Engineering Drug Delivery

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Capstone Design Project- University of Oklahoma - Spring 2003

Introduction

Based on extensive research of all aspects of the process and economic analysis, the Controlled Release Osmotic Drug delivery of is a feasible, and profitable venture. The type of delivery system to be used will be a capsule taken orally, consisting of a semi-permeable membrane, and making use of osmotic pressure to slowly release the drug over a predetermined time frame. The drug can be designed and produced in Norman, Oklahoma and distributed to the national market from that location.

Tamsulosin hydrochloride, commonly known as Flomax® is the active ingredient of the drug and is marketed towards men past middle age. Flomax® is used to treat the symptoms of an enlarged prostate--a condition technically known as benign prostatic hyperplasia or BPH. The major symptom associated with BPH is trouble urinating. BPH is obviously only experienced by men and rarely causes symptoms before age 40. However, more than half of men in their sixties and as many as 90 percent in their seventies and eighties have some symptoms of BPH.

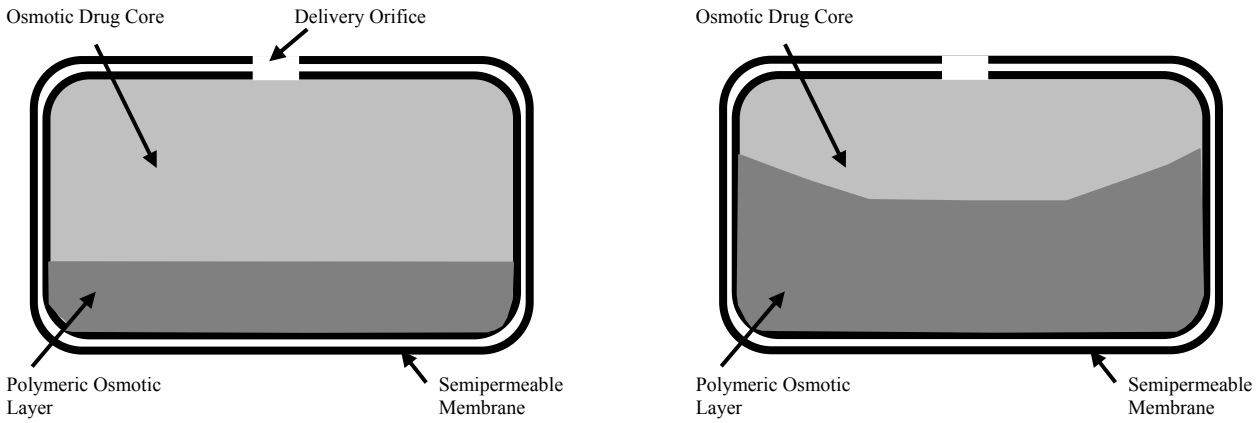
Controlled Release Drug Delivery Systems

Three main categories exist for controlled release (CR) oral drug delivery systems: matrix, reservoir and osmotic. In matrix systems, the drug is embedded in a polymer matrix and the release takes place by partitioning of the drug into the polymer matrix and the release medium. In contrast, reservoir systems have a drug core surrounded/coated by a rate controlling membrane. However, factors like pH, presence of food, and other physiological factors may affect drug release from conventional CR systems. Osmotic systems utilize the principles of osmotic pressure for the delivery of drugs. A major advantage of drug release from these systems is that it is largely independent of pH and other physiological parameters, and it is possible to modulate the release characteristics by optimizing the properties of the drug and system. For these reasons, osmotic release systems will be the focus of this design.

There are several osmotic design possibilities that were considered by CORRN Consulting. They all fall under the category of osmotically controlled oral drug delivery systems. The two main tablet systems researched were: Elementary osmotic pumps (EOP) and Push-pull osmotic pumps (PPOP). CORRN Consulting recommends using the push-pull osmotic pump system due to the low solubility of tamsulosin hydrochloride which can be better handled by a PPOP system.

Drugs having extremes of water solubility can be delivered via the push-pull osmotic pump. As shown in Figure 1, it is a tablet consisting of two layers coated with a semipermeable membrane that allows water to pass into the concentrated drug without allowing the drug to exit anywhere but the delivery orifice. The drug along with osmagents is present in the upper compartment whereas the lower compartment consists of polymeric osmotic agents. The drug

compartment is connected to the outside environment by the delivery orifice. After coming in contact with the aqueous environment, the polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice.



Before Operation **During Operation**

Figure 1. Schematic diagram of proposed design.

Important to the design of the pill are several mathematical theories involving the release of the drug through the force of osmotic pressure. The complex derivation of these formulas will not be seen here, but the key equations used to formulate the mathematical model of the delivery system are very relevant and shown below. First, osmotic pressure arises from the fundamental law that the chemical potential of solvent in a solution and a pure liquid must be the same if they are in contact through a semi-permeable membrane at the same pressure. In other words, the solute lowers the chemical potential on the solution side of the membrane and results in water moving across the membrane to the solution side. This continues until equilibrium is reached. At equilibrium, the hydrostatic pressure, ρgh, is equal to the osmotic pressure. The equation for osmotic pressure for this system is reduced to:

$$\Pi = RTc_B \qquad [1]$$

Where Π is the osmotic pressure, R is the gas constant, T is temperature and c_B is the concentration of the solute in g/Liter. Finally, the changing volume of an elementary osmotic pump can be described with the help of equation [1] to give us:

$$v(t)_{EOP} = \frac{A_S KRTc_B}{h} t \qquad [2]$$

Where v(t) is the volume with respect to time, A_s is the surface area of the semi-permeable membrane, K is a factor of the permeability of the membrane, and h is the thickness of the membrane. This equation is fundamental to understanding how an elementary osmotic pump system will deliver the medication to the body.

Push pull osmotic pump theory

Hydrogels have high capacity for holding water and have a large affinity for water. This affinity draws most of the water entering the system into the hydrogel. The remaining water that enters the system converts the drug layer into a saturated solution. As the solution is formed, it is forced out of the pill orifice by the expanding hydrogel. In this case, the hydrogel is selected in order to expel the entire top compartment from the system. This means that the hydrogel must have the ability to at least swell to a final volume equal to the tablet.

The release profile of the drug solution in this case is described by the equilibrium swelling time for the specific hydrogel. The assumption is made that the influx of water due to osmosis creates a situation where there is an infinite water reservoir available for the hydrogel. In this case, the swelling hydrogel's expansion is consistent with equilibrium swelling. In order to maintain the desired zero-order kinetics, a hydrogel must be selected that has a linear relationship of swelling ration versus time. The mathematical model for this linear release profile is determined by:

$$v(t)= \beta\, t \qquad [3]$$

Where β is the slope of the equilibrium volume swelling ratio and depends on many factors including type of gel, degree of crosslinking, temperature, etc. β is determined from empirical data for each individual hydrogel.

Design

Membrane:

As mentioned above, the choice of a rate-controlling membrane is an important aspect in the formulation development of oral osmotic systems. Since the membrane in osmotic systems is semipermeable in nature, any polymer that is permeable to water but impermeable to solute can be selected. Because the pill will also need to be ingested, biocompatibility is a necessity for the selected polymer. These are Cellulose Acetate (CAB) and Composite Polyamide (CPA). Depending on which group of material used, the membrane achieves significantly different levels of performance.

Cellulose acetate (CA) is the material that was chosen for the semipermeable membrane. The decision was based on the fact that cellulose acetate has been widely used to form rate-controlling membranes for osmotic systems. In addition, cost of CA is relatively low, and the permeability of CA is relatively high.

The thickness of the membrane was determined by setting the flux of water through the top compartment equal to the flux in the bottom compartment. The influx of water to the bottom compartment is described by the PPOP model, and the EOP model applies to the top compartment. Setting the derivative of the volume with respect to time of equation [2] equal to equation [3] leads to:

$$\left.\frac{dv}{dt}\right|_{BC} = \left.\frac{dv}{dt}\right|_{TC} \Rightarrow \beta = \frac{A_S KRTc_B}{h} \Rightarrow h = \frac{A_S KRTc_B}{\beta}$$

The thickness was calculated to be 259 μm. The design thickness was actually 250 μm. The decrease in thickness ensures the top drug layer will be in solution as the hydrogel forces it through the orifice. This prevents clogging.

Orifice:
The orifice is 1.25 mm in diameter. This diameter does not create to large of a pressure drop (which was calculated using the Hagen-Poiseuille equation relation pressure drop to flowrate). The diameter was not chosen to be larger because a larger diameter could lead to significant diffusion of drug from the orifice

Contents of the Drug:
The push layer of the tablet is composed of 18.4 mg poly(acrylic acid) hydrogel crosslinked with ethylene glycol dimethacrylate (EGDMA), which is an expansive hydrogel. The main reason that PAA was chosen is that its swelling is linear with time. This leads to a constant release profile. Also, it is a cheap material to purchase, stable, so it will not react with the active ingredient, and accomplishes the necessary task.

The drug layer consists of 0.4 mg the active ingredient in the system, tamsulosin hydrochloride, sodium chloride, in order to produce the osmotic pressure gradient, as well as an inert drug for binding purposes and 0.1 mg salt to drive the osmotic pressure. The inert drug in this layer is 0.112 g microcrystalline cellulose. Several reasons contributed to the selection of microcrystalline cellulose for the inert. Among these are its remarkable binding capabilities, its exceptional hardness, and its ability to be disintegrable in the tablet. The final dimensions of the drug are 1.0 cm in diameter 0.5 cm in height for a total volume of 0.39 cm^3. Inside dimensions include a 0.016 cm^3 push layer and a 0.374 cm^3 drug layer.

FDA Approval

In order to reach production, two aspects of the project must be approved by the FDA. First, the novel drug delivery system (the drug tablet itself) must be approved. The development cost and time required for introducing a novel drug delivery system is $20-50 million and 3-4 years respectively. It is impossible to predict ahead of time exactly how much money this approval process will require, so an average of $30 million was generally assumed, but much deviation to this cost was allowed for the risk analysis of the project. Luckily, all materials used in the new design have already been pre-approved by the FDA in other capsule designs. This saves an enormous cost of approving a new chemical entity in the design which would run approximately $500 million and an added ten year pre-production investment.

The Second factor needing approval for this venture is the manufacturing process. The process and location must meet minimum FDA requirements for equipment, packaging and personnel, as well as several other factors. On top of this, each individual piece of equipment must be validated by an outside contractor before approval can be attained. Validation costs vary by machine and contractor both, but an average estimation for the entire equipment cost is 12 percent.

Fabrication Process

Machine design and fabrication have been extensively researched for the area of tabletizing and mass production. The process flow for the fabrication of tablets is shown in the diagram on the following page. The drug layer and osmotic layer will go through the same process, excluding blending. The plant will therefore need two of the same model of machines to accommodate the production capacity needs of consumers and to make the process flow more efficient. Included in this plant layout are many essential systems required to be approved by the FDA. These include: CDA-the process air system, A dust collection system, HVAC-the heating, ventilation, and air conditioning system, the USP water system, the waste water treatment system, and the nitrogen supply system.

Financial Analysis

The Total Capital Investment has been estimated at $61, 557, 000 with a pre-production time investment of four years for both construction and the FDA approval process necessary before the product can be presented to the public. The TCI centers around a total equipment cost of $6, 672, 500. The equipment cost can be predicted very accurately as most prices were quoted from vendors for specific machinery.

Raw materials alone shall have an annual cost of $75 million. Similarly, the production costs and high standards of quality control lend to a total annual manufacturing cost of $156 million. Though the investment capital required for this venture is large, the annual income far outweighs the expenses associated with the process. Based on our market strategy, the plant has been design to produce 300 million tablets per year. Current prices obtained from pharmaceutical companies indicate that these tablets can be sold for approximately one dollar per tablet for an annual income around $300 million before taxes. This profit margin allows the company to repay the capital investment only a year and a half after production begins and gives a margin of safety to investigate risk analysis and worst-case scenarios.

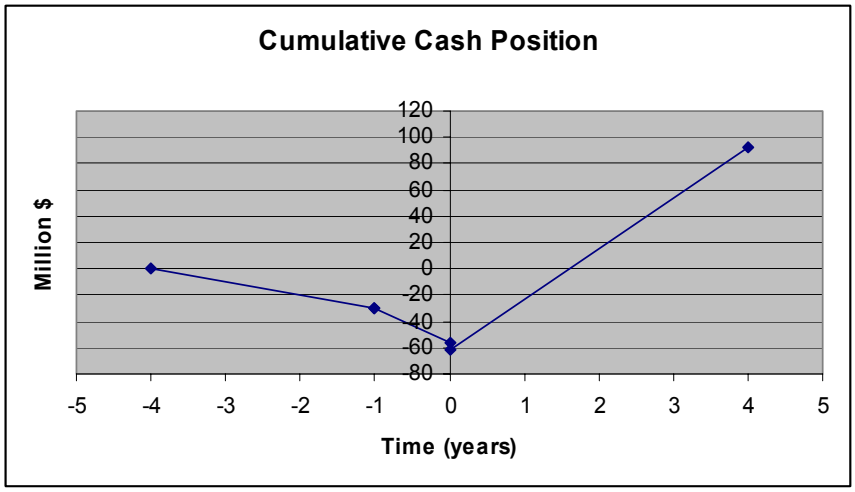
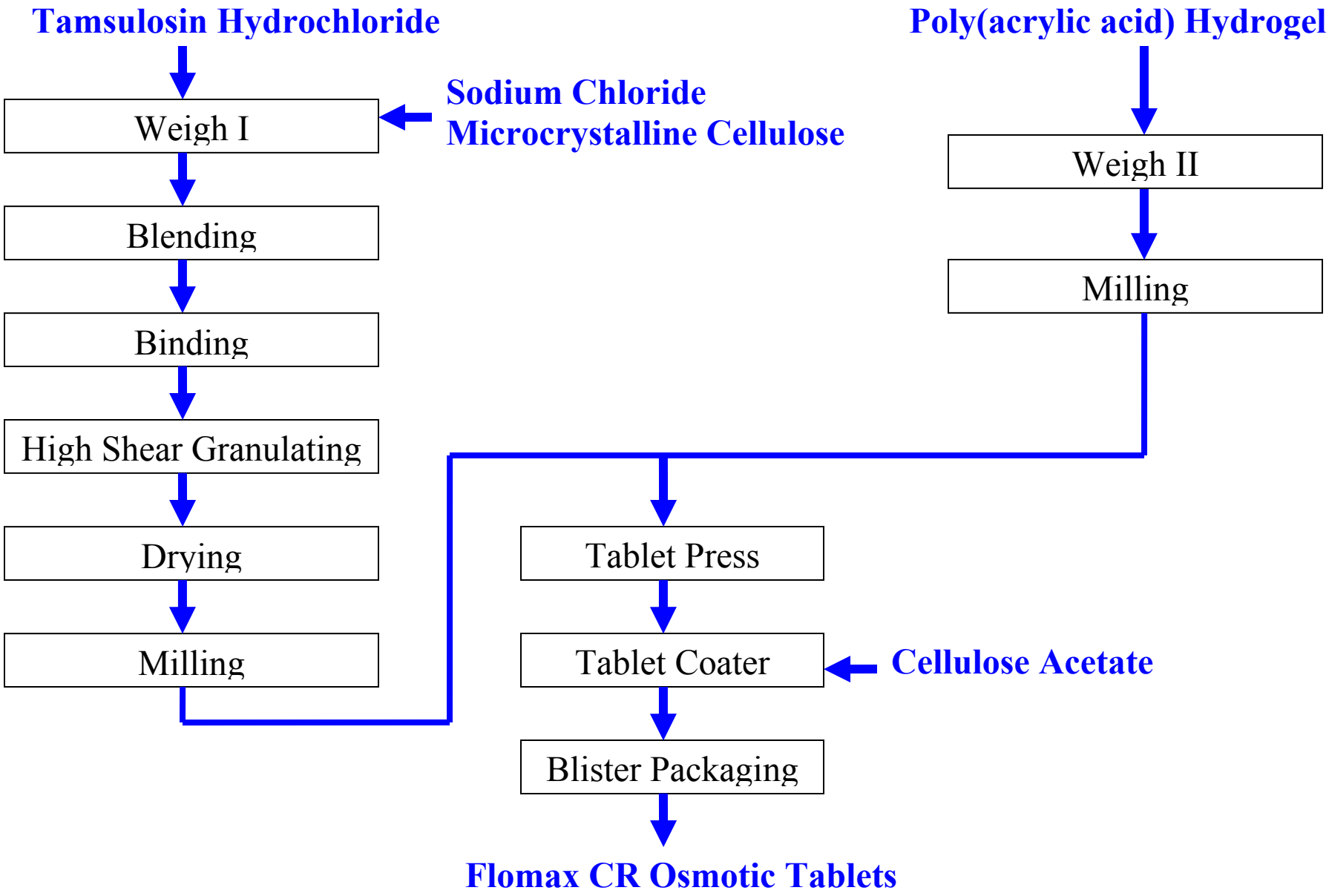


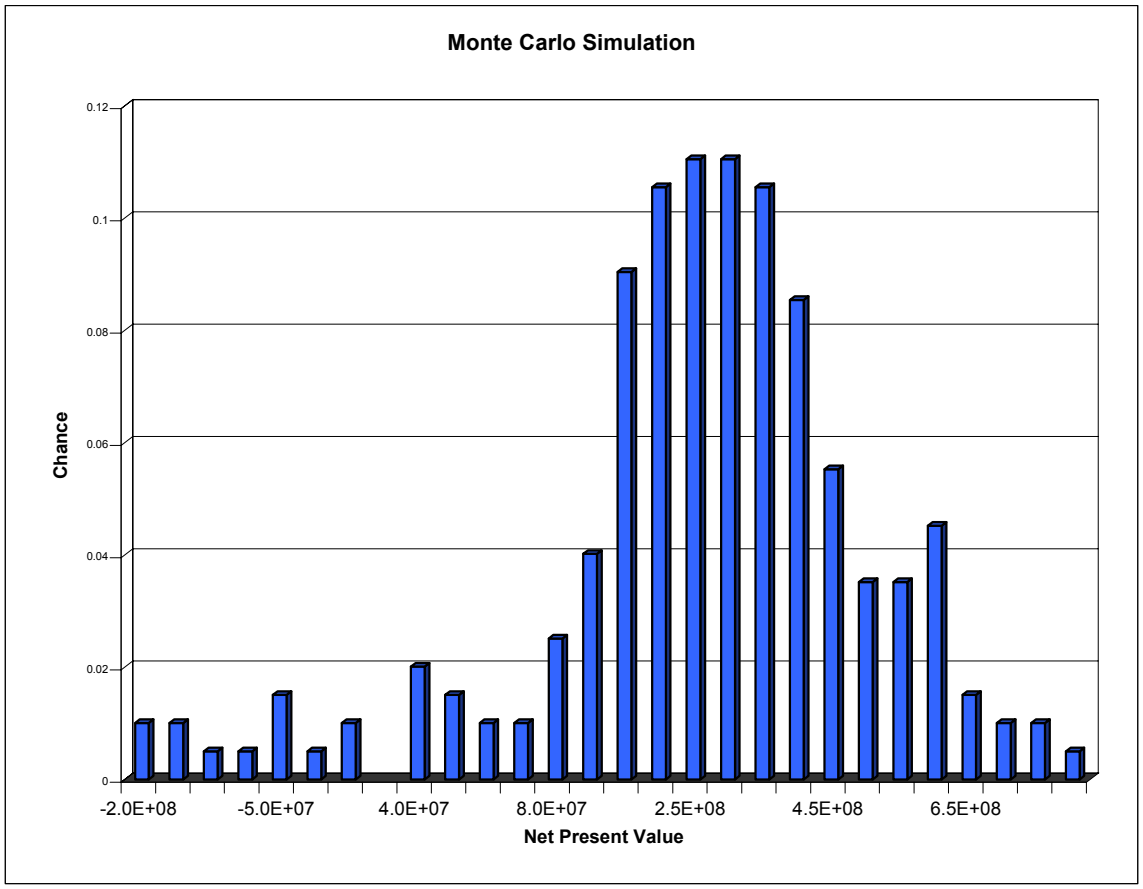
Fig 2: Cumulative Cash Position over 8 yrs.

Process Flow Diagram



Risk Analysis:

Montecarlo Simulations were run to determine the sensitivity of the cumulative cash position with the variance of several unknown factors in the TCI, the product costs, and the demand of the pill itself. The result of these simulations are shown below and they reveal that there is only about 6-7 % of loosing money.



Conclusion:

It has been determined that a push pull osmotic pump will be the preferable system for delivering the drug tamsulosin hydrochloride in a slow, time released format. This venture, while requiring a large initial investment, has the potential to be highly profitable. In fact, conservative estimates have the project reaching a financial break-even point in under two years; a good sign that helps reduce the risk of the venture in an unendingly progressing market vulnerable to change with future pharmaceutical advances. CORRN Consulting recommends proceeding in the engineered drug delivery proposal.