FORMULATION DEVELOPMENT OF A POLYMER-DRUG MATRIX WITH A CONTROLLED
RELEASE PROFILE FOR THE TREATMENT OF GLAUCOMA

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ABSTRACT

Formulation Development of a Polymer-Drug Matrix With a Controlled Release Profile for the Treatment of Glaucoma

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Glaucoma is the leading cause of blindness in the United States accounting for 9-12% of all cases of blindness. Currently, the front line treatment for glaucoma are prostaglandins that may have to be taken up to several times a day. Even with proper treatment, roughly 11% of the patients using the treatment are non-compliant and lose their vision. In this project, ForSight Laboratories has developed a pharmaceutical drug delivering implant with the capability of sustaining long-term release of a prostaglandin as a new way to treat the condition. This project reports the product development of a polymer drug matrix with a controlled release in order to better treat glaucoma. Accompanying product development, a mathematical model was created in order to strengthen the understanding of the dosage profile and to predict long term dosages.

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1. Background of Project

Glaucoma is the leading cause of blindness in the United States and typically affects people over the age of 60. It is estimated that between 1 and 3 percent of the white and Asian population and between 3 and 9 of the black population will develop primary open angle glaucoma (POAG), the most common form of glaucoma. By 2020, 600,000 people worldwide are estimated to go blind from the disease annually.

Intraocular pressure (IOP) is responsible for maintaining the globular shape of the eye and plays a key role in glaucoma. IOP is determined by three factors:

1. The rate of aqueous humor production.
2. Resistance to aqueous outflow across the trabeculum, especially in the juxtacanalicular meshwork, and
3. The level of episcleral venous pressure.

Patients typically exhibit fluctuations in IOP throughout the day. Normally the IOP is in a state of equilibrium fluctuating between 12 and 20mmHg. Typical daily IOP profiles are seen in Figure 1.1. Some patients exhibit a morning rise, where their IOP is significantly elevated in the morning. Others exhibit an inverse IOP variation, with an afternoon rise of IOP, while others may exhibit a biphasic diurnal change in IOP with two distinct IOP rises and falls during the day

Figure 1.1 Diurnal Fluctuations in IOP (Nema, 2012)

Glaucoma is a group of conditions that affect the optic nerve. In the majority of cases, damage to the optic nerve is caused by increase in IOP due to inadequate flow of aqueous humor, as illustrated in Figure 1.2.

Figure 1.2 Pressure Inside the Eye Due to Aqueous Humor Build-Up (Samuels, 2013)

Aqueous humor is produced inside the anterior chamber of the eye and flows through the interior and posterior chambers. The majority (85-95%) of outflow from the eye occurs through the trabecular meshwork-Schlemm's canal-venous system route in the anterior chamber of the eye. A closer look at the anterior chamber is illustrated in Figure 1.3 below. The angle of the anterior chamber is necessary in understanding the mechanisms of glaucoma. The angle is created between the anterior chamber being

anteriorly bounded by the posterior surface of the cornea and posteriorly by the anterior surface of the iris and the anterior surface of the lens. The angle of the anterior chamber is a peripheral recess formed by the root of the iris and part of the ciliary body (Figure 1.3).

Figure 1.3 Anatomy of the Anterior Chamber and its Angle (Nema, 2012)

While surgical treatments for glaucoma are available, glaucoma medications, in the form of eye drops, are used as front-line treatments. Medications used to treat glaucoma include:

1. Prostaglandins – latanaprost (Xalatan), bimatoprost (Lumigan) and tafluprost (Zioptan)
2. Beta-Blockers – timolol (Timoptic, Betimol)
3. Carbonic Anhydrase Inhibitors – dorzolamide (Trusopt)
4. Alpha Agonists – apraclonidine (Iopidine) and brimonidine (Alphagen)

Prostaglandins are hormone like substances that help widen blood vessels by mimicking natural prostaglandins in order to increase the drainage of aqueous humor to

help reduce IOP. Prostaglandins are typically the first medication used to treat glaucoma. Beta-blockers lower the pressure inside the eye by inhibiting the production of aqueous humor. Beta-blockers are usually administered in higher dosages relative to prostaglandins because only a small amount of the drug is absorbed by the cornea while the rest enters the bloodstream and cause adverse side effects such as lowered heart rate and interference with other beta-blocker medications. Carbonic anhydrase inhibitors (CAIs) are normally prescribed when other glaucoma drugs do not work. CAIs reduce the rate of aqueous humor production and may improve blood flow in the retina and optic nerve. Alpha agonists reduce the production of aqueous humor and increase drainage.

To combat this condition, ForSight Labs has been developing a way to minimize non-compliance to current glaucoma treatments. ForSight Labs is a center for innovating ophthalmic products and aims to develop a product that will change the way glaucoma is treated. Their vision statement is reproduced below:

“ForSight Labs is focused on developing and applying solutions to improve the sight, care, and quality of life of visually impaired patients. Our environment is creative and collaborative; a place where entrepreneurs and investors work together to drive innovative technologies through concept, development, and ultimately commercialization in high-impact eye care companies

Each day millions of people rely on their vision and suffer when it is lost. There are few disabilities as impactful to quality of life as the loss of vision. The number of people

with impaired vision in the US, including blindness, is expected to more than double over the next three decades. Recent estimates of the cost of vision loss in the US exceed \$50 billion dollars annually. ForSight Labs brings together highly motivated and capable team members, clinicians and investors focused on starting and sustaining efforts to deliver innovative solutions to the ophthalmic community and the patients it serves.”

ForSight Vision5 is developing an Ocular Insert capable of treating POAG. This project report outlines the developmental phase of a product capable of applying an active pharmaceutical ingredient (API) into the eye for the sustained release of an efficacious dose over a long period of time. The goal of the pilot product is to treat Glaucoma patients by effectively decreasing intraocular pressure in the eye by 30% or greater.

This project report aims to highlight the early stages of development of a polymeric drug releasing device. Following initial development, process parameters were optimized for a larger scale production and a desired performance profile. After development of a product, the degree of control over its performance is highlighted with the application of an empirically derived mathematical model.

The goal of the project is to develop a device capable of releasing an efficacious dose of an API for at least 120 days and develop a model that could accurately (>90%) forecast the release profile of the device. The mathematical model of the release rate profile was created to address a bottleneck of R&D and minimized the length of time empirically derived data is necessary. Throughout the product development cycle,

studies were employed to test proper wash conditions and other situations to which the Insert will be subjected in hopes of formulating a controlled release. The model allowed for this bottleneck to diminish from up to 180 days to 28 days.

2. Production of an Ocular Insert

2.1. Product development

Figure 2.1 The Medical Device Development Pathway (CDRH Innovation Initiative, 2011)

In the medical device development pathway (Figure 2.1), the first step towards bringing a product to market is discovery and ideation. The regulatory process affects a significant portion of the device development pathway and should accommodate the iterative, cyclical nature of device design and development. At ForSight Laboratories, the focus is to achieve proof of concept through research and development of a product. One of the first hurdles of the development pathway begins with proof of concept. A good proof of concept should ideally be very cheap and easy to manufacture while sufficiently solving the problem at hand. The cost of the product is one factor that will determine the viability of the product and if it will move into the next stages of development.

Fabrication of the device involved five main steps: formulation, molding, assembly, washing, and packaging and sterilization. Formulation of a polymer/drug

matrix requires a delicate blend of the starting materials in order to achieve a homogenous formulation with a desired physical properties for ease of handling. Molding of the formulation is achieved by using a mold milled in a computer numerical controlled (CNC) machine and filled through a transfer press tailored to achieve an optimal fill. In order to finalize the product, the molded segments must be assembled. Assembly requires the use of an optical microscope and soldering iron to build the final ocular insert. Washing treats the product in order to reduce its bio burden and leads to a product with the desired release rate profile. Packaging and sterilization are necessary steps to finalize the product packaging prior to use.

Throughout the process, quality control maintains that the process and system under which all changes are done by maintaining a quality document system where everything is properly documented according to FDA compliance standards. Failure to adhere to quality control standards may result in failing FDA approval.

2.2. Formulation of a Drug Polymer Matrix

Silicone was chosen as a material to be used for sustained delivery of an appropriate API because of its chemical inertness, biocompatibility, ease of fabrication, and appropriate mechanical strength. Silicones can be designed with various cure chemistries to accommodate various product needs. Silicone systems can be cured by platinum catalyzed addition reactions, tin catalyzed condensation reactions, or peroxide and oxime reactions. Among all the different cure chemistries, the platinum catalyzed silicone systems contain no volatile byproducts and have fast curing rates. A platinum

catalyzed silicone system from our sourced supplier was selected for formulating sustained release products (Figure 2.2).

Figure 2.2 Silicone Cross-Linking (DOW Corning, 2013)

During the early stage of product development, a 7% drug loaded matrix produced the desired sustained release rate. The 7% drug-matrix was formulated using proprietary methods. Over time, a higher dosage with a longer release rate profile was desired. With the higher dosage form, a new formulation was developed since direct scaling up of the 7% formulation was not feasible.

The matrix approach was chosen over a reservoir approach for formulating the API into the silicone mainly due to the ease of manufacturing. The drug is mixed homogenously into the silicone and then molded into the desired geometry using well-established conventional molding equipment. Sustained release formulations with a range of drug loadings in silicones of different hardness have been evaluated.

2.3. Molding

Initially, molds were produced in batches of 20 segments. Molding development investigated diameters as well as designs of the final product. As manufacturing was developed, a higher production rate was desired resulting in a 40-up mold capable of producing double the segments per transfer press cycle. The silicone segments were injection molded and cured at elevated temperature using quality control approved process instructions as guidance.

2.4. Assembly

After the silicone formulation is molded into segments, they must be assembled into the final product. For every ocular insert produced, two segments are needed. Assembly requires the proper training of operators in order to have a high degree of reproducibility. Manufacturing development introduced more automated aspects of the process; however, operators remained essential to producing a viable ocular insert (Figure 2.3).

Figure 2.3 Assembly Process

2.5. Wash

Once the product is assembled, each insert is treated in order to produce a final product with the desired release rate profile. The development of the wash method was a large focus of the research and development phase. The ideal release rate has a zero-order profile over the length of time that drug is to be released. This is normally achieved through a reservoir system where the reservoir constantly feeds drug through an inert shell to the media. The inert shell is necessary to act as a rate limiting gradient; otherwise a high burst of drug would be seen. Since the design of the product utilizes a drug matrix instead of a reservoir system, an initial burst of drug was unavoidable. In order to mitigate the burst, washing is necessary. It was found that washing in water at elevated temperature for several days was needed to achieve the desired release rate of API at early time periods.

2.6. Packaging and Sterilization

Each ocular insert was then packaged in a plastic tray and sealed in a foil pouch as shown in Figure 2.4. The packaged inserts were then sterilized via irradiation at a commercial e-beam facility at a sterilizing dose of 17.5 kGy.

Figure 2.4 Pouching

3. Product Testing

Test methods were developed to assure that each insert is made as uniformly as possible. The two main modes of testing the chemistry of the product are through Content Uniformity and Assay and Impurities Determination, and Release Rate testing. Generic results in the form of high performance liquid chromatography (HPLC) chromatograms are included to show what typical responses would be from the HPLC outputs. Actual results can be seen in the model development sections of this report.

3.1. Content Uniformity and Assay and Impurities Determination

3.1.1. Background

An HPLC analytical assay method for determining the API content and related impurities in Ocular Inserts was developed. The API and its impurities are analyzed by gradient reversed-phase HPLC with UV detection at 210nm.

3.1.2. Methods and Materials

An Agilent 1100 High Pressure Liquid Chromatographic System consisting of a high pressure pump, and inline degasser, a column compartment with thermostat, an autosampler, a UV absorbance detector, and an automated data collection system was used for sample analysis. The HPLC column consisted of a Zorbax Eclipse Plus C-18, 3.5µm, 4.6mm X100mm. All solvents used were HPLC grade. The API and API related impurities and standards were supplied by the API manufacturer.

3.1.3. Procedure

Mobile phase A for the HPLC was methanol/acetonitrile/water (10/10/80 v/v/v) with 0.05% H₃PO₄. The solution was mixed well prior to use.

Mobile phase B for the HPLC was methanol/acetonitrile/water (10/40/50 v/v/v) with 0.05% 85% H₃PO₄. The solution was mixed well prior to use.

Diluent Solution was methanol/acetonitrile/water (14/14/72 v/v/v). The solution was mixed well prior to use.

API reference standard was prepared at a concentration of ~150µg/mL. This was achieved by accurately weighting 7.50mg of API into a 50mL volumetric flask. The flask was filled up half way with diluent solution and diluted to the mark with water (the diluent amount is negligible and aids the dissolution of API in the solvent). Two standards were produced in the same fashion and labeled as “Working Standard” and “Check Standard.” The nominal concentrations of the standards were determined using the following equation:

$$\text{Standard concentration (}\mu\text{g/mL)} = \frac{W_s \times P \times 1000}{V},$$

Where:

W_s = Recorded weight of API or Ref Standard (mg)

P = Purity of API based on Certificate of Analysis (CofA) for that particular lot

V = Size of the volumetric flask (mL)

1000 = conversion factor for mg to μg

An LOQ (Limit of Quantitation) Standard was prepared at a concentration of $\sim 0.15\mu\text{g/mL}$. Into a 50mL volumetric flask, 50 μL of API Stock Standard solution ($\sim 150\mu\text{g/mL}$) was pipetted. The flask was diluted with Diluent Solution and mixed well prior to use.

API resolution solutions of the impurities were prepared by first preparing stock solutions at a $\sim 10\mu\text{g/mL}$ concentration by pipetting 10 μL of API related impurity stock solutions into 10mL of 2-propanol (IPA) in a glass vial and mixed well prior to use. Resolution solutions were prepared by pipetting 40 μL of the API related impurity solutions into an HPLC vial, 20 μL of API stock standard solution ($\sim 150\mu\text{g/mL}$) and 170 μL of water into the same vial. The vial was mixed using a vortex shaker prior to use.

For content uniformity analysis, samples were prepared by placing $\sim 70\text{mg}$ of cured drug-matrix into a 40mL glass vial referred to as the stock sample vial. To each vial, at least 20mL of dichloromethane (DCM) was added and the vial was sonicated for 100 minutes. All pieces of the drug-matrices were placed into 40mL glass vials already containing 5mL of DCM. The 40mL vials were sonicated for 10minutes and mixed for 5 seconds. The 5mL solutions were transferred into the 20mL solutions. The solutions were then dried at 37°C inside a fume hood by utilizing nitrogen gas to expedite the evaporation process. After the samples were fully dried, a glass pipette was used to reconstitute the residual with 25mL of methanol. The caps were placed on and tightened and sonicated for 5 minutes to achieve complete dissolution. This solution

was stored at 2-8°C when not in use. Final sample preparation involved diluting 1mL of the sample solution with 2mL of water.

For assay and impurities, up to 10 individual samples were combined as a composite. Drug-matrices were cut into sizes which fit into a 40mL glass vial. At least 30mL of DCM was added into glass vials in order to completely immerse the pieces. The vials were capped tightly and sonicated for 100minutes. Sonication steps identical to content uniformity were followed (e.g. 30mL + 5mL DCM). Final solution was prepared by adding 1mL of the stock sample to a 10mL volumetric flask. The flask was filled with Diluent solution to volume.

The HPLC chromatographic conditions were a flow rate of 0.7mL per minute with an injection volume of 20µL, a column temperature of 50°C, a detection wavelength of 210nm, and a total run time of 20minutes. (Due to the use of a previously approved pharmaceutical, the known impurities generated have an absorbance at ~190nm. Since this wavelength tends to be very noisy when using a photodiode array detector, a more controllable wavelength was used). The gradient program is shown below in Table 3.1:

Table 3.1 Gradient Program of Mobile Phase Mixing.

Time (min)	% Mobile Phase A	%Mobile Phase B
0	95	5
1	95	5
5	40	60
16	40	60
17	95	5
20	95	5

Chromatographic injection procedure followed equilibrating the HPLC system with mobile phase until a stable baseline is achieved. An injection of the working standard solution (~150µg/mL) may be done prior to starting the HPLC sequence to verify the retention time, USP tailing factor, and USP plate counts of the API peak. Mobile Phase A was injected at least once, followed by an injection of the diluent solution to ensure no interference with the API retention time. Sensitivity solution was injected to evaluate the method's sensitivity.

System Suitability

System Suitability parameters outline acceptance criteria for acceptable data. First a blank is injected to ensure no peak interference. Five working standard injections are prepared and must have a relative standard deviation of the retention time and peak areas within ±2%. Next, there is a sensitivity - LOQ check where the signal-to-noise ratio for the API yielded from the LOQ Standard injection must be ≥ 10. A standard confirmation is then necessary and is done by evaluating the response factor from the check standard injection for the API; it must be within 98% - 102% of the average response factor from the 5 replicate working standard injections. The percent difference

$$\% \text{ Difference} = \frac{\text{Peak Area of Check Standard} \times \text{Conc. of Working Standard}}{\text{Avg. Peak Area of Workign Standard Injections} \times \text{Conc. of Check Standard}} \times 100$$

The tailing factors of the API peak from all working standard injections must be ≤ 2 . The column efficiency is then checked by analyzing the column theoretical plate counts for the API peak from all the Working Standard injections and must be $N \geq 2000$. The resolution factor for the API related impurity peaks relative to the API peak must be ≥ 1.5 . The % difference of the peak areas for each bracketing standard must be $\leq 2\%$ of the average peak area from the 5 replicate Working Standard injections.

Sample calculations

Measured API Content (μg)

Calculate the response factor for each Working Standard

$$RF = \frac{C_{Std}}{A_{Std}}$$

Where:

RF = Response factor (concentration/peak area)

C_{Std} = Expected API concentration in Working Standard ($\mu\text{g/mL}$)

A_{Std} = Peak area of API for Working Standard

The concentration of the sample solution is calculated from the average response factor of the standard curve.

$$C_{Smp} = A_{Smp} \times RF_{Avg}$$

Where:

C_{Smp} = Measured API concentration in sample ($\mu\text{g/mL}$)

A_{Smp} = Peak area of API in sample (provided by HPLC)

RF_{Avg} = Average of the five response factors calculated for each Working Standard solution.

The total API content in μg is calculated by multiplying the sample concentration by the total volume of MeOH and dilution factor.

$$\text{Measured API Content } (\mu\text{g}) = C_{Smp} \times V_{Smp} \times DF$$

Where:

C_{Smp} = Measured API concentration in sample ($\mu\text{g}/\text{mL}$)

V_{Smp} = Total volume of MeOH (e.g., 25 or 35 mL)

DF = Dilution factor (e.g., 3 or 10)

API Assay

The assay value for each content uniformity and assay sample is calculated by:

$$\text{Assay} = \frac{\text{Measured API Content } (\mu\text{g}) \times 100}{\text{Label Claim } (\mu\text{g})}$$

Where:

For pre-cured mix and cured segments: Label Claim = Weight of sample x %API Loading

For Ocular Inserts: Label Claim = as specified in Material Specification

Impurity Calculations

HPLC chromatograms of the API assay samples are compared to the HPLC chromatograms of the blanks (Diluent Solution and Mobile Phase A). % Impurity are calculated based on the peak area of all peaks detected $\geq 0.1\%$ peak area in the analysis region of the chromatogram. The API and API related impurities, along with any

extraneous peaks that meet the aforementioned criteria in the assay chromatograms of the samples must be accounted for in the total peak area.

For each of the peaks detected, calculate its % purity by using the following formula:

$$\% Purity = \frac{Peak Area \times 100}{Total Peak Area} - \% Impurities$$

For known impurities, a response factor was determined relative to the main API response factor and used to calculate % Impurities.

3.1.4. Results and Discussion

Typical chromatograms achieved when analyzing samples for content uniformity and assay and impurities are reproduced below.

Figure 3.1 Chromatogram of a Blank

Figure 3.2 Chromatogram of API Working Standard Solution (150 µg/mL)

Figure 3.3 Chromatogram of LOQ (0.15 µg/mL)

Figure 3.4 Chromatogram of API and Impurities

Figure 3.5 Chromatogram of Assay Sample

3.2. Release Rate Kinetics

3.2.1. Background

Determining the drug release rate is achieved in a method similar to the assay and impurities methods. The API content in elution media at different time points was analyzed by a 5 minute HPLC. The release rate media were replaced with fresh 5mL of 0.5% PBS/SDS solution at each testing time-point.

The purpose of this test method is to determine drug release rate ($\mu\text{g}/\text{day}$). The average daily drug release rate ($\mu\text{g}/\text{day}$) as well as the cumulative API released over an extended period will be determined by an *in vitro* test method developed by Forsight Vision5. API release is analyzed by reverse-phase HPLC with UV detection at 210 nm

3.2.2. Methods and Materials

An Agilent 1100 High Pressure Chromatographic System as described previously was used for sample analysis. Rainin Pipet-Lite series L-5000, L-1000, L-200, and L-20 pipets were used. A calibrated Mettler Toledo XS105 was used. An incubator set to 37°C was used to store samples. Class A volumetric glassware was used. Final samples were stored in HPLC vials with PTFE/Silicone Pre-Slit Septa caps. Reagents used include HPLC grade water, HPLC grade acetonitrile, HPLC grade methanol, HPLC grade phosphoric acid, phosphate buffered saline (PBS) pH 7.4, sodium dodecyl sulfate (SDS), and reference standards of API were used.

3.2.3. Procedure

Release rate media was prepared by using 0.01M PBS solution with 0.05% SDS. Ocular inserts were weighed prior to use and placed in 15mL plastic vials. Into each plastic vial, 5mL of release media was added and the vials were capped. The start time was begun and considered as $t=0$. The vials were incubated at 37°C. At each of the sampling time points, samples were taken within 2 hours of the specified time point. The vials were gently swirled to ensure sample homogeneity. The release media was transferred from the sample vial into a separate clean vial and submitted for HPLC

analysis. Analyzed samples were stored indefinitely at ambient temperatures. To the empty sample vials, and additional 5mL of release media was added. Incubation was continued at 37°C in an incubator until the next sampling time point. The amount of API obtained was recorded. The drug release rate ($\mu\text{g}/\text{day}$) and the cumulative amount was calculated at each time point.

HPLC diluent and API standards were prepared as following the method outlined in the assay and impurities section of testing. The mobile phase was methanol/acetonitrile/water (10/37/53, v/v/v) with 0.05% of 85% H_3PO_4 . The increase in polarity of the solvents relative to the Content Uniformity and Assay and Impurities Determination in section 3.1 is utilized in order to increase the throughput of any drug particles. The method utilized a 5 minute isocratic run time. Calculations of peak areas to release rates were carried out in the same fashion as section 3.1.

3.2.4. Results and Discussion

The resulting peak areas from the chromatograms were used to calculate release rates. The release rate profiles were determined as $\mu\text{g}/\text{day}$ in order to track the dosage of drug released into the eye. The release rate values are crucial to model development.

Figure 3.6 Chromatogram of Mobile Phase

Figure 3.7 Chromatogram of LOQ (0.15 µg/mL)

Figure 3.8 Chromatogram of API Working Standard Solution (15 µg/mL)

Figure 3.9 Chromatogram of Release Solution Sample

4. Product Development

After proof of concept has been established, and bench-top production has begun, the growth of the company occurs with pre-clinical investigations, regulatory filings, and clinical studies. During this stage, the goal for product development is to develop a product that can be made reproducibly with high quality so that pre-clinical and clinical evaluations generate valid results. While design changes fall under the realm of engineering, formulation and wash development fell under the realm of chemistry.

4.1. Formulation Development

Two formulation changes done to the product while scaling up batch production involved increasing the drug dose and changing the Durometer hardness of silicone. A higher drug loading was necessary in order to achieve a desired release rate. With the 7% formulation, the product was only capable of sustaining the desired release rate for 3 months. With higher drug loading, the product gives a higher release rate sustainable for up to 6 months. Saturation of the polymer matrix with the higher drug loading required different properties from the silicone in order to better contain the drug matrix.

4.1.1. Effect of Drug Loading on Release Rate

Formulation development first started with a Shore 10A durometer silicone. The loading of API into this silicone was varied from 5% up to 20%. Silicone segments with different drug loading were molded and API release rates monitored over a period of 3-6 months. As anticipated from a matrix based formulation, there was an apparent

"initial burst" of drug, followed by a gradual decrease of release rate, eventually reaching a sustained steady-state level over time.

The drug release rate was found to increase with an increase in drug loading, as shown in Figure 4.1. This appears to indicate concentration gradient driven drug diffusion across the silicone matrix

Figure 4.1 Release Rate of API as a Function of Drug Loading

A working hypothesis: The higher drug release rate for higher drug loading may be due to the higher drug concentrations near the surfaces of ocular inserts. In addition, as more drug gets loaded and dispersed in the insert, more "drug channels" may be formed in the silicone matrix that would facilitate drug release from the inner portion of the Ocular Insert, as illustrated in Figure 4.2.

Figure 4.2 Channel Formation in the Silicone Matrix Over Time (t)

The drug release rate continues to decline over time even though the estimated cumulative drug release over the time period studied is around 16% drug loading, indicating that the distance drug molecules need to travel from the inner bulk of the insert to the surface also likely plays a role in drug release rate.

Among all the different loadings in this silicone, 20% drug load appeared to meet the target drug release rate profile. However, the 20% API in these soft silicone inserts exhibited inconsistent mechanical properties and also appeared difficult to remove from the mold without breaking.

4.1.2. Effect of Different Silicones on the Release Rate

As an effort to improve the mechanical properties and manufacturability of the Ocular Inserts containing 20% drug load, a different silicone with the same cure properties, a higher durometer was tested with a Shore 30A hardness rating, and a tensile strength of 1350 psi compared to 750 psi for the initial 10A silicone (amongst other physical property differences). The silicone segments prepared at 20% load in this harder silicone appeared to have significantly improved mechanical strength and were

also easier to handle during manufacturing. Due to proprietary constraints, these two silicones will solely be referred to as 10A or 30A silicone.

The surface morphologies of the silicone segments prepared with 10A silicone vs. 30A silicones are shown in Figure 4.3. It appeared that the silicone segments made with the harder silicone have much smoother surfaces than those made with the softer silicone.

Figure 4.3 Surface Morphology of Silicone Segments Containing 20% API in Alternative Silicones

Representative drug release rates of silicone segments containing 20% API in each of the silicones are presented in Figure 4.4. Both the silicones appear to result in similar release rate profiles, suggesting that silicone physical property differences have little impact on drug release from the silicone matrix.

The slightly higher initial burst on day 1 for the softer silicone formulation may be related to surface deformities, which might have led to an effective increase in total surface area. A higher standard deviation in release rate is also observed for 20% API in the softer silicone, further supporting that a harder silicone is a better option for

formulating higher drug load because of more consistent drug release rate, less surface deformities, improved mechanical properties and ease of manufacturability.

Figure 4.4 Release Rate of Ocular Insert Made with Silicones 10A and 30A

4.2. Effect of Wash on the Release Rate

Once molded and assembled, the insert is treated with a washing step. Different wash conditions produced different release rates. After the wash method was established, modeling the release rate could be done in order to develop a more understandable product profile.

Washing procedures were studied with Ocular Inserts and Silicone Segments with the goal of reducing the initial burst and obtaining a zero-order release rate profile. The results of the development of washing studies are shown below.

4.2.1. Unwashed 7% API, 10A Silicone

The release rate of API from inserts made with 10A silicone and 7% drug loading, without washing is shown below in Figure 4.5.

Figure 4.5 Unwashed Release Rate

While this design demonstrated a potentially acceptable release rate profile, a lower initial release rate was desired. The goal of the following studies was to find the ideal washing conditions that would reduce the Day 1 burst and achieve a zero-order release rate profile.

4.2.2. 7% API/10A Silicone Matrix Water Washing Studies

Silicone Segments made with 10A silicone and 7% API loading were washed for different lengths of time with water, followed by a 15 minute 70% IPA wash and a 1 minute 70% IPA rinse. The results for the non-irradiated silicone segments are shown below in Figure 4.6.

Figure 4.6 Effect of Water Wash Length on Release Rate

Silicone segments washed with water have a lower burst when compared to samples washed with IPA only (see Figure 4.7). The results also indicated that a longer water wash will result in a lower initial burst and release rate. However, the effect of this appears to be lessened as the wash length increases (i.e., there is a larger difference between a 20 hour and 48 hour water wash compared to the difference between the 48 hour and 96 hour water wash).

Figure 4.7 Reductions in Burst due to IPA Wash Versus Water Wash

A further study was initiated to find the ideal water wash length that would reduce the initial burst to an appropriate level while allowing a reproducible manufacturing wash procedure with. Ocular Inserts in this study were made with 7% API in a 10A matrix.

The washing container used for all previous studies that utilized washing, either with IPA or water, was a large glass jar (unless otherwise specified, as for individually washed samples). Samples would be placed inside the same jar and the appropriate wash medium would be added.

A Washing Tray, which would segregate all Ocular Inserts during washing, was introduced in order to improve the manufacturing flow of the product. A large polypropylene washing basin was used to hold the Washing Tray, and the basin was then filled with the washing medium. This basin was then stored in a shaking incubator

set at 60°C and 55 RPM for the duration of the wash. All Inserts were washed and then irradiated.

Figure 4.8 Effect of Water Wash Length on Release Rate Using Washing Manufacturing Conditions

The data shown in Figure 4.8 demonstrates that both a 48 and 72 hour water wash reduce the initial burst from Ocular Inserts, while still maintaining a long term release rate profile comparable to unwashed samples. The 48 hour wash was chosen due to ease of manufacturing.

4.2.3. 20% API/30A Silicone Matrix Studies

In order to produce a product that could deliver an acceptable dose for 6 months rather than 3 months, a higher drug loading of the silicone matrix was attempted. This was expected to increase the release rate, but also increase the initial burst of drug from the Inserts. Therefore, studies were conducted to find the ideal washing conditions

to maintain the increased release rate of drug while keeping the initial drug burst from the device in an acceptable range.

Silicone Segments were made with 20% API loading in the 30A silicone matrix and were washed individually in glass vials containing water that were stored inside an oven set at 60°C for 48 hours. Following the water wash, samples were washed with 70% IPA for 15 minutes followed by a 1 minute 70% IPA rinse. Figure 4.9 shows the data for this study, and compares it with data from a previous 7% drug loading study with similar washing conditions.

Figure 4.9 20% Drug Load vs. 7% Drug Load Effect of Water Wash on Release Rate Comparison

This study demonstrated that increasing the drug loading from 7% to 20% increases the burst as well as the long term release rate profile. The 48 hour wash followed by the 70% IPA wash still removes enough of the API so that the initial burst is acceptable.

Although the studies described above demonstrated that a 20% API loading provides a higher release rate profile than a 7% load, and a 48 hour wash is adequate to remove the initial burst, additional testing was done to confirm the effect of wash length on release rate.

Ocular Inserts made with 19% API (though deviation from 20% occurred during formulation, release rate profiles were deemed equivalent) in a 30A silicone matrix were washed individually in plastic jars containing water that were stored inside a shaking incubator set at 55 RPM and 60°C. Samples were washed in water for different lengths of time (6 hours, 24 hours, and 48 hours), and a 15 minute 70% IPA wash at room temperature followed the water wash.

Figure 4.10 Effect of Water Wash Length on Release Rate of 19% API loaded matrix

As expected, the results demonstrated the correlation between wash length and initial release rate (increasing the wash length lowered the initial release rate), as was demonstrated by a similar study done with 7% drug loaded samples (see Figure 4.10).

The long term release rate was not significantly affected however, as the release profiles for all samples began to converge around Day 30.

The release rate of the 48 hour wash sample was also very similar to the release rate seen from the 48 hour washed samples described above, indicating repeatability

The previous studies utilizing a 20% API loading demonstrated the feasibility of using an increased drug loading to increase the long term release rate. The next step was to show that the washing process was transferrable to a larger scale 'manufacturing wash' set-up.

Ocular Inserts made with 20% API in a 30A silicone matrix were washed in a custom Teflon tray that separated all Ocular Inserts. This tray was submerged into a polypropylene basin filled with water pre-heated to 60°C, and the basin was held inside a shaking incubator set at 50 RPM and 60°C. The Ocular Inserts were washed for 48 hours in the shaking incubator. Upon removal, Ocular Inserts were washed with 70% IPA for 15 minute at ambient conditions.

Figure 4.11 Feasibility of the Manufacturing Washing Configuration for 20% API loaded product

The results shown in Figure 4.11 from the basin wash indicate that using the manufacturing washing configuration provided a release profile similar to that seen from samples washed individually. To confirm repeatability of the manufacturing wash process, 10 additional samples were tested (Figure 4.12).

Figure 4.12 Repeatability of the Manufacturing Conditions

Although the repeat samples average release rate profile was slightly higher, the basin washed and repeat basin washed samples release rate profiles fell within a relative standard deviation of 10%, as displayed in Figure 4.13 below:

Figure 4.13 20% Drug Load, 48 Hour Wash Comparison

4.2.4. Results and Discussion

While the 7% load configuration can increase the release rate profile to over 4 $\mu\text{g/day}$ through 118 days, it also produces a large burst of API. It was found that washing Ocular Inserts using 50, 70 or 99% IPA can moderate the burst significantly, although washing with 99% IPA had the potential to affect both the initial burst and the long term release more than when washing with 50 or 70% IPA. For example, washing Ocular Inserts with 50% IPA for 15 minutes can reduce the burst from approximately 110 $\mu\text{g/day}$ to 68 $\mu\text{g/day}$, while still maintaining a high release rate profile. Washing with 99% IPA also reduces the burst but lowers the overall release profile.

Though the day1 burst was reduced to 68 µg/day, it was desired to reduce the burst still further. This was accomplished by washing Ocular Inserts in water at high temperatures for an extended period of time, followed by a 15 minute 70% IPA wash. Washing in water at 60°C for 48 hours reduced the burst from approximately 68 µg/day to 18 µg/day, while maintaining the long term release rate profile.

Clinical data suggested that higher dosing was more desirable resulting in a 20% loaded product. Through testing, results indicated a long term release rate approximately double that of the 7% loading was achievable. Burst moderation was achieved with identical water wash parameters used with the 7% loaded product. For example, Ocular Inserts washed inside a water filled basin placed inside a shaking incubator set at 60°C for 48 hours produced a burst well under 60 µg/day while still maintaining a release rate profile eluting over 8 µg/day by day 92.

A previous study had shown that the day 1 drug release burst for 20% API in the 30A silicone is in the range of 200-300 µg/day, which is well above a desirable level. In order to bring the day 1 burst release of the drug to a more acceptable level, the Ocular Inserts were washed for different lengths of time in water at 60°C with continuous shaking. The data in Figure 4.14 show that a 10-hour wash brought the burst release of drug on day 1 to approximately 70 µg/day, while the 48-hour and 72-hour washes brought the day 1 burst release to approximately 30-40 µg/day, an acceptable level. As both 48-hr and 72-hr water washes result in satisfactory day 1 burst profiles, the 48-hr

wash time was recommended as a good overall balance for product performance and manufacturing efficiency.

Figure 4.14 Effect of Water Wash Time on Release Rate of 20% API loaded product

4.3. Manufacturing Reproducibility

The 20% API in a 30A silicone formulation has been prepared multiple times using the same lot of drug substance and different lots of silicone to evaluate batch to batch reproducibility. The data in Figure 4.15 show that three different batches of Ocular Inserts manufactured with the recommended 48-hr water wash followed by 15-min 70% IPA rinse provide very similar release rate profiles

Figure 4.15 Reproducibility for Three Different Batches

A 20% API in a 30A silicone formulation has been successfully developed. The formulation together with an appropriate manufacturing process has achieved acceptable assay and impurity levels, and desirable drug release profile. A water wash at 60°C for 48 hours incorporated into the manufacturing process prior to pouching has been found to bring down the Day 1 initial burst to a desirable level. A reproducible drug release profile has been demonstrated for at least three consecutive development batches.

5. Understanding the Mechanisms of Release

5.1. Purpose

Mathematical modeling of the release rate of materials from polymer matrices is of particular interest to formulation chemists. One of the goal when developing any medical device is to develop the ability to control the properties of any system. Control of the formulation allows for optimization of the product; optimization allows for a tighter parameters during the manufacturability of the product. If the release rate of the device can be accurately predicted, it would show a certain degree of control over the system.

5.2. Controlled Release of Diffusion Based Processes

Diffusion is the transport of small molecules by random molecular motion of individual molecules from an area of high concentration to low concentration. Figure 5.1 below shows a typical schematic of this phenomenon analogous to the system developed by ForSight Labs. Diffusion is a spontaneous process; it increases entropy, decreases Gibbs free energy, and is therefore isothermal dynamically favorably.

Figure 5.1 Drug Release Mechanism Analogous to System Developed At ForSight

There are several factors that contribute to the transport process including the nature of the polymer, nature of cross links, effect of plasticizers, nature of penetrants, presence of fillers, effect of temperature, and presence of other variables that may be included in the system. The nature of the polymer includes the extent of unsaturation, degree of crystallinity, and the nature of substituents.

Different degrees of crosslinking density of the same polymer results in different physical properties such as glass transition temperatures (T_g). An increase in diffusion coefficient is seen with decreasing T_g (George, 2001). Diffusivity has been shown to decrease linearly with an increase in crosslink density until a maximum degree of crosslinking is reached resulting in a leveling off effect of diffusivity (Barrer, 1948). For the same polymer with the same crosslink density, diffusion depends on the nature of crosslinks. In addition different solvent solutions of drug release affect the release rate differently. For example, benzene solutions swell more than corresponding bulk crosslinked networks having the same crosslink density which would decrease the rate of diffusivity (George, 2001).

Additional factors that contribute to transport processes are still significant, but fall outside the scope of the variables affecting the drug polymer matrix discussed in this report. For example, addition of plasticizers to a polymer results in an increased segmental mobility which in turn usually increases penetrant transport, e.g. in the presence of solvents (George, 2001). The nature of the penetrant determines the degree to which the molecule diffuses from the polymer matrix. Fillers and temperature

effects may increase or decrease the diffusivity of the molecule as well. The effects of all these variables that affect the release rate are captured mathematically in the diffusion coefficient of the model. The larger the diffusion coefficient, the higher the rate of release.

The aim of this project was to establish an understanding of the mechanisms relating solubility and transport in the polymer membrane to their molecular properties. The initial driving factor of the silicone-matrix drug delivery system developed at ForSight is diffusion. However, as at some point in time, the mechanism of diffusion is overcome by the formation of channels due to the saturation of the matrix by the API. The kinetic model intends to develop a quantitative mechanism for determining the diffusion of API from the silicone matrix as well as the potential formation of a channel guided release mechanism.

The development of the model was necessitated by a need to interpret the response of release rate. The model was developed at a time when the focus of research and development was to optimize the washing parameters in order to determine the desired release rate profile. The main issue with release rate determination was that it was limited to empirically derived real time data. Since the goal was to achieve a sustained release of API over many months, this became the main bottleneck of R&D. As the amount of data grew, a need to understand how changes in the wash would affect the overall release profile was necessary and resulted in the

development of the predictive model. This model minimized the time needed to understand the results.

The objectives of designing a model for controlled drug delivery systems are to:

1. Optimize the release rate development process
2. Elucidate the physical mechanisms of drug transport
3. Aid in the design new drug delivery systems based on release expressions
4. Predict drug release rates from and drug diffusion behavior through polymers

The purpose of mathematical models is to ultimately help optimize the design of a therapeutic device to yield information on the performance of the device as well as show the degree of accuracy through predictive models, thus avoiding excessive experimentation

Figure 5.2 Release Rate Profiles of 7% and 20% Drug Loading Used for Modeling

Release rate profiles as seen in Figure 5.2 are broken down into several sections when applied for mathematical modeling. Release kinetics follow a well-defined behavior: first a rapid initial release (termed the “burst”) followed by a slow near-zero

order release rate. The goal is to develop a model that both accurately models and has the capability of predictively determines release data.

5.3. A Background of Mathematical Modeling

5.3.1. Fick's Law and its Analogous Counterparts

Adolf Fick was able to empirically derive an equation for diffusion in 1855. Inspired by many prominent scientists of his day, Fick's laws of diffusion are analogous to the laws of transport and flow developed by Darcy (flow of liquid through a porous medium), Ohm (flow of current through two points) and Fourier (flow of heat). Their respective fundamental laws are described below.

Adolf Fick was the first to propose laws that govern the transport of mass through diffusive means. In addition to inspiration indirectly drawn from Ohm, Fourier, and Darcy, Fick was directly inspired by earlier experiments in diffusion by Thomas Graham. Although Thomas Graham was unsuccessful in his efforts, Fick was able to further Graham's understanding and arrived at his successful laws of diffusion.

Fick's experiments dealt with measuring the concentrations and fluxes of salt diffusing between two reservoirs through tubes of water. His laws were primarily concerned with diffusion in fluids, because diffusion in solids was not considered possible at the time. Today, Fick's laws form the core of our understanding of diffusion in solids, liquids, and gases in the absence of bulk fluid motion (for liquids and gases). When a process does not follow Fick's laws, we refer to the process as non-Fickian.

Though Fick is credited with development of the understanding of the phenomena of diffusion, the evaluation of diffusion of solids was modeled by Noyes and Whitney in 1897 with the following equation:

$$\frac{dM}{dt} = KS (C_s - C_t)$$

where M is the mass transferred over time, t, by dissolution from the solid particle over a surface, S, under the driving force of the concentration difference ($C_s - C_t$) where C_t is the concentration at time t and C_s is the equilibrium solubility of the solute at the experimental temperature. The rate of dissolution dM/dt is the amount dissolved per unit area per unit time and can generally be expressed in units $\text{g}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$.

To better fit more complicated systems, these fundamental models have been manipulated by the incorporation of appropriate variables. Additionally, the development of these models has allowed for their application in other systems. For example, the diffusion mechanism which was first explained by Fick has since been modified by many scientists over the years into workable formulas for explaining the diffusion of pharmaceuticals. Though these models give credence to the Fick, they have been aptly renamed and are specific for their own systems. The proceeding sections gives insight into these models which have been applied to drug release from matrices.

5.3.2. Higuchi Model

The first model aimed to describe drug release from a matrix system was developed by Higuchi in 1961. Initially developed for planar systems, it was later

developed into applications that incorporated multiple geometries and porosities.

Several assumptions made by Higuchi include:

- i. Initial drug concentration in the matrix is much higher than drug solubility;
- ii. Drug diffusion takes place only in one dimension (“edge effect must be negligible”);
- iii. Drug particles are much smaller than the channels through which they travel;
- iv. Matrix swelling and dissolution are negligible;
- v. Drug diffusivity is constant;
- vi. Perfect sink conditions are always attained in the release environment.

These same assumptions are the basis for the other mathematical models discussed in this report.

The basic model described by Higuchi is expressed by the equation:

$$f_t = Q = A\sqrt{D(2C - C_s)C_s Ct}$$

where f_t is the cumulative fraction of drug in a given area at time t , Q is the amount of drug released in time t per unit area A , C is the initial drug concentration, C_s is the drug solubility in the matrix media and D is the diffusion coefficient in the matrix substance.

The fundamental understanding of application of models on release kinetics was effectively established by Higuchi. Future model developers typically have their foundation in principles that Higuchi established (Dash, 2012).

5.3.3. Korsmeyer-Peppas Model (The Power Law)

In an effort to develop a more versatile kinetic model, Korsmeyer-Peppas proposed a model based on empirically derived data to describe drug release from polymeric systems in 1983 (Korsmeyer et al 1983):

$$\frac{M_t}{M_\infty} = kt^n$$

where M_t/M_∞ is a unit less cumulative fraction of drug released at time t , k is the release rate constant and n is the release exponent. While modifications of the Korsmeyer-Peppas model enables its application to various geometries, it is principally due to the position and simplicity of the n -variable that the model is typically applied to cylindrical shaped matrices when found in the most basic form. Depending on the value of the n -variable, the characteristics of the polymer matrix can be elucidated. A value of $n = 0.5$ indicates a Fickian diffusion drug transport mechanism. For cylindrical matrices, a value of $n \leq 0.45$ is the most commonly found. A value of $0.45 < n < 0.89$ corresponds to non-Fickian transport, $n = 0.89$ for Case II relaxational transport, and $n > 0.89$ for super relaxational transport. To determine the exponent n , drug release data in the initial range of $M_t/M_\infty < 0.6$ are used to simulate the release profile. Release kinetics modeled under the Korsmeyer-Peppas method are best plotted as log cumulative percentage drug release versus log time (Dash 2012).

Table 5.1 Interpretation of Diffusional Release Mechanisms from Polymeric Films

Release Exponent (n)	Drug Transport Mechanism	Rate as a Function of Time
0.5	Fickian diffusion	$t^{-0.5}$
$0.45 < n < 0.89$	Non-Fickian transport	t^{n-1}
0.89	Case II transport	Zero Order Release
Higher than 0.89	Super case II transport	t^{n-1}

5.3.4. Hixon-Crowell Model

In 1931, Hixson and Crowell recognized that a particle's "regular" area is proportional to the cube root of its volume represented by the equation:

$$W_0^{1/3} - W_t^{1/3} = \kappa t$$

where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the remaining amount of drug in the pharmaceutical dosage form at time t and κ is a constant which incorporates the surface-volume relation.

This model is most useful in systems where there is a change in surface area and diameter of the pharmaceutical, such as in tablets. When this model is applied, release kinetics are typically viewed by plotting the cube root of drug percentage remaining in the matrix versus time. The model assumes that the diminishing dimensions of the pharmaceutical remain relative to each other (Dash 2012).

5.3.5. Weibull Model

Weibull's model is loosely based off the Weibull distribution discovered in 1951 to describe a particle size distribution. The Weibull distribution is a probability density

function which was empirically derived and which has been adapted to the dissolution/release process.

The equation used when applying the Weibull model follows the form:

$$M = M_0 \left[1 - (e)^{\frac{(t-T)^b}{a}} \right]$$

where M is the amount of drug dissolved as a function of time t, M_0 is the total amount of drug being released, T accounts for the lag time measured as a result of the dissolution process, a denotes a scale parameter that describes the time dependence, while b describes the shape of the dissolution curve progression. For $b=1$, the shape of the curve corresponds exactly to the shape of an exponential profile with the constant $k=1/a$ resulting in the equation:

$$M = M_0 \left[(1 - e)^{-k(t-T)} \right]$$

The shape of the curve becomes sigmoidal for values of $b > 1$.

One application of the Weibull model is to determine the time when 50% (w/w) and 90% (w/w) of drug released from the formula is achieved:

$$t_{(50\% \text{ or } 90\%)} = \left[-a \ln \frac{M_0 - M}{M_0} \right]^{\frac{1}{b}} + T$$

This application allows for comparison of release profiles of pharmaceuticals for product development (Dash 2012).

5.3.6. Baker-Lonsdale Model

This model was first developed by Baker and Lonsdale in 1974 from the Higuchi model and was used to describe drug release from spherical matrices such as microcapsules or microspheres. The generic equation of the model follows:

$$f_1 = \frac{3}{2} \left[1 - \left(1 - \frac{M_t}{M_\infty} \right)^{2/3} \right] \frac{M_t}{M_\infty} = k_t$$

where k corresponds to the slope. Release kinetic data is most readily applied to linearized data in the form $[d(M_t/M_\infty)]/dt$ with respect to the root of time inverse (Dash 2012).

5.3.7. Selection of an Appropriate Model

The most commonly applied models used to describe release phenomena are the Higuchi model, the Zero order model, the Weibull model, and the Korsmeyer-Peppas model. A summary of mathematical models can be seen in Table 5.2.

Table 5.2 Mathematical Models Used to Describe Drug Dissolution Curves.

Zero Order	$Q_t = Q_0 + K_0 t$
First Order	$\ln Q_t = \ln Q_0 + K_1 t$
Second Order	$Q_t/Q_\infty (Q_\infty - Q_t) = K_0 + K_0 t$
Hixson-Crowell	$Q_0^{1/3} - Q_t^{1/3} = K_1 t$
Weibull	$\log[-\ln(1-(Q_t/Q_\infty))] = b \times \log t - \log a$
Higuchi	$Q_t = K_H \sqrt{t}$
Baker-Lonsdale	$(3/2)[1 - (1-(Q_t/Q_\infty))^{2/3}] - (Q_t/Q_\infty) = K t$
KorsMeyer-Peppas	$Q_t/Q_\infty = K_k t^n$

Selection of an appropriate model can be quantified using the coefficient of determination, R^2 , which gives an appropriate fit of the model. For the determined models, the fit of the model was calculated using:

$$R^2 = \frac{SSR}{SST} = \frac{SSR}{SSR + SSE}$$

SSR is the sum of squares due to regression determined by $SSR = \sum (\hat{Y} - Y_{\text{mean}})^2$. SSE is the sum of squares due to error determined by $SSE = \sum (Y - \hat{Y})^2$. SST is the total sum of squares. Depicted in Figure 5.3, $\hat{Y}$ is the predicted value for each Y. Since regressions are not exact fittings, there usually is some difference between each Y value and the fitted Y value. Y_{mean} is the average of all empirically derived Y values.

Figure 5.3 Diagram for Determining Y-Values.

5.4. Model of 7% Drug Loading Washed in 70% IPA for 15min

5.4.1. Development of a Model

The Korsmeyer-Peppas model was chosen for developed drug-polymer matrix developed due to its ease of application and robustness when applied to cylindrical matrices. At ForSight, derived data was reported as release rate over a predetermined interval of analysis (Day 1, 2, 4, 7, 14, 21, 28, 58, 88, 118, 148, 178). The release rate data tended to result a higher value of the actual release rate due to it inherently taking a running average of the data. For example, when sampling a release rate at a 30-day interval, the value tended to be higher since it involved taking a moving average of the

previous 30-days. In order to more accurately view the data, a necessary conversion to cumulative amount was needed.

5.4.2. Results and Discussion

In order to convert the release rate data to cumulative release, an accurate measure of the total drug content was needed. The assay data in Table 5.3 shows an average device weight in mg and amount of drug in micrograms and was obtained using the Content Uniformity and Assay and Impurities determination outlined in Section 3.1 of this report. An average recovery through HPLC analysis tended to yield 97% and was used as a conversion factor to aid modeling. Resulting data is shown in Tables 5.3 and 5.4.

Table 5.3 Assay Data From 7% Drug Loaded Device

Wash Method	Device Weight (mg)	Amount of Drug in Device (µg)	97% recovery
70% IPA for 15min	64.372mg	4506.04	4370.86µg

Applying the assay data to the release rate yields the cumulative fraction of drug through the following equation:

$$\frac{Release\ Rate_2 - Release\ Rate_1}{Time\ Point_2 - Time\ Point_1} \div Amount\ of\ Drug\ in\ Device$$

Table 5.4 Release Rate Data of 7% Device and Converted Cumulative Amounts

Day	Release Rate ($\mu\text{g}/\text{day}$)	Cumulative (μg)	Cumulative Fraction
1	59.8	59.8	0.01
2	34.6	94.4	0.02
4	24.7	143.72	0.03
7	19.1	201.08	0.05
14	13.42	295.02	0.07
21	10.0	364.74	0.08
29	8.2	430.02	0.10
57	5.0	570.02	0.13
88	4.5	710.76	0.16
118	3.8	824.16	0.19
148	3.7	935.16	0.21

Figure 5.4 Cumulative Release Model Predicted Fit Versus Experimental of 7% Drug Loading Washed in 70% IPA for 15min

Application of a power regression fit according to Fick's law from the total available data and results for the Day 1-148 fit are seen in Figure 5.4. The modeled cumulative release fit is used to back calculate the release rate shown in Figure 5.5. While the model is a good fit relative to the real data upon initial view, discrepancies in release rate can be seen with the model resulting in a slightly higher predicted release rate.

Figure 5.5 Release Rate: Model Developed Versus Experimental of 7% Drug Loading Washed in 70% IPA for 15min

The full data model fit in Figures 5.4 and 5.5 show how closely the experimentally derived data follows power law functions and allowed for accurate use for predictive modeling. Because of the availability of data through day 148, predictive models could be instantly measured against real experimental data before being applied to new systems. Figure 5.6 shows the progression of the model as more time points became available relative to the empirical data.

Figure 5.6 Cumulative Release: Prediction Intervals Versus Experimental of 7% Drug Loading Washed in 70% IPA for 15min.

Predictive models utilized a maximum of data through Day 28 since the majority of the release rate burst was diminished by this point and tended to show a near zero-order release rate past this point. Additionally, sampling time points were taken at Day 1, 2, 4, 7, 14, 21, and 28. Past Day 28, sampling time points were taken every 30 days. The time cost was greater than the marginal increase in model accuracy.

The predicted cumulative fractions were roughly 5% above the modeled fit by Day 150, the resulting release rate predictions were within $3\mu\text{g}$ for the Day 7 model and $1\mu\text{g}$ for the Day 28 model. Since this difference was deemed within acceptable limits, the model was applied to other different wash conditions with different release rate profiles.

Figure 5.7 Release Rate: Prediction Intervals Versus Experimental of 7% Drug Loading Washed in 70% IPA for 15min

Graphically represented in Figure 5.7, a measurement of the fit of the models is tracked through analyzing their R^2 values as summarized in Table 5.5. The Predictive models result in a higher degree of accuracy than the full modeled fit and the Fickian Fit, though all fits are above 95% accurate. As the model utilized more data points, the

predicted fit approaches a 99% coefficient of determination. Calculation of the goodness measure of fit can be found in Appendix A.

Table 5.5 Measure of Fit of Model Based on Amount of Data

Data Range	Model	R ² of Release Rate Model vs Empirical Data
Days 1-7	$y = 0.0138x^{0.6219}$	0.976
Days 1-14	$y = 0.014x^{0.6048}$	0.984
Days 1-21	$y = 0.0141x^{0.593}$	0.986
Days 1-29	$y = 0.0143x^{0.584}$	0.987
Days 1-148	$y = 0.0152x^{0.538}$	0.976
Fickian Fit	$y = 0.0168x^{0.5}$	0.950

5.5. Model of 20% Drug Loading Washed in Water for 48hours at 60°C

5.5.1. Development of a Model

The 20% Drug/Silicone matrix presented significant challenges. By increasing the drug loading in the polymer matrix, the characteristic behavior of the silicone was significantly changed. Previously, the 7% loaded device behaved under near ideal diffusion based mechanisms. However, the 20% loaded matrix showed signs of a change in the mechanism of release due to the increase in drug loading. This change in the matrix was signaled during formulation developments where the 10A silicone was incapable of incorporating the higher drug load without affecting the physical properties of the silicone and required an alternative silicone in order to maintain structural properties post curing. In addition, the nonlinear increase in release rate that occurred between 10% and 15% drug loading indicated that a new mechanism of release may exist.

5.5.2. Results and Discussion

Table 5.6 Assay Data From 20% Drug Loaded Device

Wash	Device Weight (mg)	Amount Drug (μg)
48hrs @ 60°C	70.56	12132.0

After wash, the amount of drug in each insert averaged 12mg (Table 5.6). The resulting release rate was once again converted to cumulative fractions shown in Table 5.7.

Table 5.7 Release Rate and Cumulative Release Data from 20% Drug Loading

Day	Release Rate ($\mu\text{g}/\text{day}$)	Cumulative (μg)	Cumulative Fraction
1	36.68	36.68	0.003
2	24.42	61.11	0.005
4	22.06	105.22	0.009
7	21.21	168.86	0.014
14	18.01	294.95	0.024
22	15.18	416.37	0.034
28	13.93	499.95	0.041
60	11.35	863.25	0.071
91	9.54	1158.99	0.096
120	8.05	1275.77	0.105
150	6.86	1378.70	0.114

The final product had a significant drug load increase from 7% to 20% and was washed at 48hours at 60°C. The application of the normal model fit showed a cross between the experimental data and the regression model fit between at Day90 (Figure 5.8).

Figure 5.8 Cumulative Release Model Predicted Fit Versus Experimental of 20% Loading Washed in Water for 48hours at 60°C

While the intersection was present when viewing the data as a cumulative fraction at Day 90, the only intersection for the release rate view was at Day 30 (Figure 5.9). This overlap was investigated and theorized as one of the main reasons for the differences caused between experimentally derived and modeled data.

Figure 5.9: Release Rate Model Developed Versus Experimental of 20% Loading Washed in Water for 48hours at 60°C

The resulting predictive models deviated from experimental data by ~5% by Day 150 (Figure 5.14). This inaccuracy was investigated and attributed to a change in the release rate mechanism of the device that was not observed with the 7% loading.

Figure 5.10 Cumulative Release Model Predicted Fit Versus Experimental of 20% Loading Washed in Water for 48hours at 60°C

The cumulative release view of data tended to highlight discrepancies. Resulting in a ~4 μ g difference between empirical and predicted data by Day 150 (Figure 5.15).

Figure 5.11 Release Rate: Prediction Intervals Versus Experimental of 20% Loading Washed in Water for 48hours at 60°C

The resulting release kinetics fit of the 20% modeled fit with 48 hour wash at 60°C showed a roughly ~95% goodness of fit (Table 5.11). Calculation of the goodness measure of fit can be found in Appendix C.

Table 5.11 Measure of Fit of Model Based on Variable Amounts of Data

Data Range	Model	R ² of Release Rate Model vs Empirical Data
Days 1-7	$y = 0.003x^{0.7835}$	0.963
Days 1-14	$y = 0.003x^{0.7935}$	0.942
Days 1-21	$y = 0.003x^{0.7933}$	0.942
Days 1-28	$y = 0.003x^{0.7919}$	0.946
Days 1-150	$y = 0.0032x^{0.7449}$	0.973

6. Conclusions

Application of a direct Korsmeyer-Peppas fit as a prediction model resulted in a less than ideal fit of the actual release rates. During release rate determinations, it can be seen that regardless of the range of data used to forecast a predicted release rate, the predicted release rate values are significantly higher than the experimental values.

The first generation model involved fitting the known Korsmeyers-Peppas model. However an iteration of the model was necessary in order to achieve a higher degree of accuracy. Initially, this modification of the model was not necessary for the 7% Loading since application of the basic Korsmeyers-Peppas model showed a high degree of accuracy. For the higher 20% drug loading, a need for modification of the model was necessary, due to several competing theories as to why the power law fit no longer sufficed.

The release profile of this insert is over 180 days. This extended length of time was not something that Korsmeyer's Peppas likely accounted for when they developed their initial model. The power law fit is ideal when the cumulative release fraction is <0.6 . Even after 180 days, the 20% loaded insert only showed $<15\%$ of total drug released. This slow release is due to the low diffusion coefficient of drug in the silicone matrix. In addition, the power fit is best for Fickian diffusion based mechanisms of release. While this mechanism held true with 7% drug loading, the 20% drug loading showed a power coefficient that indicated both Fickian diffusion and a non-Fickian mode of transport as the mechanism of release. This dual mechanism may change over

time resulting in a different contribution of each mechanism during different periods of time. For example, the release mechanism may initially have been purely due to Fickian diffusion. As drug diffused over time, channels were formed within the polymer matrix. The mechanism of channel formation in this case is analogous to non-Fickian transport since Fickian diffusion is based on “random walk” of molecules. When enough drug was removed from the surface, the main mode of release was through the channels, resulting in a need to modify the power law fit in order to account for the mechanism changes. While The Korsmeyer-Peppas fit was ~95% accurate there was room to improve resulting in a second generation model.

This second generation model was a mixture of two models based off of the power law. The first model included the burst and the initial release time points. The second model took into account the later release profile. The final model was an average of the two models and resulted in higher degree of accuracy. While the model is still in development, the initial developments are shown in Appendix D.

Process optimization was achieved by the development of a model. Reduction in R&D time constraints significantly reduced the real-time nature of data release.

Model developments in the future may be able to incorporate temperature, drug loading, and solution system variables. While it has proven difficult to correlate a dependence from one system to the next (i.e. 37°C → 60°C, 7% loading → 20%, or PBS media to IPA), the developed model has the potential to be accurate in predicting the outcomes while keeping those aforementioned variables constant.

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Appendix A

7% Drug Loading, 15min 70% IPA Wash

Predictive Model Day 1-7								
$y = 0.0138x + 0.6219$								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.01	0.00	60.32	0.52	43.32	1876.4 4	-0.50	0.27
2	0.02	0.00	32.51	-2.09	15.51	240.42	2.10	4.39
4	0.03	0.00	25.01	0.31	8.01	64.18	-0.30	0.10
7	0.05	0.00	19.82	0.72	2.82	7.96	-0.70	0.52
14	0.07	0.00	15.57	2.15	-1.43	2.03	-2.20	4.64
21	0.09	0.01	12.76	2.76	-4.24	18.01	-2.80	7.59
29	0.11	0.01	11.13	2.93	-5.87	34.43	-2.90	8.60
57	0.17	0.04	9.14	4.14	-7.86	61.86	-4.10	17.10
88	0.22	0.06	7.46	2.96	-9.54	91.08	-3.00	8.74
118	0.27	0.08	6.52	2.72	-10.48	109.93	-2.70	7.37
148	0.31	0.09	5.91	2.21	-11.09	122.98	-2.20	4.89
Sum		0.03		19.31	19.13	2629.3 2		64.20

Predictive Model Day 1-14								
$y = 0.014x + 0.6048$								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.01	0.00	61.19	1.39	44.19	1952.9 4	-1.40	1.94
2	0.02	0.00	31.87	-2.73	14.87	221.02	2.70	7.47
4	0.03	0.00	24.23	-0.47	7.23	52.29	0.50	0.22
7	0.05	0.00	19.00	-0.10	2.00	4.00	0.10	0.01
14	0.07	0.00	14.77	1.35	-2.23	4.98	-1.30	1.82
21	0.09	0.00	11.99	1.99	-5.01	25.14	-2.00	3.94
29	0.11	0.01	10.40	2.20	-6.60	43.61	-2.20	4.82
57	0.16	0.03	8.46	3.46	-8.54	73.00	-3.50	11.94
88	0.21	0.05	6.84	2.34	-10.16	103.26	-2.30	5.47
118	0.25	0.06	5.94	2.14	-11.06	122.35	-2.10	4.57
148	0.29	0.07	5.36	1.66	-11.64	135.40	-1.70	2.77
Sum		0.02		174.73	13.04	2737.9 9		44.98

Predictive Model Day 1-21								
y = 0.0141x0.593								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.01	0.00	61.63	1.83	44.63	1991.76	-1.80	3.35
2	0.02	0.00	31.33	-3.27	14.33	205.38	3.30	10.69
4	0.03	0.00	23.63	-1.07	6.63	43.95	1.10	1.15
7	0.04	0.00	18.39	-0.71	1.39	1.94	0.70	0.50
14	0.07	0.00	14.19	0.77	-2.81	7.89	-0.80	0.59
21	0.09	0.00	11.44	1.44	-5.56	30.86	-1.40	2.09
29	0.10	0.01	9.88	1.68	-7.12	50.63	-1.70	2.84
57	0.16	0.02	7.99	2.99	-9.01	81.17	-3.00	8.95
88	0.20	0.04	6.42	1.92	-10.58	111.91	-1.90	3.69
118	0.24	0.05	5.55	1.75	-11.45	131.04	-1.80	3.07
148	0.27	0.06	5.00	1.30	-12.00	144.00	-1.30	1.69
Sum		0.02		74.80	8.47	2800.53		38.59

Predictive Model Day 1-29								
y = 0.0143x0.584								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.01	0.00	62.50	2.70	45.50	2070.55	-2.70	7.31
2	0.02	0.00	31.19	-3.41	14.19	201.33	3.40	11.63
4	0.03	0.00	23.38	-1.32	6.38	40.66	1.30	1.75
7	0.04	0.00	18.10	-1.00	1.10	1.20	1.00	1.01
14	0.07	0.00	13.88	0.46	-3.12	9.72	-0.50	0.21
21	0.08	0.00	11.14	1.14	-5.86	34.32	-1.10	1.30
29	0.10	0.00	9.59	1.39	-7.41	54.89	-1.40	1.94
57	0.15	0.02	7.72	2.72	-9.28	86.16	-2.70	7.39
88	0.20	0.03	6.17	1.67	-10.83	117.25	-1.70	2.79
118	0.23	0.04	5.32	1.52	-11.68	136.43	-1.50	2.31
148	0.26	0.05	4.78	1.08	-12.22	149.35	-1.10	1.16
Sum		0.00		48.27	6.77	2901.87		38.81

Day 1-148 Fit								
$y = 0.0152x^{0.538}$								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.02	0.00	66.44	6.64	49.44	2444.02	-6.60	44.05
2	0.02	0.00	30.03	-4.57	13.03	169.70	4.60	20.91
4	0.03	0.00	21.80	-2.90	4.80	23.03	2.90	8.42
7	0.04	0.00	16.40	-2.70	-0.60	0.36	2.70	7.28
14	0.06	0.00	12.22	-1.20	-4.78	22.85	1.20	1.44
21	0.08	-0.01	9.57	-0.43	-7.43	55.21	0.40	0.19
29	0.09	-0.01	8.10	-0.10	-8.90	79.17	0.10	0.01
57	0.13	0.00	6.37	1.37	-10.63	113.06	-1.40	1.87
88	0.17	0.01	4.97	0.47	-12.03	144.82	-0.50	0.22
118	0.20	0.01	4.21	0.41	-12.79	163.58	-0.40	0.17
148	0.22	0.01	3.74	0.04	-13.26	175.89	0.00	0.00
Sum		0				3391.69		84.55

Fickian Fit								
$y = 0.0168x^{0.5}$								
Day	Predicted Cumulative Release	Difference from Cumulative	Predicted Release Rate	Difference From Real Release Rate	SSR	SSR	SSE	SSE
1	0.02	0.00	73.43	13.63	56.43	3184.39	-13.60	185.79
2	0.02	0.00	31.03	-3.57	14.03	196.95	-31.00	962.25
4	0.03	0.00	21.64	-3.06	4.64	21.49	-21.60	467.17
7	0.04	0.00	15.90	-3.20	-1.10	1.21	-15.90	251.77
14	0.06	0.00	11.56	-1.86	-5.44	29.54	-11.50	132.67
21	0.08	-0.01	8.87	-1.13	-8.13	66.04	-8.80	77.49
29	0.09	-0.01	7.41	-0.79	-9.59	91.96	-7.30	53.57
57	0.13	0.00	5.71	0.71	-11.29	127.45	-5.60	31.34
88	0.16	0.00	4.36	-0.14	-12.64	159.70	-4.20	17.58
118	0.18	0.00	3.65	-0.15	-13.35	178.25	-3.40	11.73
148	0.21	-0.01	3.21	-0.49	-13.79	190.23	-2.90	8.64
Sum		0.00		0.00		4247.20		2200.00

Appendix B
20% Drug Loading, 48hours 60°C Wash

Predictive Model Day 1-7								
$y = 0.003x^{0.7835}$								
Day	Predicted Cumulative Release	Difference from Experimental Cumulative	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	0.00	0.00	36.40	-0.28	19.37	375.04	0.28	0.08
2	0.01	0.00	26.25	1.83	9.22	85.05	-1.83	3.36
4	0.01	0.00	22.59	0.53	5.56	30.96	-0.53	0.29
7	0.01	0.00	19.78	-1.43	2.75	7.57	1.43	2.04
14	0.02	0.00	17.23	-0.78	0.20	0.04	0.78	0.61
22	0.03	0.00	15.29	0.11	-1.74	3.04	-0.11	0.01
28	0.04	0.00	14.21	0.28	-2.82	7.93	-0.28	0.08
60	0.07	0.00	12.65	1.30	-4.39	19.23	-1.30	1.68
91	0.10	0.01	11.20	1.66	-5.83	33.95	-1.66	2.77
120	0.13	0.02	10.41	2.36	-6.62	43.83	-2.36	5.57
150	0.15	0.04	9.87	3.01	-7.17	51.33	-3.01	9.03
Average:		0.01		0.78		657.99		25.51

Predictive Model Day 1-14								
$y = 0.003x^{0.7935}$								
Day	Predicted Cumulative Release	Difference from Experimental Cumulative	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	0.00	-26.25	36.40	-0.28	19.37	375.04	0.28	0.08
2	0.01	-22.59	26.69	2.27	9.66	93.28	-2.27	5.14
4	0.01	-19.77	23.13	1.07	6.10	37.20	-1.07	1.14
7	0.01	-17.21	20.38	-0.84	3.35	11.19	0.84	0.70
14	0.02	-15.26	17.86	-0.15	0.83	0.68	0.15	0.02
22	0.04	-14.18	15.93	0.75	-1.10	1.20	-0.75	0.57
28	0.04	-12.60	14.87	0.94	-2.16	4.68	-0.94	0.88
60	0.08	-11.13	13.30	1.95	-3.73	13.94	-1.95	3.79
91	0.11	-10.30	11.85	2.31	-5.18	26.87	-2.31	5.32
120	0.13	-9.73	11.04	2.99	-5.99	35.83	-2.99	8.97
150	0.16	0.16	10.49	3.63	-6.54	42.73	-3.63	13.20
Average:		-14.44		1.33		642.65		39.80

Predictive Model Day 1-21								
$y = 0.003x^{0.7933}$								
Day	Predicted Cumulative Release	Difference from Experimental Cumulative	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	0.00	0.00	36.40	11.98	19.37	375.04	0.28	0.08
2	0.01	0.00	26.68	4.62	9.65	93.11	-2.26	5.11
4	0.01	-0.01	23.12	1.91	6.09	37.07	-1.06	1.12
7	0.01	-0.01	20.36	2.35	3.33	11.11	0.85	0.72
14	0.02	-0.01	17.84	2.66	0.81	0.66	0.17	0.03
22	0.04	-0.01	15.92	1.99	-1.11	1.23	-0.74	0.55
28	0.04	-0.03	14.85	3.50	-2.18	4.74	-0.92	0.85
60	0.08	-0.02	13.28	3.74	-3.75	14.04	-1.93	3.74
91	0.11	0.00	11.83	3.78	-5.20	27.01	-2.29	5.26
120	0.13	0.02	11.03	4.17	-6.00	35.98	-2.98	8.89
150	0.16	0.16	10.48	-6.55	-6.55	42.90	-3.62	13.11
Average:		0.01		3.11		642.90		39.44

Predictive Model Day 1-28								
$y = 0.003x^{0.7919}$								
Day	Predicted Cumulative Release	Difference from Experimental Cumulative	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	0.00	0.00	36.40	11.98	19.37	375.04	0.28	0.08
2	0.01	0.00	26.62	4.56	9.59	91.94	-2.20	4.83
4	0.01	-0.01	23.04	1.83	6.01	36.15	-0.98	0.97
7	0.01	-0.01	20.28	2.27	3.25	10.55	0.93	0.87
14	0.02	-0.01	17.76	2.58	0.73	0.53	0.26	0.07
22	0.04	-0.01	15.83	1.90	-1.20	1.45	-0.65	0.42
28	0.04	-0.03	14.76	3.41	-2.27	5.15	-0.83	0.69
60	0.08	-0.02	13.19	3.65	-3.84	14.75	-1.84	3.39
91	0.11	0.00	11.74	3.69	-5.29	27.97	-2.20	4.84
120	0.13	0.02	10.94	4.08	-6.09	37.08	-2.89	8.35
150	0.16	0.16	10.39	-6.64	-6.64	44.09	-3.53	12.46
Average:		0.01		3.03		644.70		36.97

Predictive Model Day 1-150								
$y = 0.0032x^{0.7449}$								
Day	Predicted Cumulative Release	Difference from Experimental Cumulative	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	0.00	0.00	38.82	0.52	21.79	474.91	-2.14	4.59
2	0.01	0.00	26.24	-2.10	9.21	84.80	-1.82	3.31
4	0.01	0.00	21.99	0.31	4.96	24.56	0.07	0.01
7	0.01	0.00	18.80	0.72	1.77	3.12	2.41	5.82
14	0.02	0.00	15.97	2.16	-1.06	1.12	2.04	4.15
22	0.03	0.01	13.87	2.76	-3.16	9.98	1.31	1.71
28	0.04	0.01	12.73	2.93	-4.30	18.47	1.20	1.43
60	0.07	0.04	11.10	4.14	-5.93	35.22	0.25	0.06
91	0.09	0.06	9.62	2.96	-7.41	54.93	-0.08	0.01
120	0.11	0.08	8.82	2.72	-8.21	67.40	-0.77	0.59
150	0.13	0.10	8.28	2.21	-8.75	76.57	-1.42	2.02
Average:		0.03		1.76		851.07		23.71

Appendix C

Second Generation Model

Figure 1 Application of Korsmeyers-Peppas Predictions to 20% Drug Loaded Devices under 72hour 60C Water Wash.

An entirely empirically based model was developed in order to achieve the highest degree of accuracy. Previously, model developments were based on Korsmeyer-Peppas fit which utilized the cumulative release fraction in order to elucidate the release mechanism. The newest model was still based on the power function in order to ease its application.

The old model, shown above, resulted in a higher predicted value for day 180 release rate. This error in prediction indicated a change in the mechanism of release and required a second generation model to be developed. This model would be broken down into two parts: one for initial time points of the curve during which release is diffusion controlled, the other for

the later part of the curve during which release is not diffusion controlled, and then combined to form a final model.

In this case, a model was produced with both the release rate and cumulative fraction in order to produce the most accurate predictive model. Model developments are shown below.

Model 3 Final			
$y = 36.412x^{-0.297}$			
	Empirical Release Rate	Theoretical Release Rate	Difference from Real
1	33.18	36.41	3.23
2	27.90	29.64	-0.54
4	23.46	24.12	0.66
7	20.40	20.43	-1.49
14	17.15	16.63	-3.13
21	15.50	14.74	-3.06
28	14.42	13.53	-2.27
35	13.64	12.67	-1.53
42	13.03	12.00	-1.60
49	12.54	11.46	-1.14
56	12.13	11.02	-0.78
63	11.78	10.64	-0.56
70	11.47	10.31	-0.29
84	10.96	9.77	0.17
91	8.57	9.54	-0.06
107	8.17	9.09	0.09
120	7.89	8.78	0.38
133	7.65	8.52	0.52
150	7.38	8.22	0.82
179	7.00	7.80	1.00

Predictive Model Day 1-180						
$y = 36.412x^{-0.297}$						
$y = 0.0032x^{0.7449}$	Predicted Release Rate	Difference From Experimental Release Rate	SSR	SSR	SSE	SSE
1	36.41	3.23	22.20	492.80	3.23	10.43
2	29.64	-0.54	15.43	238.05	1.74	3.03
4	24.12	0.66	9.91	98.19	0.66	0.44
7	20.43	-1.49	6.22	38.68	0.03	0.00
14	16.63	-3.13	2.42	5.85	-0.52	0.27
21	14.74	-3.06	0.53	0.28	-0.76	0.58
28	13.53	-2.27	-0.68	0.46	-0.89	0.79
35	12.67	-1.53	-1.54	2.37	-0.97	0.94
42	12.00	-1.60	-2.21	4.89	-1.03	1.06
49	11.46	-1.14	-2.75	7.57	-1.08	1.17
56	11.02	-0.78	-3.19	10.18	-1.11	1.23
63	10.64	-0.56	-3.57	12.75	-1.14	1.30
70	10.31	-0.29	-3.90	15.22	-1.16	1.35
84	9.77	0.17	-4.44	19.72	-1.19	1.42
91	9.54	-0.06	-4.67	21.82	0.97	0.94
107	9.09	0.09	-5.12	26.22	0.92	0.85
120	8.78	0.38	-5.43	29.50	0.89	0.79
133	8.52	0.52	-5.69	32.39	0.87	0.76
150	8.22	0.82	-5.99	35.89	0.84	0.71
179	7.80	1.00	-6.41	41.10	0.80	0.64

Figure 2 The newly derived model is >95% accurate, when applying a directly applied model to the empirically derived data and is not susceptible to outliers.