Case Study in Product Design: Microcapsule-Based Drug Delivery

Leann Johnson, Mark McClendon and Miguel Bagajewicz*

The University of Oklahoma

Department of Chemical, Biological and Materials Engineering

100 E. Boyd St., T335, Norman OK 73019

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(*) Corresponding Author: Bagajewicz@ou.edu

Abstract

In this paper consumer modeling is performed to determine the selling price and the expected demand of a micro-capsule drug delivery method. The method is based on long acting microspheres and a computer simulation that calculates a mass of drug loaded microspheres to achieve a target Blood Plasma Drug Concentration (BPDC) Once pricing is addressed, the profitability of producing microsphere injections, specifically for alcoholism, in the pharmaceutical market.

Introduction

Significant advances in drug delivery technology have been made over the past two decades. One of the most important of these advances is the development of long acting drug injections. These long acting drug injections allow for a drug to be continually released for time periods exceeding one month (Vernon, 2005). Future research and advances will allow for drug release to be extended for time periods much longer than one month. This biotechnology has obvious implications, such as higher patient compliance and the convenience of one dose opposed to multiple doses. Many drugs such as Haloperidol (a psychosomatic drug) and Naltrexone (an opioid antagonist drug) have recently been made available as long acting injections in the form of microspheres. The benefits of long acting drug injections are so great that many more drugs will soon be made available in the form of long acting microspheres. Prescribing these long acting medications is no easy task. Doctors will need tools and methods to aid them in achieving optimal blood plasma drug concentrations (BPDC) in their patients.

Currently, when doctors write a prescription, they would like to believe that their instructions will be followed very carefully. Patient compliance has been associated with a positive doctor-patient relationship and trusting their primary care provider (Berry, 2008). DiMatteo et al. (2002) found that adherence to doctor's orders produced a good outcome in nearly 26% more patients than no adherence to the orders.

Even with the benefits associated with following a doctor's prescriptions, patient adherence to medical advice is often less optimal and does not appear to be influenced by specific social or demographic characteristics (Miller, 1997). Interventions such as written instructions, drug warnings, special counseling and telephone check-ups have been unsuccessful in persuading patients to follow their treatment plans. This problem is especially prevalent in patients with psychological disorders such as schizophrenia (McDonald, 2002).

Another method to combat the problem of patient compliance has been through long-acting or slow-release drug injections. In theory, a long-lasting injection will ensure that the correct dose is administered to the patient and that the patient is adhering to the prescribed plan set forth by their doctor (Keith, 2004). This type of slow-release injection has obtained support from clinical research of antipsychotic medications. Ideally, long-acting/slow-release injections would help doctors by increasing patient compliance.

Doctors prescribe drugs based on optimal Blood Plasma Drug Concentrations (BPDC) (Merck Pharmaceuticals, 2007). For example, the drug aspirin has an optimal BPDC of 8 mg/L to treat migraines; therefore, it is desired for the patient's BPDC to remain at 8 mg/L for the duration of the treatment (Ross-Lee, 1982). Optimal BPDC are to be determined by clinicians and will be based on drug type, disease, and previous trials. The determination of optimal

BPDC is beyond the scope of this project, therefore, optimal BPDC are assumed to be known by the doctors when prescribing medicine. When the BPDC is optimized the disease is treated but the drug remains below toxic levels.

Consumer model is very important for product design and pricing. In a product design model, the consumers' needs are examined and different aspects of a product are enhanced for optimal product design. Ideally, the combination of optimal consumer needs will produced the most utility or happiness for the customer and the most profit for the manufacturer (Bagajewicz, 2007). The factors used in this consumer model and price optimization for microsphere production will be discussed in more detail.

This article is organized as follows: We first discuss the slow drug delivery background and then the microcapsule delivery in particular. We then continue to discuss drug clearance assessment followed by our mathematical model for a prescription and the optimization procedure. We continue with manufacturing details, the economics and pricing.

Slow Drug Delivery Background

The most common form of prescibed medication is through oral pills. (Drug Delivery Technology, 2008) Oral administration of drugs has many drawbacks. One major drawback is that a patient will have a varying BPDC during the treatment. The highest concentration of drug occurs shortly after the medication is taken and the lowest concentration occurs shortly before the medication is taken. (Drug Delivery Technology, 2008) This effect is illustrated in figure 1. The varying BPDC will correlate to fluctuations in the patient's symptoms and side effects of the drug, i.e. high concentrations will treat the disease but cause unwanted side effects, while low concentrations won't treat the disease but won't cause unwanted side effects. The ideal situation is to have the BPDC to remain at the optimal concentration for the entire treatment.

Using long acting slow delivery means, like the microspheres we later describe in this article it is possible to achieve fairly constant optimal BPDC levels for extended periods of time unattainable by a single oral dose. (Varde, 2004). Microspheres can be engineered to release drugs at varying rates. Therefore, an injection of microspheres can be specialized to individual patients in order to achieve many different BPDC. After an injection of long acting microspheres the drug concentration rises first until the metabolic consumption of the drug equals the release rate from the microspheres. The BPDC then plateaus until all the drugs have been release from the microspheres. Finally the concentration naturally decreases due to metabolic consumption of the drug. This process is illustrated in figure 2.

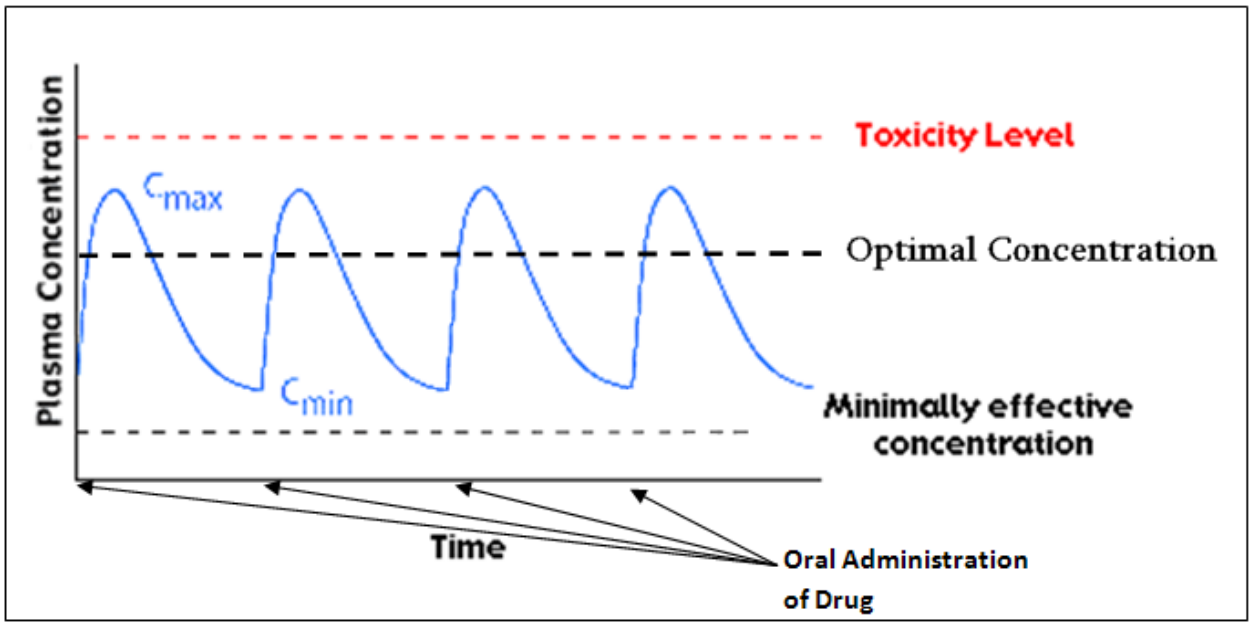

Figure 1: Blood plasma drug concentration after multiple oral doses of a drug.

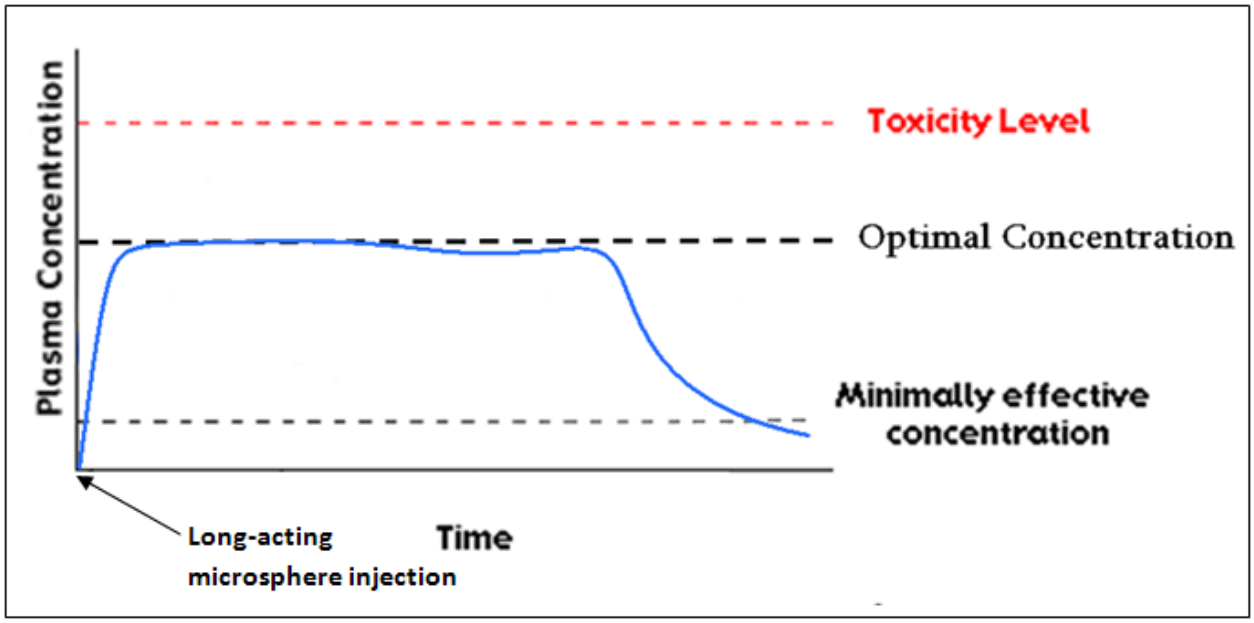

Figure 2: Blood plasma drug concentration after single long-acting slow delivery of a drug.

Microspheres Mechanism for Slow Drug Delivery

Microspheres as a drug delivery system are tiny spheres made of polymer(s), approximately 1-100 µm in diameter, with the drug molecule(s) of interest either distributed throughout or encapsulated within each microsphere. There are several methods of microsphere preparation, including spray-drying, spray-freeze-drying, solvent evaporation, and

phase separation methods. (Banga, 2006) The most common methods are interfacial polymerization, solvent extraction/evaporation, polymer extrusion, spray drying, and coacervation or precipitation. (Varde, 2004) Most techniques involve dissolving the drug in an emulsion of the polymer, and then somehow removing the continuous phase. Filtration may or may not be necessary to achieve a monodisperse size distribution, which is often desired as diameter strongly affects drug release rate.

Release Mechanism

Drug molecules may either diffuse out of polymer microspheres or be released as the polymer degrades. All polymers chosen for use as microspheres are biodegradable, and each polymer has its own pattern of degradation. Many factors affect the rate of drug release, such as polymer chemistry, polymer molecular weight, copolymer composition, interactions between polymer and drug, presence of excipients, size of microsphere, and the molecular weight and initial concentration of drug(s) within the microsphere. Because there are so many controllable factors, it has been demonstrated that microspheres may be especially fabricated to be bulk-eroding or surface-eroding, which expedites drug delivery in different ways. (Varde, 2004) Similarly, microspheres have been designed to resist degradation for a period of time, so that most of the drug molecules inside are delivered via diffusion rather than degradation. (Varde, 2004)

Long-acting microspheres are typically injected intramuscularly, where the drugs will release over time and diffuse to a nearby blood vessel. This has the advantage of achieving high bioavailability (often 100%, since the first-pass effect is avoided), while simultaneously being long-acting. In this way, microspheres can sustain release for periods impossible by other means, such as oral drug delivery. (Varde, 2004)

Usage

The microspheres to be used in this research will be produced from poly(D,L-lactide-co-glycolide), or PLGA. PLGA typically follows a degradation cycle of hydration, initial degradation, further degradation, and solubilization. (Wu, 2001) However, the use of a high molecular weight PLGA will be employed to decrease the degradation rate of the microspheres. The microspheres in this research shall be made using an emulsion-solvent extraction/evaporation method. This method is the most common method used by academic researchers for applications of this nature. (Varde, 2004) This method begins with the emulsification of a solution containing the polymer, the drug (this research deals with the impregnation of microspheres with Piroxicam), and a small amount of stabilizer. The solvent used will be ethyl acetate, and the stabilizer will be poly(vinyl alcohol) (PVA). The PLGA will be pre-formed, unlike some other microsphere fabrication techniques that involve polymerization. The solvent is then extracted from the continuous phase and permitted to evaporate, leaving behind droplets of the polymer-rich that will begin to harden. These hardened microspheres will then be filtered as necessary, washed, and lyophilized, leaving only the desired drug-impregnated polymer microspheres of desired size.

This work relies on drug release models to compute how the drug molecules leave microspheres of different sizes and drug loading concentrations. Combining these release models with models of the human metabolism, a solving application can optimize the quantity and mass distribution (among a set microspheres prepared different ways) of extended-release microspheres required to achieve a given target blood concentration for a given period of interest.

Prescription methodology

Prescribing of long acting microspheres is a precise process. Once a patient is injected with microspheres, they cannot be removed. Therefore, both the drug release rate and metabolic clearance must be taken into account. Otherwise, the patient will have BPDC that are too high or low for the duration of the treatment. For a doctor to use this computer simulation they must follow this procedure.

Step 1: The patient is injected with the desired drug intravenously. This injection does not contain microspheres. It is only used to increase the body's BPDC.

Step 2: The BPDC of that drug is measured for a period of time long enough to determine the metabolic clearance of the drug. It is important that the target blood concentration falls within the range of measured BPDC. The data collected at this step will be in the form of time points and their respective BPDC.

Step 3: The data obtained in step 2 is inputted into the prescription program. The doctor also inputs patient characteristics, desired BPDC, and duration of the treatment. The output of the program will be a prescription of microspheres.

Step 4: The dosage prescribed by the program is injected into the patient.

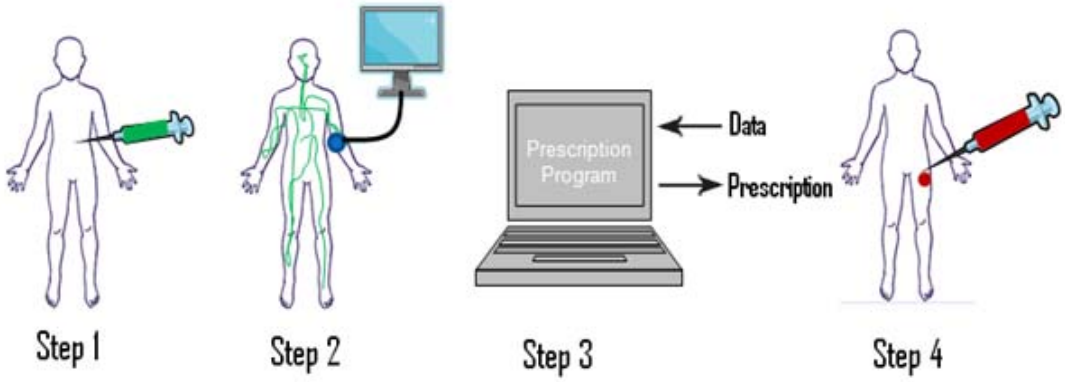

Figure 3: Prescription process

Models ofDrug Clearance

The loss of drug molecules from the blood stream is referred to as metabolic clearance, and it happens through two main pathways; excretion and metabolism. Excretion primarily occurs through urine; while metabolism of drugs occurs mostly in the liver. (Merck Pharmaceuticals, 2007) The factors affecting excretion and metabolism are numerous. These

factors include the following; drug type, drug concentration, drug-drug interactions, age, sex, weight, physical activity, genetic factors, external influences, disease state, organ function, and food. (Saladax, 2008)

Today, the standard method of dosing drugs is based on a patient's body surface area. However, there is a significant amount of inter-patient variability in blood plasma drug concentrations (BPDC) when drugs are prescribed based on patient's body surface area. (Baker, 2002) The difference in BPDC between two different patients can be as large as 50 fold when given the same prescription based on body surface area. This suggests that ideal drug prescriptions must take into account the individual patient's metabolic clearance. (Saladax, 2008)

Drug metabolic clearance of humans, much less individual patients, cannot be predicted using established thermodynamic and kinetic models. (Andersson, 2004) Andersson and Bredberg attempted to model in vivo clearance of four well known drugs based on in vitro kinetics and protein bonding. Andersson and Bredberg concluded there study saying, "Quantitative predictions of hepatic clearance using the well stirred prediction model and CL_{int} calculated from enzyme kinetic measurements were not useful. Including and excluding protein binding resulted in under- and overestimation, respectively, of in vivo clearance."

Drugs can be metabolized by oxidation, reduction, hydrolysis, hydration, conjugation, condensation, or isomerization. The method of metabolization, and thus the metabolic clearance, is dependent upon the drug itself. (Merck Pharmaceuticals, 2007) Therefore, a general model describing the metabolic clearance that can be applied to all drugs is unrealistic. Even when the specific drug is known, as with Andersson's and Bredberg's study, the metabolic activity cannot be predicted with any kind of useful certainty.

As of now, individual pharmokinetics cannot be determined by evaluating patient characteristics, such as age, weight, and sex. Instead the patient's pharmokinetics must be determined by administering a drug then measuring the patient's BPDC. This method is termed Therapeutic Drug Management (TDM). (Saladax, 2008) TDM causes some inconvenience to patients, because the drug must be injected and the resulting BPDC must be measured for a period of time. Although it is inconvenient, TDM has been used since the 1960's and produces accurate models of metabolic clearance. (Saladax, 2008)

A promising alternative to TDM is the use of in *silico* modeling to predict metabolic clearance. Hodjegan and Tucker (Rostami-Hodjegan, 2007) have shown that large databases can be used to predict the metabolic activity of individual patients with a useful degree of accuracy. Their method of *in silico* modeling correlates many patient variables to statistically predict the most likely metabolic clearance rate. This technique would eliminate the need for TDM, because the metabolic clearance can be statistically predicted based on patient/drug characteristics rather than measuring the clearance through TMD. The problem is that there is not an extensive database of metabolic activity of patients. Therefore, the methods outlined by Hodjegan and Tucker cannot be applied to predict metabolic clearance. However, as the method of TDM is used more often, a large database of patient metabolic activity will accumulate. In the future, when enough data has been collected *in silico* statistical modeling of metabolism will be possible. Thus, the method of TDM will eventually eliminate itself.

Mathematical Model For Prescription

This section outlines a simulation that is designed to aid doctors in prescribing long acting microspheres. The program is divided into three main parts; Microsphere Release Model, Metabolic Model, and BPDC Optimizer. The microsphere release model describes the rate at which microspheres release a drug into the blood stream. The Metabolic Model describes the rate at which the drug is removed from the bloodstream. The BPDC Optimizer combines the Microsphere Release Model and the Metabolic Model to predict the BPDC at time points after the injection of long acting microspheres. The BPDC is also used to solve for the correct dosage of microspheres to achieve a target BPDC.

Release model

Although there are many factors that contribute to the release rate of drugs from microspheres, the single most important factor is microsphere diameter. *Inherent viscosity* here refers to the ratio of the relative viscosity to the mass concentration of the polymer (typically in cm^3/g). The empirical model was created to fit published data (Figure 4)

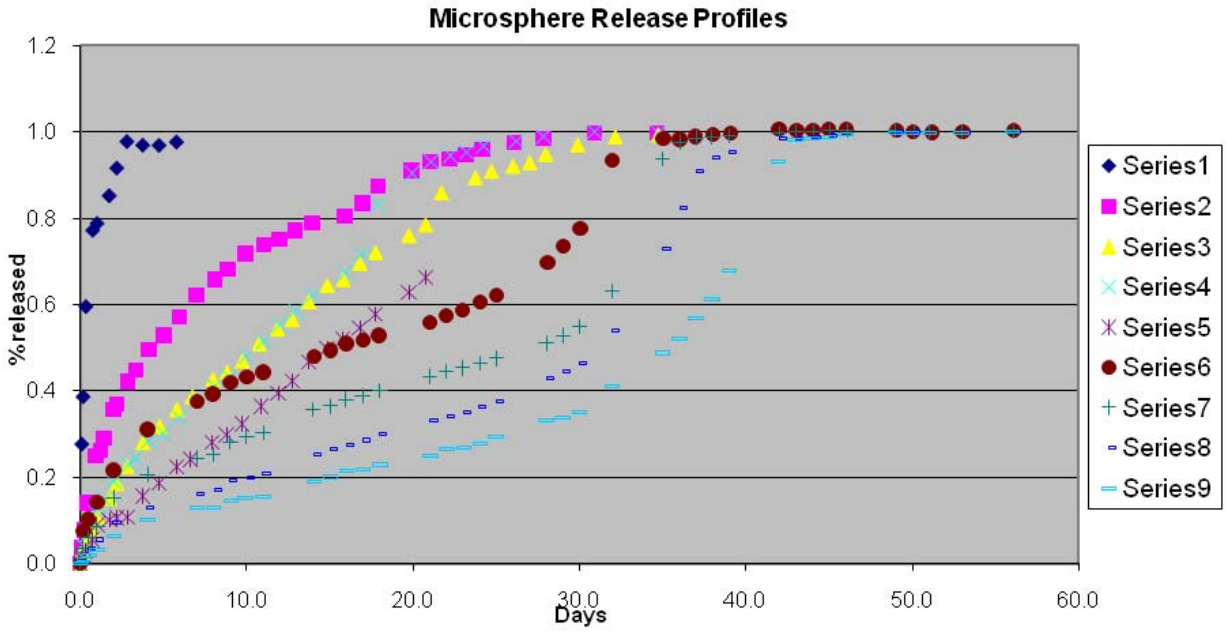

Figure 4

Using an equation of the following form:

Equation 1

$$\%\,released = \frac{At^B + C\left(\frac{t}{H}\right)^D + E\left(\frac{t}{G}\right)^F}{1 + C\left(\frac{t}{H}\right)^D + E\left(\frac{t}{G}\right)^F}$$

where t is the time in days, starting from t=0, and A, B, C, D, E, F, G, and H were all parameters adjusted for each specific microsphere type. However, it was found that C, D, E, and H do not change significantly for the assortment of microsphere release profiles considered. Specifically, C=-3.153, D=32.472, E=22, and H=60.092. This resulted in the following equation:

Equation 2

$$\%\,released = \frac{At^B - 3.515\left(\frac{t}{60.092}\right)^{32.473} + 22\left(\frac{t}{G}\right)^F}{1 - 3.515\left(\frac{t}{60.092}\right)^{32.473} + 22\left(\frac{t}{G}\right)^F}$$

After review of several different microsphere types, it was determined due to practical and economic considerations that not all reviewed microspheres would be required. This is because many microspheres have what would be redundant release profiles in the context of creating a target composite drug release profile. The following is a table for the A, B, F, and G values for the non-redundant microspheres to be used in the empirical drug release model:

Table 1

Size	10 um	10 um	10 um	10 um	10 um	50 um	50 um	50 um	50 um
I.V.	0.170	0.390	0.590	0.820	1.080	0.390	0.590	0.820	1.080
A	0.721	0.266	0.112	0.118	0.051	0.165	0.091	0.044	0.024
B	0.229	0.412	0.646	0.601	0.836	0.408	0.513	0.664	0.793
F	22.286	18.476	19.119	8.139	12.807	22.977	33.931	19.676	22.286
G	44.720	29.471	34.649	27.907	32.801	34.983	36.452	40.669	44.720

These values resulted in the following fits:

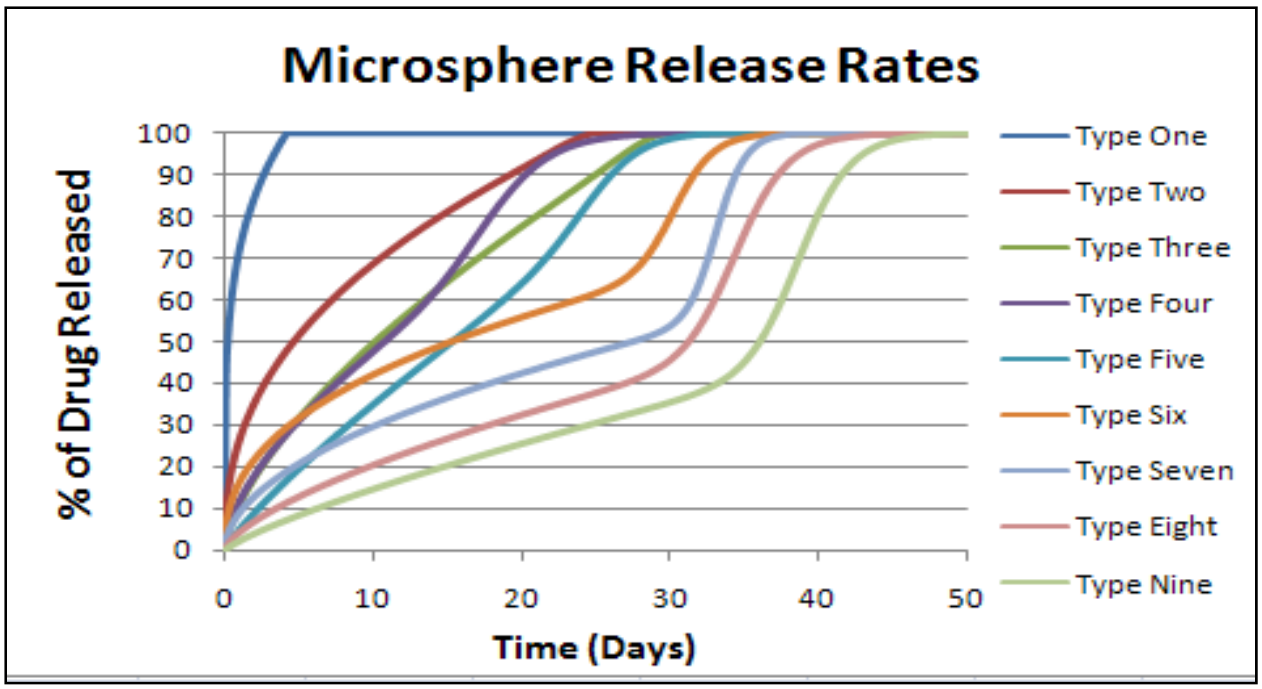

Figure 5.

In comparison with the source data, the parameters seem to achieve very close fits.

By combining different quantities of each microsphere, a composite release rate may be achieved that is one of the user's own choosing (described further below).

Metabolic model

The computer program outlined in this paper bases the metabolic clearance on a simple power law model. The power law model is based on the data obtained from the Therapeutic Drug Management (TDM). The following steps outline the process through which the metabolic clearance is modeled.

Step 1: The data obtained from TDM is inputted into the program. The data must be in the form of time and a BPDC for each time point. It is assumed that the drug is at semi-steady state with the body; meaning that the only observable changes in BPDC are a result of metabolic clearance. An example of non-semi-steady state would be the adsorption phase of the injection. The adsorption phase of the injection can last from 10 to 1000 seconds, depending on the individual and drug. (Dershwitz, 2000) During the adsorption phase, the drug molecules are saturating the surface of target tissues to the point of equilibrium with the surrounding fluids. A sample data of TDM was found for the drug Piroxicam in the literature, shown below in table 2. (Heeb, 2003)

Table 2

Time (hrs)	0.154839	0.924638	1.92753	4.01472	5.94748	7.95829	11.9799	23.9678	48.0293
Conc. (mg/L)	1000	769.992	623.153	517.027	439.788	388.319	302.748	147.085	57.1159

Step 2: A tri-exponential equation is fitted to the inputted data. Most Drugs exhibit an exponential decay in concentration when plotted against time. (Yamaoka, 1978) To more accurately describe data obtained from TDM a multi-exponential equation can be used. (Dershwitz, 2000) (Rawlins, 1977) A tri-exponential equation (equation 3) was chosen to fit to the TDM data, because increasing the equation to a quad-exponential plot did not improve the R^2 value by a significant degree. The equation is shown below:

Equation 3

$$\text{Conc} = Ae^{-\alpha(t)} + Be^{-\beta(t)} + Ce^{-\gamma(t)}$$

The parameters A, B, C, α, β, and γ were found by using the least squares method (table 3). The Excel function "solver" was used to minimize the sum of square error between the TDM data and the tri-exponential function by changing parameters A, B, C, α, β, and γ.

Table 3

A	alpha	B	beta	C	gamma
28.723	-0.0048	632.953	0.0710	411.445	1.122

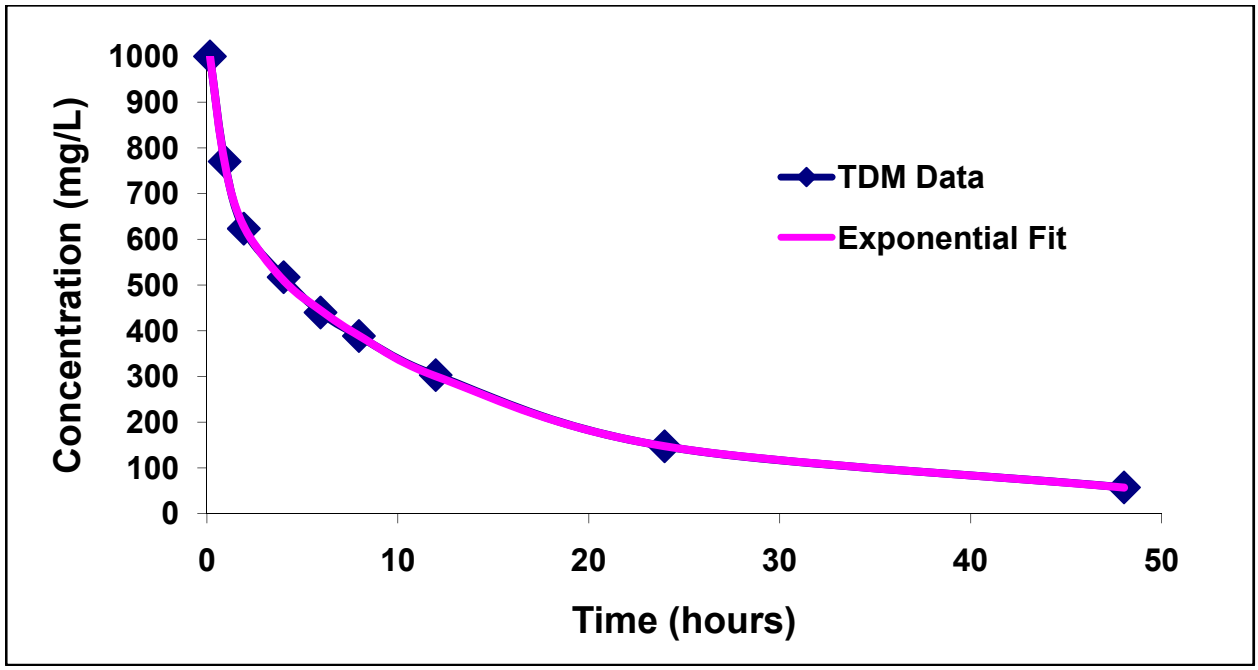

Figure 6

Step 3: The derivative of the tri-exponential curve represent the change in concentration with time or in other words metabolic clearance. The metabolic clearance rate is thus represented by the following equation.

Equation 4

$$\frac{d(Conc)}{dt} = -\alpha Ae^{-\alpha(t)} - \beta Be^{-\beta(t)} - \gamma Ce^{-\gamma(t)}$$

The values of A, B, C, α, β, and γ have already been found. By plugging in the values for these parameters a plot of clearance rate vs. time is produced (shown below).

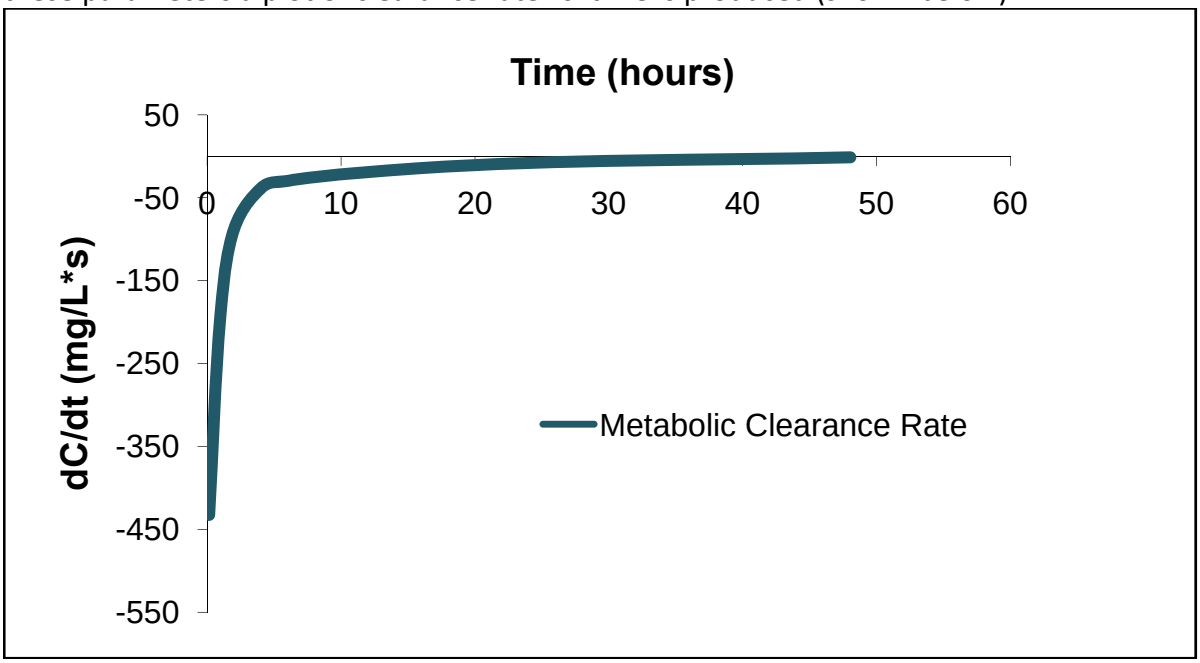

Figure 7

Step 4: Now there is a function that represents both concentration and metabolic clearance as functions of time. However, neither of these functions are directly related to time. The metabolic clearance should be a function of concentration, because the the body does not care how long it has been since the drug injection; the body is metabolizing the drug at a rate depending on drug concentration. (Dershwitz, 2000) Therefore, at each time point from the TDM data a value of concentration and clearance is obtained (the concentration is the TDM concentration, not the tri-exponential fit concentration).

Table 4

Concentration (mg/L)	1000.0	770.0	623.2	517.0	439.8	388.3	302.7	147.1	57.1
Clearance (mg/L*s)	-432.6	-205.6	-92.1	-38.8	-29.9	-25.5	-19.1	-8.0	-1.3

A plot of this data yields a curve that seems to follow a power law model.

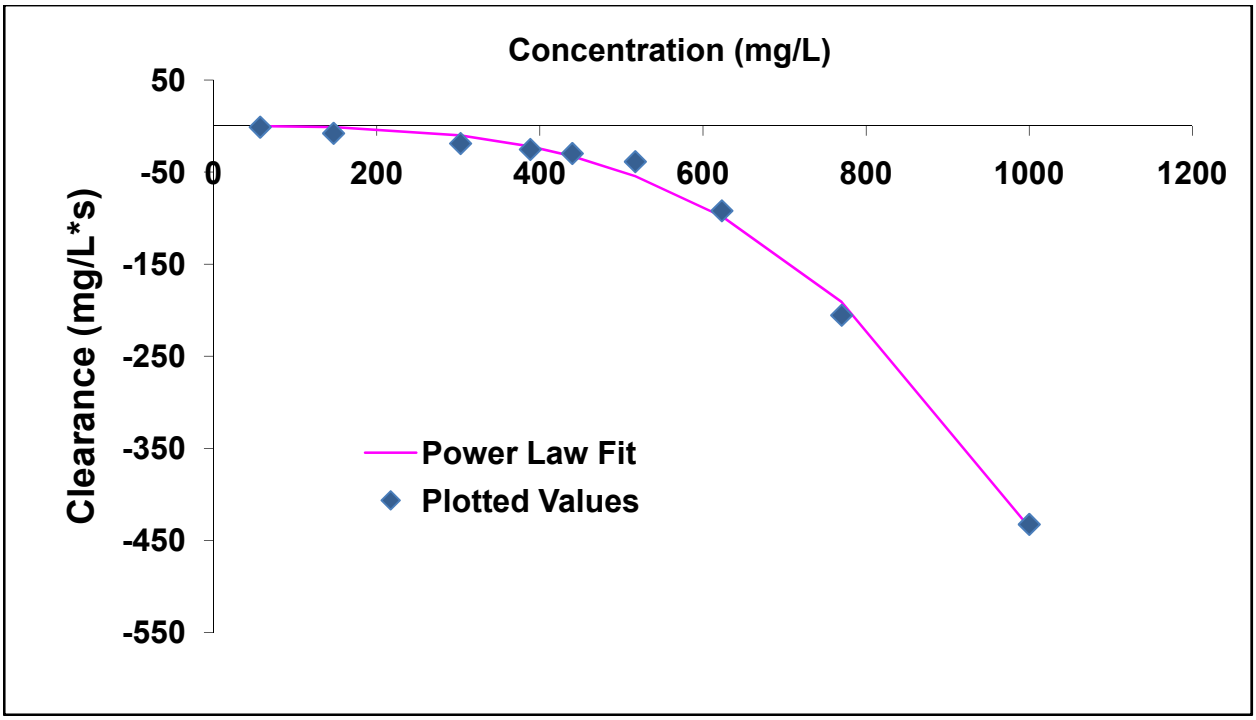

Figure 8

Equation 5

$$\frac{d(Conc)}{dt} = -D * (Conc.)^{\delta}$$

A power law equation, equation 5, was fit to this data. Once again, the sum of squares error method was applied to fit the equation to the data. Excels "solver" function was used to minimize the sum of squares error between the values and the power law equation by changing the parameters D and δ. The R^2=0.979 value showed that this equation fits the data well with D=1.51E-07 and δ= 3.15.

Finally metabolic clearance is described as a function of concentration. This power law equation of metabolic clearance is used in the BPDC optimizer described in the following section. It is important to note that this simple power law model is only applicable in the concentration range measured during TDM, because it is not based on physical properties or kinetics of the drug. The main assumption in this model is that the drug clearance is only a function of concentration.

Microsphere Prescription Model

The Blood Plasma Drug Concentration (BPDC) Optimizer combines the metabolic model and the microsphere release model to predict future BPDC by picking the appropriate blend of

microspheres. The Optimizer also has the capability to solve for a microsphere dosage to achieve a target BPDC . The inputs into the optimizer are listed below.

INPUTS

- Drug Release Rate (from the Microsphere Release Model)
- Metabolic Clearance Parameters D and δ (from the Metabolic Model)
- Patient's Weight
- Max BPDC
- Medicated Period
- Initial Ramp Period
- Final Ramp Period

The simulation is currently set up to run on the empirical data model of microsphere release rate of Piroxicam. There are nine types of microspheres possible to use in the injection, although, the program rarely ever selects all nine types to achieve a target BPDC. Each of these microspheres releases the drug at a different rate; therefore, a combination of different types of microspheres will produce a different overall release rate of drug. This is useful because it allows the release rate of drug to be specified to an individual patient's metabolism.

Calculating Future BPDC

The simulation works by breaking up the medicated period into minor intervals (0.1 days). At each time intervals the concentration is found by adding the change in concentration to the previous time intervals concentration. This formula is then applied to each consecutive time intervals' concentration until it covers the time period of interest (100 days for the current set up). This method is outlined in the equations below.

Equation 6

$$C_{t=n+1} = C_{t=n} + \Delta C_{t=n+1}$$

$C_{t=n}$ is the concentration at time = n*(time interval) and $\Delta C_{t=n+1}$ is the change in concentration at time = (n+1)*(time interval). The $\Delta C_{t=n}$ is found by adding the change in concentration due to metabolic clearance to change in concentration due to microsphere drug release.

Equation 7

$$\Delta C = \Delta C_{microsphere} + \Delta C_{metabolism}$$

The $\Delta C_{microsphere}$ is found using the microsphere release model. As stated before, the total mass released from each microsphere is defined at each time interval by the Microsphere release model. Therefore, the drug mass released during each time interval is the total mass released during that time interval minus the total mass released during the previous interval.

Equation 8

$$\left(\Delta C_{microsphere}\right)_{t=n+1} = \frac{\left(Total\ Mass\ \mathrm{Re}aleased\right)_{t=n+1} - \left(Total\ Mass\ \mathrm{Re}aleased\right)_{t=n}}{Plasma\ Volume}$$

The plasma volume is calculated by the patient's weight. Standard values of percent blood by weight and percent plasma by blood were used to calculate volume. (blood weight) /(body weight)=0.7, (plasma weight)/(blood weight)= 0.55, and plasma density=1.06 g/cc.

The $\Delta C_{metabolisim}$ is the clearance of the drug and it is calculated with the power law model defined in the metabolic model section.

Equation 9

$$\left(\Delta C_{metabolisim}\right)_{t=n+1} = \left(time\ \mathrm{int}erval\right)\left(-D\right)\left(C_{t=n}\right)^{\delta}$$

An expanded form of equation 6 looks like equation 9

Equation 10

$$C_{t=n+1} = C_{t=n} + \left[\left(Total\ Mass\ \mathrm{Re}aleased\right)_{t=n+1} - \left(Total\ Mass\ \mathrm{Re}aleased\right)_{t=n}\right]/\left(Plasma\ Volume\right) + \left(time\ \mathrm{int}erval\right)\left(-D\right)\left(C_{t=n}\right)^{\delta}$$

An "if" statement was used to insure that the concentration never becomes negative. If the calculated concentration is negative then the program reports a zero. Figure 10 shows the resulting BPDC after an injection of a random dosage of microspheres (shown in table 5), a body weight of 150 lbs, and the metabolic parameters found in the metabolic model section.

Table 5

MS Diameter	10 um	10 um	10 um	10 um	10 um	50 um	50 um	50 um	50 um
Inherent Viscosity	0.17	0.39	0.59	0.82	1.08	0.39	0.59	0.82	1.08
Mass of Microspheres	0.0005	0.001	0.002	0.001	0.0005	0.001	0.0005	0.002	0.002

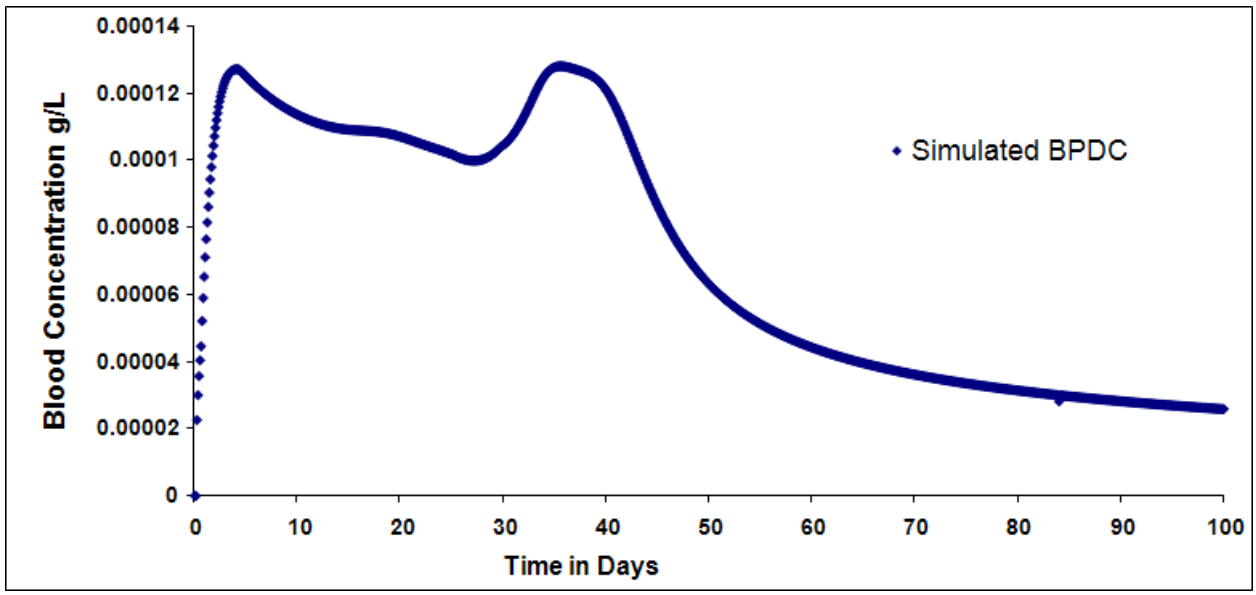

Figure 9

Solving for the Prescription

The following inputs are used to specify the target BPDC for the duration of the treatment; Max BPDC, Medicated Period, Initial Ramp, and Final Ramp. The initial ramp period is the time period it takes the BPDC to rise to the Max BPDC; the medicated period is the time period that the BPDC is held at the Max BPDC; and the final ramp is the time period it takes the BPDC to fall to zero. For example, specifying Max BPDC=0.0001 g/L, Medicated Period=30 days, Initial Ramp=3 days, and Final Ramp=30 days will result in the target BPDC concentration shown in figure 11. The initial ramp period was designed because a doctor may want a patient to slowly adjust to a drug rather than just starting the patient's BPDC at the Max BPDC. The final ramp period was designed so that a doctor has the option to wean the patient off the drug.

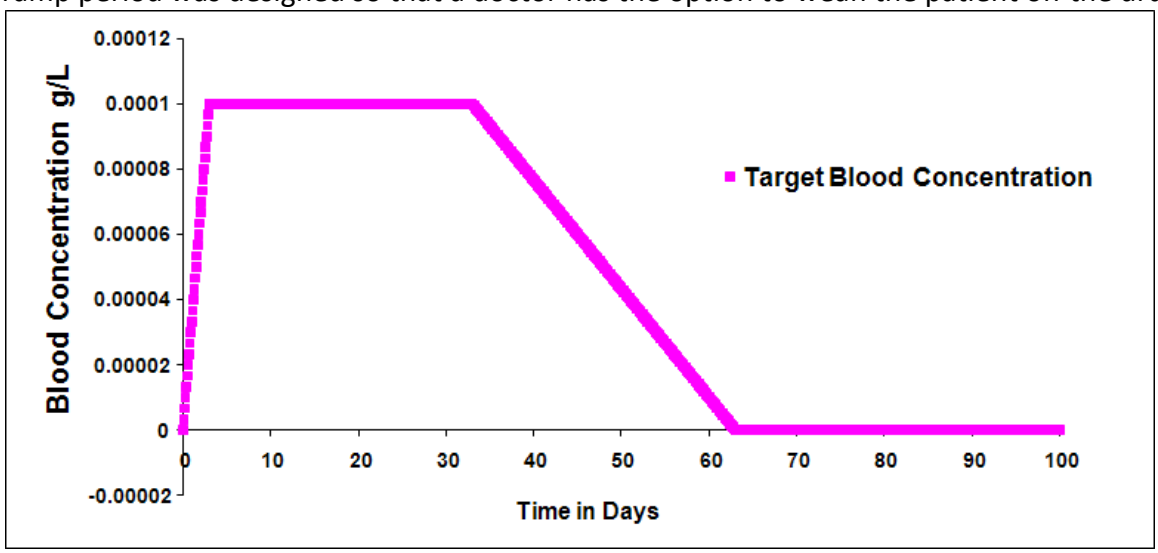

Figure 10

The desired result of injecting long acting microspheres into a patient is to achieve a BPDC profile that closely resembles the target BPDC profile. To achieve the optimal BPDC profile the sum of squares method is applied. The square error is the difference between the simulated BPDC and the target BPDC. The sum of squared errors is minimized using "solver" by changing the mass of each type of microsphere. One constraint when running solver is that the masses of the microspheres must be greater or equal to zero. The initial masses of microspheres should be set to zero before running solver.

The simulation was used to solve for a prescription that would achieve a BPDC shown in figure 11. The inputs are shown in table 6, the microsphere prescription is shown in table 7, and the BPDC is plotted in figure 12. The BPDC profile shows that the simulated BPDC is very close to the target BPDC. The major deviation occurs at 50 days when the drug is being cleared from the body. At this point all the drug has been released from the microsphere and the only change in concentration is due to the metabolic clearance. Therefore, the deviation from the target BPDC is a result of the patient's metabolism.

Inputs

Table 6

Input	Patient's Weight (lbs)	Max BPDC (g/L)	Medicated Period (days)	Initial Ramp Period	Final Ramp Period	D	delta
Value	150	0.0001	30	3	30	1.5E-07	3.15334

Prescription

Table 7

MS Diameter	10 um	10 um	10 um	10 um	10 um	50 um	50 um	50 um	50 um
Inherent Viscosity	0.17	0.39	0.59	0.82	1.08	0.39	0.59	0.82	1.08
Mass of Microspheres	0	0	0.0013	0.0011	0.0019	0.0014	0.00058	0.0002	0

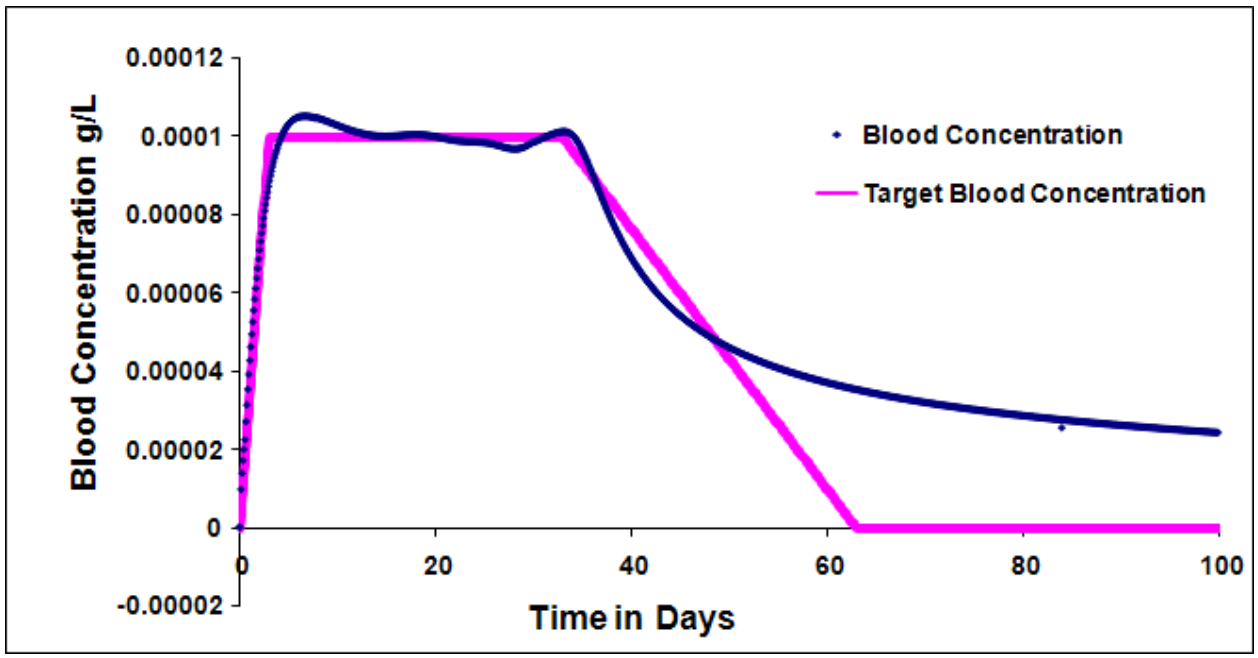

Figure 11

Continuous Injection

Most of prescription drugs are taken for periods longer than 30 days, and some drugs are taken indefinitely. Therefore, if long acting microspheres are to be used to achieve optimal BPDC for periods longer than approximately 40 days the patient will need to get multiple injections. A multi-injection simulation was created to allow for a second injection. The only difference between the multi-injection simulation and the single injection was equation used to calculate ΔC. The ΔC value must also include the drug released from the microspheres of the previous injection.

Equation 11

$$\Delta C = \left\lfloor \Delta C_{microsphere} \right\rfloor_{injection1} + \left\lfloor \Delta C_{microsphere} \right\rfloor_{injection2} + \Delta C_{metabolisim}$$

The multi-injection simulation requires an input that the single injection simulation did not include, injection day. The injection day allows the simulation to determine the initial concentration and the amount of microspheres that are still releasing drug from the first injection. For the second injection it is possible to change the target BPDC, medicated period, metabolic clearance parameters, and patient weight.

Shown in figure 13 is the result of the multi-injection simulation. The second injection was simulated to be 33 days after the injection calculated in the "Solving for Prescription" section. The inputs to the simulation are shown in table 8 the resulting microsphere dosage is shown in table 9. This same method can be applied to the consecutive injections beyond the second injection.

Table 8

Input	Patient's Weight (lbs)	Tgt Blood Conc (g/L)	Injection Day	Medicated Period	D	delta
Value	150	0.00012	33	40	1.5E-07	3.15334

Table 9

MC Diameter	10 um	10 um	10 um	10 um	10 um	50 um	50 um	50 um	50 um
Inherent Viscosity	0.17	0.39	0.59	0.82	1.08	0.39	0.59	0.82	1.08
Mass of Microspheres	**0**	**0**	**0.00121**	**0.0012**	**0.0103**	**0.0007**	**0.00062**	**0.00388**	**0.00407**

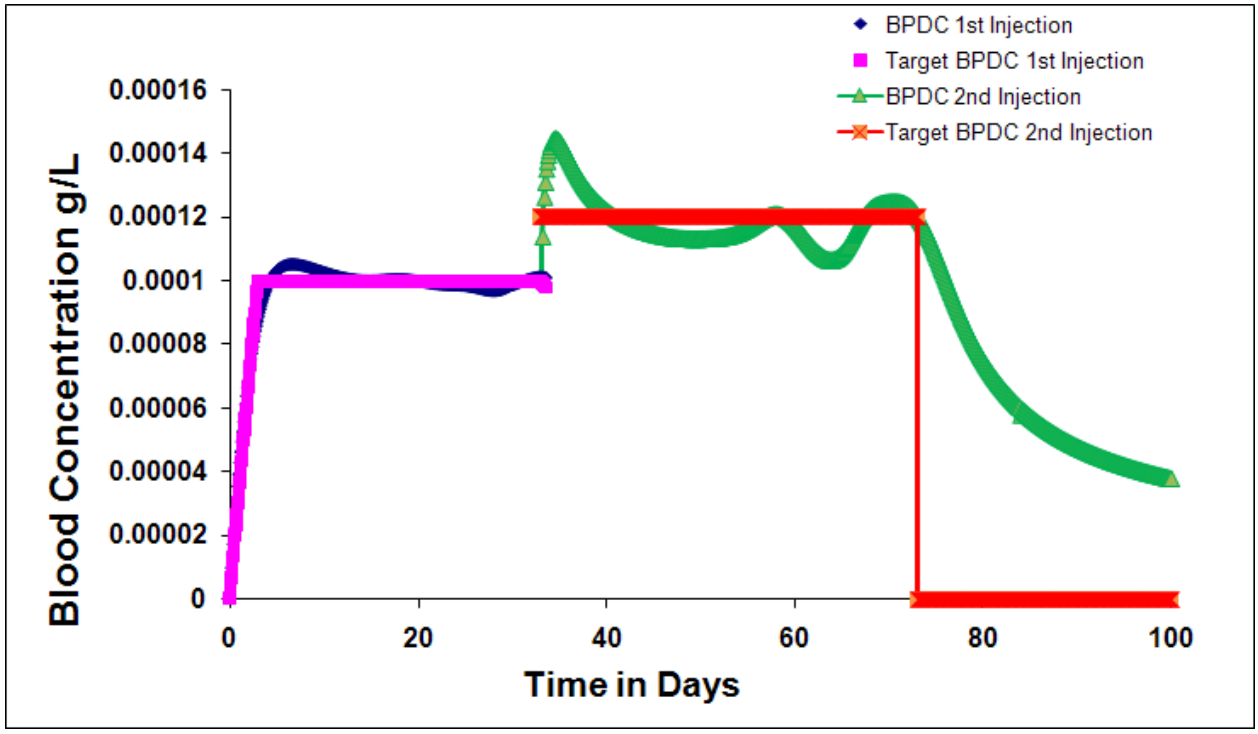

Figure 12

Manufacturing Details and Costs

The manufacturing costs associated with the production of microspheres were assessed to determine an optimal price. The raw materials and equipment necessary to produce the dry microspheres will be discussed. For PLGA microspheres, solvent used was ethyl acetate and the stabilizer will be poly (vinyl alcohol). The drugs encapsulated in the microsphere can vary widely in price. For this economic analysis, the drug Naltrexone was used in the microsphere.

The technique that was examined to produce microspheres is known as the Emulsion-solvent extraction/evaporation technique. This method is often used in drug delivery research and is one of the most common methods for producing microspheres from a variety of common polymers. The first step in this process is the emulsification (stirring) of a solution containing the polymer, drug, and a small amount of stabilizer. This will form a mixture that can then be put into an extraction system. This system is similar to a centrifuge and it will extract the solvent, leaving the polymer-rich phase which will then begin to harden in droplet form. These droplets are then filtered and lyophilized. This process will sublime (freeze dry) the microspheres to remove any excess water. This leaves only the desired polymer with encapsulated drug throughout.

Economics

Consumer Demand Model

The first analysis of demand for the new microsphere delivery system used a consumer demand model with constant elasticity of substitution. Using this model, it was assumed that the doctors would be the consumers. All parameters in this equation related to the doctors' knowledge and preference of medications. However, it was determined through interviews with Norman-area physicians that doctors do not consider the price of medication in the same manner as consumers when prescribing medication to patients. Therefore, this model is incomplete and will not accurately reflect the demand for the new drug delivery system or the doctor's decision making process when choosing which medication and drug delivery system to prescribe to patients. (Bagajewicz)

The consumer model described below will apply to situations where patients will be purchasing their medication out-of-pocket. This model will be used to describe the demand for the new medication at different prices when the patients do not have insurance coverage, and they must pay for their medication in full. The consumer (patient) will not have any bargaining power with the pharmaceutical company (as is often the case with insurance providers); therefore, the price that is set by the drug manufacture will be constant and will determine the demand for the new drug. Price and demand involving insurance companies will be discussed later in this paper. The equation below was derived under the assumption that there will be constant elasticity of substitution.

Constant elasticity of substitution implies that as the demand for one good goes to zero, the demand for the alterantive good will increase linearly. Also, if the value of rho is less than one, then the function will be concave and we will see diminishing marginal utility as demand increases. (Bagajewicz)

Equation 12

$$p_1 d_1 - \left(\frac{\alpha}{\beta}\right)^{\rho} p_2 \left(\frac{Y - p_1 d_1}{p_2}\right)^{1-\rho} d_1^{\rho} = 0$$

P_1 = the price for the new technology

P_2 = the price for the current or competitive technology

d_1 = the demand for the new technology

d_2 = the demand for the current (competitive) technology

Y = the budget constraint for the market of interest

D = the total demand for the market of interest

This equation has two constraints. One constraint is that the demand for the new product and the demand for the existing product cannot exceed the total market demand for the product. The other constraint is that the price times the quantity demanded of the new product plus the price times the demand of the existing product cannot exceed the total market budget for those products. These constraints are represented mathematically below:

Equation 13

$$p_1 d_1 + p_2 d_2 \leq Y$$
$$d_1 + d_2 \leq D$$

Alpha Parameter

Alpha is a measure of consumer knowledge of a product. For different types of drug delivery systems (i.e. daily oral medication and microsphere injections), it was assumed that the doctors prescribing the medication will need to be knowledgeable of this product. Doctors at Norman Regional Hospital as well as OU's Goddard Health Services Clinic were interviewed to determine what factors they considered when prescribing a new drug. From these interviews, it was evident that they had extensive knowledge of the medications and delivery systems they would prescribe to patients. However, doctors do not consider the price of medications when they prescribe, so there high value of alpha will not factor into the demand equation.

A patient's knowledge of medication will change over time. At first, the consumer (patient) will have relatively little knowledge of the new medication. Patients will find out about new drugs through advertising campaigns, communicating with doctors, and also by word-of-mouth. Research has previously been conducted on the changing alpha value over time (Clemente-Harl, 2006). During the first year, a consumer's knowledge of the drug will be very low. Over time, approximately 2 to 3 years, through advertising and communication, the consumer's knowledge will increase. Finally, after the new drug (or delivery system) has been on the market for approximately 5 years, the consumer's knowledge of the drug will plateau at an approximate constant value of 0.9.

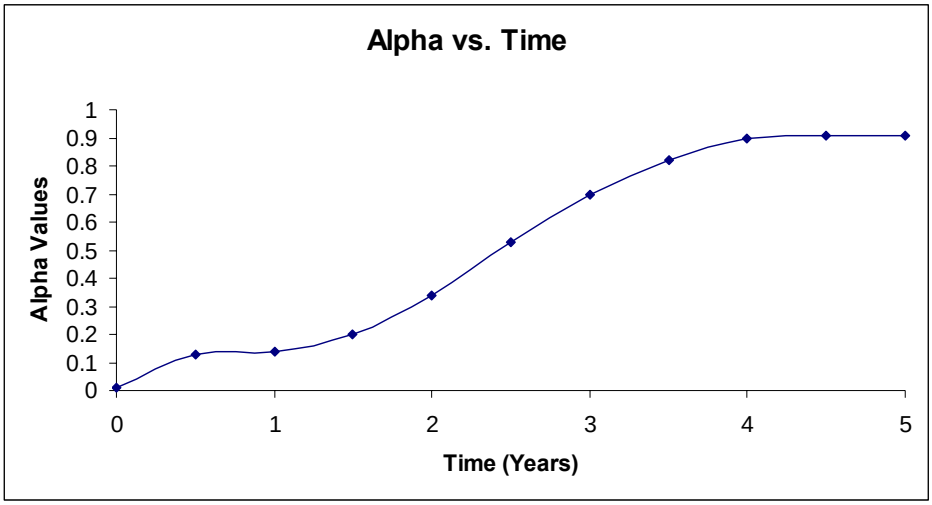

Figure 13

It is anticipated that this trend will be very similar to the trend observed when considering a new drug delivery system. Advertising and other forms of communication about the microsphere injections will need to be factored into the total cost. The parameter ρ was also assumed to be a constant of 0.75. Rho is determined by market factors and is generally between 0.7 and 0.8.

Beta Parameter

The beta parameter is a measure of how much a consumer will prefer one product over a second product. It is anticipated that the consumer will prefer a drug delivery system that is highly effective, convenient and has few side effects. It was determined through FDA research that as long as the drug encapsulated in the microsphere is identical to the drug present in the oral medication, then the standard FDA trials will not be necessary because the active ingredients in the medication have not been changed. However, when this is taken into account, the efficacy, from an active drug ingredient standpoint, of the two drug delivery systems must be assumed to be identical.

For economic analysis, the drug Naltrexone was studied. This is a drug that is taken by people who have a problem with alcohol addiction. One common problem with the oral form of this drug is patient adherence to the medication. For the beta parameter, it was determined that a microsphere injection of Naltrexone and the oral pill will differ by proportion of patients relapsing. Relapsing is defined as consuming any alcoholic beverage. (Kranzler, 2004) The proportion of people not having a relapse over time was used to determine a patients' satisfaction with the delivery system. It was assumed that this parameter will be important to consumers when considering using medication to abstain from alcohol.

As seen in Figure 15, the microsphere injection is slightly more effective over a longer period of time when examining relapsing behavior. Relapsing behavior was then related to consumer satisfaction with the drug delivery system as seen in Figure 16. It was assumed that the greater proportion of people that did not relapse, then the higher the satisfaction with the drug delivery system.

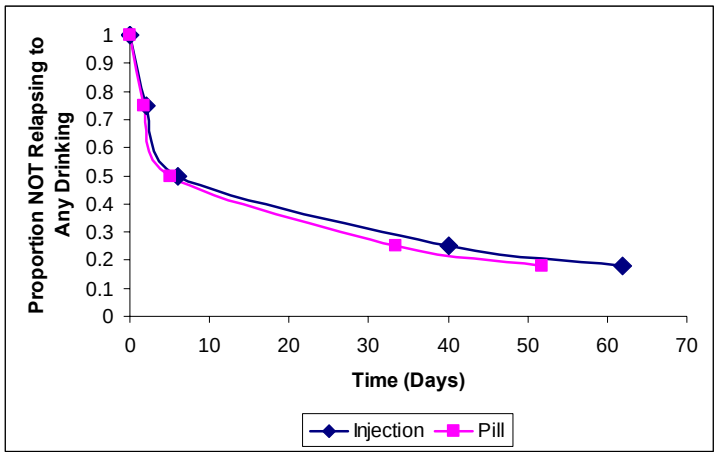

Figure 14

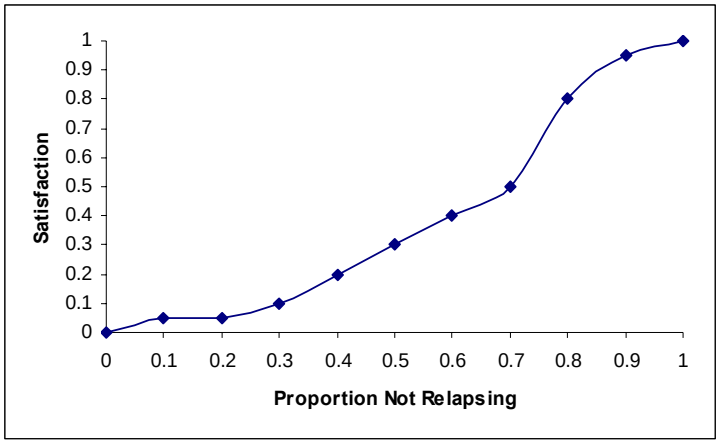

Figure 15

Using a time period of 30 days (approximately 1 month), it was determined that satisfaction of not relapsing was approximately 0.11 for the microsphere injection and approximately 0.09 for the oral daily pill. Side effects, such as dizziness, headache, and nausea were categorically (not quantified) reported when using both the microsphere injection and the oral daily pill (Roozen, 2007); therefore, this parameter was not taken into account to determine beta values. More research should be conducted to determine the other significant difference between the microsphere injection and oral pill delivery systems.

Convenience was also used as a factor when determining the value of beta. The satisfaction values for an extended release injection and an oral pill were determined through interviews with classmates. It was determined that an extended release injection that will last 30 days will be more convenient than an oral pill that a patient must take every day.

Table 10

Property	Weight	Injection	Pill	H_1	H_2
Relapsing	0.75	0.11	0.09	0.305	0.22
Convenience	0.25	0.89	0.61		

Table 11

$Hi=\sum w*y_i$	Beta	1/Beta
$\beta=H_{pill}/H_{micro}$	0.72	1.39

When this method is utilized, it was determined that the beta parameter will be approximately 0.72. Using this beta, the microsphere injection will be approximately 1.4 times preferred to the consumer over the oral daily medication. This is a fairly large beta value and will decrease the amount of product demanded. The proportion of patients not relapsing and convenience, in addition to the price of the medication, will be the most important factors when determining consumer demand. More research needs to be conducted in order to obtain a more complete picture of properties that could influence a consumer decision. Hopefully, when a more complete picture of the differences between drug delivery systems can be determined, the beta value will decrease. This decrease in beta will subsequently increase the amount of microsphere injections needed because the microsphere drug delivery system will be preferred more strongly than the daily oral medication.

Optimal Price Determination

As stated earlier, alpha was estimated to change over time. This change in consumer knowledge will affect the demand for a new drug delivery system. Alpha varied between 0.14 and 0.91 over a 5 year period. As alpha increases and more consumers learn of the new drug delivery system, then the demand will increase. As seen in Figure 17, the demand for different prices of the drug increase over time due to the increasing alpha value.

To determine the quantity demanded for the extended drug delivery system, several market parameters must be set. The price of the daily oral medication was assumed to be $150 per month, and the total budget for this segment of the consumer market was found to be approximately 3.4 million dollars in 2008. This value will change each year as medical interventions become more accepted than the customary behavioral therapies to combat alcoholism.

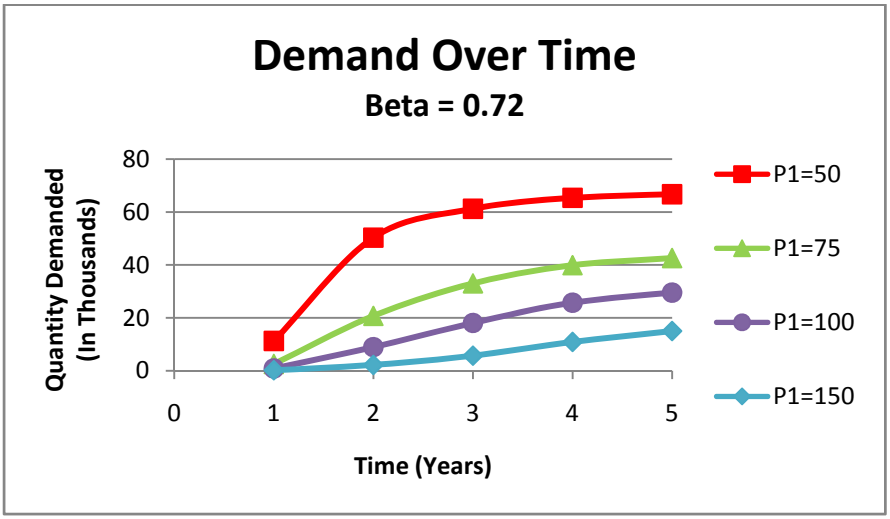

Figure 16

From Figure 17, it is evident that demand increases with a decreasing price; however, the total cost to produce the microspheres will increase with this increasing demand. To examine both of these factors and determine an optimal price to sell the microsphere, the Net Present Value (NPV) was calculated for a variety of prices over a ten year period. It was assumed that after the fifth year that the alpha value will remain fairly constant with a value of 0.91.

Net Present Value (NPV) equation (Equation 14) has several inputs. The first term is the summation of the cash flow (defined in Equation 15) divided by the interest rate for each year. The second term in the NPV equation is the sum of the cash flow, salvage value of the equipment, and working capital for the last year of production divided by the interest rate raised to the last year of production. The final term of the NPV equation is the total capital investment. The total capital investment is an estimation of the amount of money needed for the company to begin production based on the initial equipment costs.

Cash flow encompasses the profit (sales minus costs) each year multiplied by the fractional income tax rate, Φ. The fractional income tax rate was found simply by completing Form 1120-W, published and distributed by the Internal Revenue Service. Although pharmaceutical corporations are eligible for the corporate Alternative Minimum Tax rate, it usually does not apply to this industry. (Urban Institute and Brookings Institution, 2008) (American Council for Capital Formation, 2008)Because the corporate Alternative Minimum Tax (AMT) uses the corporate alternative minimum tax rate of 20%, insufficient applicable deductions and exemptions were found to necessitate AMT (Tax Policy Center, website). Quite simply, Φ is found by dividing the percentage tax rate by 100 to obtain the tax bracket in decimal form.

The cost term in the cash flow equation is composed of variable costs and fixed costs. Variable costs are dependent on the amount of product that is produced. Raw materials compose the majority of the variable costs. Fixed costs include equipment costs, rent, and taxes etc. These are costs that must be paid regardless of how much product is produced. This factor is also multiplied by a depreciation factor. For this project, straight line depreciation over a ten year period was used (Peters, 2002).

Equation 14

$$NPV = \sum_{k=1}^{n-1}\left[\frac{CF_k}{(1+i)^k}\right] + \frac{CF_n + V_S + I_W}{(1+i)^n} - TCI$$

Equation 15

$$CF_j = (S_j - C_j)(1-\phi) + \phi * d_j$$

NPV = Net Present Value

CF_j = Cash Flow at Year j

i = Interest Rate

V_s = Salvage Value of Equipment

I_w = Working Capital

TCI = Total Capital Investment

S_j = Revenue Obtained during Year j

C_j = Total Cost to Produce (Variable plus Fixed Costs)

Φ = Fractional Income Tax Rate

d_j = Depreciation Constant (Straight Line Deprecation)

When NPV was calculated and summed over a ten year operating period, the following results were obtained (Figure 17). The maximum NPV appears to occurs at a price of $75. This will be the optimal price when operating over a ten year period if the price remains the same for all ten years of operation. The NPV for the $50 and $75 prices were calculated per year and the results of this analysis can be seen in Figure 18. At all prices, the process to make the microspheres for drug deliver is not profitable during the beginning of production. It is not until the end of the first year of production that these prices become profitable. Therefore, the company must have enough funding up front to continue the process even during times that the net present value is negative.

Another interesting point in Figure 18 is the intersection of the $50 and $75 price lines in year six. If this process was continued for more than ten years, it would be more profitable to produce the product at a price of $75. Another viable option to increase profit over a ten year period would be to increase the product price by $25 in year six. Increasing the price could be accomplished if the microsphere drug delivery system is well established in the product market. This will increase the overall profit and net present value of the company. Additional research is needed in order to predict the market for microsphere drug delivery systems in year six.

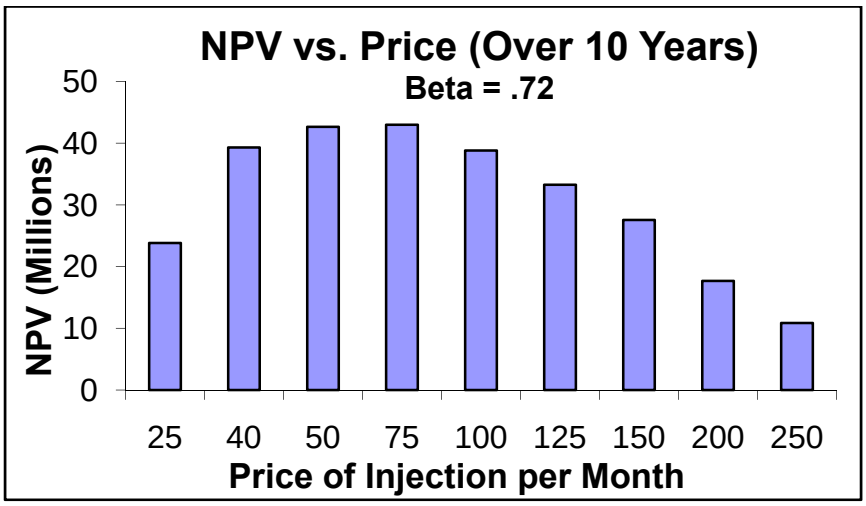

Figure 17

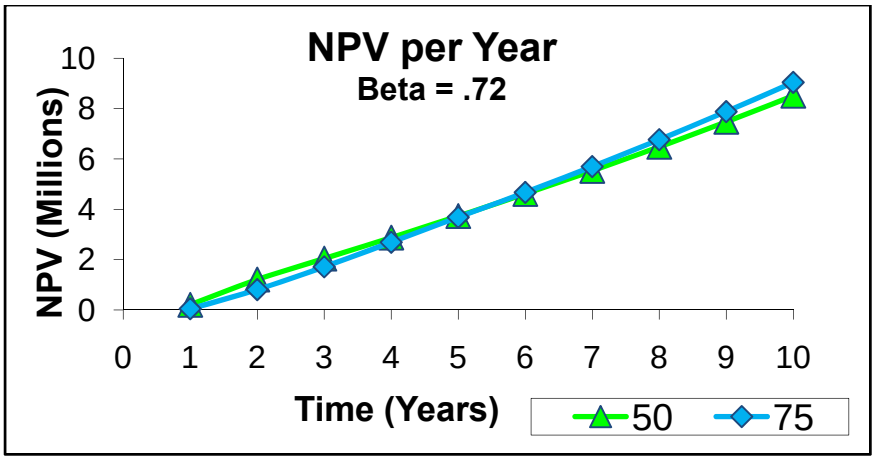

Figure 18

Comparing Different Values of Beta

One of the factors used to determine the value of beta was convenience. This factor is only a postulated value about consumer preference. To make sure that several scenarios were examined, different values of beta were used with a variety of prices for microsphere production (Figure 20). This will allow us to make educated assumptions about different pricing trends that are dependent on consumer preference.

As the price of the microsphere injections increase, different values of beta have a great effect on net present value over a ten year period. This is illustrated best when comparing the $25 price and the $200 price. For the $25 price, all NPV's are very similar and beta does not appear to have a large effect. For the $200 price, the NPV varies greatly with different values of beta. One explanation is that consumer preference plays a larger role in determining demand at a high price. The consumers for this model were patients seeking treatment for alcoholism, assuming they did not have any help from an insurance provider; therefore, they would pay for all medication out-of-pocket. Spending a large amount of money on medication every month will require a higher preference for the medication. If the consumers' preference is very high (resulting in a lower value of beta), then they will be more inclined to spend a larger amount of money. When the out-of-pocket expense is lower ($25 per month), then the consumer preference factor (beta) will not have as much influence on consumer demand for the product. It would be favorable to obtain the smallest value of beta possible. A small value of beta equates to a strong preference for the extended release injection over the oral daily pill.

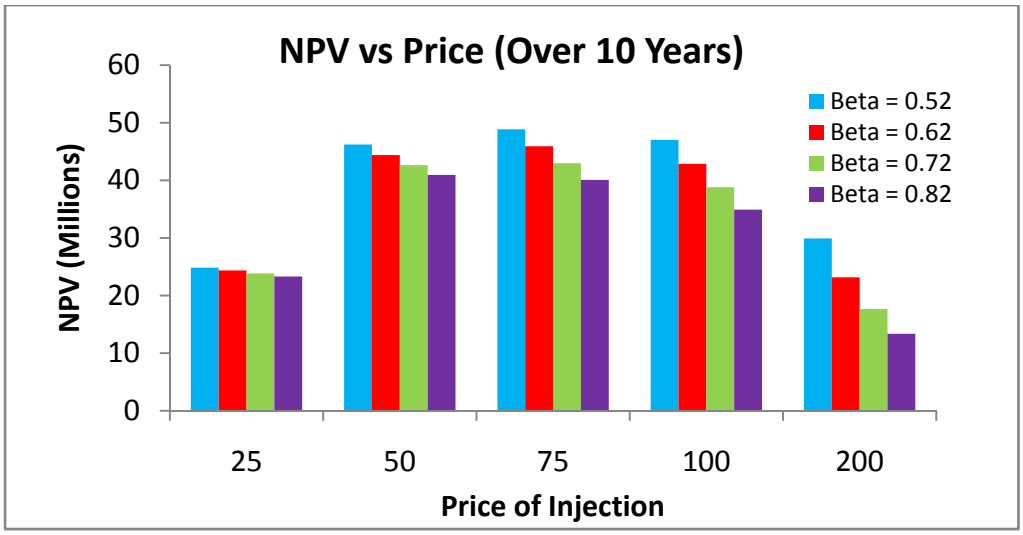

Figure 19

CEA Demand Model

One model to determine the social value of a new drug or technology is Cost-Effectiveness Analysis (CEA). This method combines medical information with microeconomics. In recent years, CEA has emerged as one of the main techniques for analyzing the healthcare industry. The center of this model is a comparison between the marginal costs and benefits between a new technology (medication) and an existing technology. This is represented mathematically in the following equation:

$$\frac{(C_I - C_C)}{(B_I - B_C)} = \frac{\Delta C}{\Delta B}$$

The subscript *I* represents the marginal costs, C_I, and marginal benefits, B_I, of the intervention or new technology; while the subscript *C* represents the marginal cost and benefits of the comparable technology C_C and B_C, respectively (Vernon, 2005).

This model incorporates the needs of the payer (policy-maker) by considering the marginal opportunity value against the benefits of the new technology. One of the main benefits utilized by CEA is the quality-adjusted-life-years (QALY's). This is a measure that takes into account the duration and quality of life. The output of CEA, for example, would be a payer's willingness-to-pay for a new treatment in the numerator divided by the QALY (Vernon, 2005)

The cost-benefit ratio obtained from this method could potentially be used when determining the demand of a new drug delivery system. Further research into modeling consumer demand will be necessary to determine how this ratio could be incorporated into the overall demand model.

Future Economic Work

General Method for Determining Pharmaceutical Price and Demand

There are three phases a drug progresses through when it is put into the market. Each phase has a different type of economic structure and different factors will affect the demand of the drug. Also, with each phase, the pharmaceutical company may decide to change the price of the drug in order to

maximize profit. Future work should determine how each of these markets will affect the price of the drug delivery system.

Phase I

During Phase I, it is assumed that the drug or new drug delivery system will be a unique type of product. The market will be monopolistic with only one drug producer acting as the monopoly. The phase occurs because most patents on new drugs will last for a period anywhere between 5 and 20 years. During this time, no generic drugs can be sold to compete with the name brand drug. Also, the new type of delivery system for a specific drug cannot be recreated by a competing firm.

The price during this phase will be determined by the elasticity of demand for the new drug or drug delivery system. For example, if a life saving drug was introduced into the market, then the demand for this drug would be very inelastic. This means that no matter what the price of the drug, there will be demand for this product. If the new drug is non-necessitous, then the demand will be very elastic and the demand will be very dependent on the price.

It is assumed that during this phase, insurance and HMO's will have very little bargaining power with the pharmaceutical companies. Bargaining power means that the insurance company will not have any drug substitutes. It will be assumed that they will provide coverage for the new drug or delivery system. Again, the elasticity of the new drug will be the primary determinant of drug price and subsequent demand.

Phase II

During this phase, other name brand drugs that will target the same disease will appear on the market. These drugs will be different enough not to violate any patents held by the first drug manufacture; however, this other name brand drug will provide a suitable substitute for the first drug. This substitute and new drug manufacture will change the market structure from a monopolistic market to a competitive market. In a competitive market, there is more than one firm producing a similar product. While in this phase, the pharmaceutical companies will compete with each other to obtain the most demand. Driven by this competition, both companies will lower their drugs' price in an attempt to gain consumer demand.

The insurance and HMO's will see a large increase in their bargaining power. Now they can change pharmaceutical companies or switch to the substitute drug. This will force the drug manufactures to lower their prices in order to satisfy the insurance companies. The bargaining power of the individual insurance company will depend on their size and number of customers in need of the specific drug. Larger insurance companies and HMO's will have more bargaining power than smaller companies with fewer customers. In order to keep the maximum number of clients, the pharmaceutical companies will lower their price during this phase.

Phase III

This phase represents the point in time when the patent has expired for the original drug, and now generic drugs are free to enter the market. The market structure will continue to be competitive with more firms and competing medications entering the market. The pharmaceutical companies that manufacture the name brand drugs will realize that they cannot compete with the cheaper generic prices; therefore, they will cease to target the section of the population that will be satisfied with the cheaper generic medication. The drug companies will focus on the segment of the market that still

requires the name brand drug and is willing to pay for it. The drug manufacturers will actually increase their price in order to maximize profits. However, the insurance companies and HMO's will have increased bargaining power during this phase because there are so many substitutes for the original name brand drug. The drug manufactures are able to increase price because the demand for the name brand drug is most likely more inelastic than the demand for the generic drug. Consumers (doctors and patients) with inelastic demand curves will be willing to pay a higher price for the original name brand drug.

Segmenting the Consumer Market

The consumer market will also need to be divided into three categories. The first category will be the percentage of consumers that have maximum insurance coverage. These insurance companies will offer some type of maximum coverage plan and will have a large amount of bargaining power with the pharmaceutical companies due to their size and amount of clients. It is anticipated that these larger companies will be willing to cover medications at higher prices than smaller insurance companies.

The second category will be the segment of the target population that has minimum insurance coverage. It is anticipated that minimum coverage will not cover the cost of certain medications, and when a particular medicine's price is too high, the insurance company will force the patient to take an alternative medication. The demand for the segment of the consumer market with insurance will be dependent only on doctor's advice and prescription requests. It is anticipated that the population in this category will follow their doctor's advice as long as the insurance will cover the cost.

Consumers that do not have health insurance coverage will also be taken into account. If consumers (patients) do not have health care coverage, then they will have to weigh the benefits of taking the drug to the cost of the medication. The consumer demand model will be used for this section of the population. The parameters of the consumer demand model will reflect the consumer preferences and knowledge. As discussed above, a consumer's knowledge of the product will change with time, and their preference for one product over another is dependent on the potential side effects and the proportion of study subjects that do not relapse when taking the medication.

Future Modeling Work

When doctors prescribe drugs they are sometimes unsure of the correct BPDC to achieve the best results. Sometimes a doctor will check up on a patient to see if the medication is working. The doctor may choose to up the dosage if the current prescription if the patient does not show improvement. Therefore, it would be ideal if the doctor could choose to raise the BPDC level during the treatment. The current simulation does not allow for this option and should be modified to do so.

As of now the excel spreadsheet looks very complicated, which it is, but a doctor will need a more user friendly version of this program. Convenient options such as buttons should be added, and the spreadsheet should be made easier to navigate by a person unfamiliar with the program.

The BPDC optimizer has shown to produce results that are logical; however, it is based on assumptions and models. It would be useful to see what degree of accuracy the model is predicting future BPDC. To determine the accuracy the optimizer, the results should be compared to experiments found in literature. As of now, no literature has been found with results that could be compared to this

research, but an extensive search of other drug experiments, besides Piroxicam, should produce comparable literature.

As of now the metabolic clearance is described only as a function of concentration through a power law model. The major assumption in the metabolic model is that the patient's metabolic rate does not change during the course of the treatment. In actuality, the patient's metabolic rate is changing, but to what degree is unknown. Natural changes in a patient's life may cause their clearance rate to change by a significant degree or a non-significant during a period of 30 days. The program should adopt this concept of metabolic fluctuations and predict a range of possible BPDC rather than a single value.

The most important change that the simulation should undergo is to incorporate the diffusion based microsphere release model. As of now the simulation is running on the empirical data of microsphere release. The diffusion based model would allow for a unique selection of microspher (Drug Delivery Technology, 2008)es to be used in the injection. Microspheres with diameters ranging from 1 to 100 μm with different molecular weights and different initial radial concentration profiles could be chosen. The unique drug release profiles of microspheres would be chosen, which would allow a more versatile simulation that could produce BPDC levels closer to the target BPDC.

Conclusions

We have created a simulation program in excel that is intended to aid doctors in the process of prescribing long acting microspheres. The simulation program is a combination of a metabolic model and a model of microsphere release rate. The metabolic model is shown to accurately predict the metabolic clearance of a drug mass from the blood stream. Using the method outlined in the Metabolic Model section the clearance rate of a drug can be described by a simple power law model .The BPDC optimizer predicts future BPDC levels and chooses the appropriate dosage of microspheres to achieve a target BPDC. The program has been adapted to prescribe microspheres releasing Piroxicam. Currently the prescription model is limited to nine types of microspheres outlined in the Microsphere Release Model section. Using more types of microspheres with unique drug release profiles will allow the simulation to create BPDC profiles that more accurately fit the target BPDC profile.

It was determined from net present value calculations that producing Naltrexone microspheres will be profitable over a ten year period. However, this process is only profitable after at least one year of production. Enough initial investments will have to be gathered to cover the non-profitable production. Assuming that enough funding is available, the optimal price of a monthly microsphere injection was found to be $75. This cost seems very low, and additional market structure analysis is needed to determine if a higher price could produce more profit. If the market proves to be more monopolistic than expected, then the microsphere manufacturer will be able to charge a much higher price for the microspheres used in extended release injections.

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