tablet 4 | 152.6 | 0.193 | 305.2 | 0.39 | 93.9 | 0.155 |
| Tablet 5 | 150.9 | 0.343 | 301.7 | 0.69 | 92.8 | 0.275 |
| Tablet 6 | 148.6 | 0.276 | 297.1 | 0.55 | 91.4 | 0.221 |
| AVG | | | 307.0 | 0.53 | 94.4 | 0.214 |
| SD | | | 9.64 | 0.129 | 2.97 | 0.0516 |
| *Time: 90 days* | | | | | | |
| Tablet 1 | 153.8 | 0.272 | 307.6 | 0.54 | 94.6 | 0.218 |
| Tablet 2 | 155.4 | 0.325 | 310.9 | 0.65 | 95.7 | 0.261 |
| Tablet 3 | 159.0 | 0.251 | 318.0 | 0.50 | 97.9 | 0.201 |
| Tablet 4 | 153.4 | 0.318 | 306.7 | 0.64 | 94.4 | 0.255 |
| Tablet 5 | 154.5 | 0.381 | 309.0 | 0.76 | 95.1 | 0.306 |
| Tablet 6 | 157.4 | 0.314 | 314.8 | 0.63 | 96.9 | 0.252 |
| AVG | | | 311.2 | 0.62 | 95.7 | 0.249 |
| SD | | | 4.42 | 0.091 | 1.36 | 0.0364 |
| *Time: 120 days* | | | | | | |
| Tablet 1 | 170.2 | 0.346 | 340.4 | 0.69 | 104.7 | 0.278 |
| Tablet 2 | 157.4 | 0.170 | 314.8 | 0.34 | 96.9 | 0.136 |
| Tablet 3 | | | | | | |
| AVG | | | 327.6 | 0.52 | 100.8 | 0.207 |
| *Time: 150 days**** | | | | | | |
| Tablet 1 | 173.3 | 0.493 | 346.5 | 0.99 | 106.6 | 0.396 |
| Tablet 2 | 158.5 | 0.328 | 316.9 | 0.66 | 97.5 | 0.263 |
| Tablet 3 | | | | | | |
| AVG | | | 331.7 | 0.82 | 102.1 | 0.329 |

*325 mg aspirin = 249.2 mg salicylic acid

** outlier, omitted from statistics

*** 40°C and 75% RH