Design and Production of a Transdermal Delivery Device for Contraception

Introduction

In this project, a transdermal drug delivery system for a generic version of the birth-control device Ortho-Evra® was designed. Transdermal systems deliver a slow release of drug into the body over time, resulting in long-term effectiveness and added convenience. This effect is particularly useful when treating people with chronic ailments. Drugs capable of being passed through the skin must have low molecular weights, low dosage, and stability in the presence of enzymes.

Transdermal systems are an innovative delivery mechanism commonly replacing oral dosage forms and other traditional forms of administration. The drug contained on the transdermal patch enters the body through the skin in contact with the patch. The drug diffuses across the layers of the skin and ultimately diffuses into capillaries for systemic delivery. The pathway through the skin taken by the drug, either through cells or around cells, depends on the properties of the drug, but typically it is assumed that drugs follow the pathway around cells. The diffusion of the drug from the patch into the skin may be represented in a mathematical model. This model accounts for each individual layer involved in the diffusion, but it also may be reduced into simpler form accounting for only the rate-determining layer. This reduced model is still useful, as the resistance of every layer except the rate-limiting layer is essentially zero. This model was used with experimental data to determine a design for a viable patch containing the drug chosen for production.

As well as the active ingredients, there are other components of a transdermal system. The components of most transdermal systems are active ingredients, adhesives, enhancers, and excipients. The enhancers are used to assist in the diffusion of the drug through the skin. The excipients are used for reasons such as skin softening and repair. The adhesives allow the patch to stick to the skin. The adhesive must have a lower surface energy than the skin and have properties that allow it to blend into the transdermal matrix.

A production facility was then designed for the manufacture of the transdermal system. The overall process and its corresponding equipment were considered and an economic analysis was completed. The storage of excess materials was considered, and the facility was

subsequently designed. Once the design of the facility was completed, the distribution of the product was then taken into consideration.

Results

Patch Design

Through patent research for transdermal systems delivering ethinyl estradiol in combination with norelgestromin, the formulation presented in Table 1 is suggested. Table 2 illustrates the total amount of each component required for the first three years of production at 16.1, 32.2, and 48.3 million patches/ year, respectively. These results attempt to model the formulation that most closely reflected the delivery rates for the active ingredients of proprietary Ortho Evra® (150 µg/24 hours for norelgestromin and 20 µg/24 hours for ethinyl estradiol [1]). The proposed size of the patch is 10 cm^2. It is proposed that this formulation be manufactured as a single-layer, matrix system. Not shown in the following tables is the solvent, hexane. Hexane will be used as a solvent to help the lower the viscosity of the solution and to ensure a well-mixed product. The hexane will be evaporated from the patch and subsequently incinerated. Therefore, its amount does not contribute to the weight of the final product.

The components of the patch are displayed in Tables 1 and 2. The active ingredients are ethinyl estradiol and norelgestromin. The remaining components serve additional roles such as adhesives, enhancers, and excipients.

Table 1: Contents of Transdermal System

Component	% on patch [2]	Component	Amount on Patch
% Ethinyl estradiol	0.2	Ethinyl estradiol	0.75 mg
% Norelgestromin	2.0	Norelgestromin	7.50 mg
% Polyvinyl pyrrolidone (PVP – CLM)	20.0	Polyvinyl pyrrolidone	75.00 mg
% Propylene glycol monolaurate (PGML)	10.	Propylene glycol monolaurate	37.50 mg
% Oleic Acid	0.5	Oleic Acid	1.90 mg
% Polyisobutylene	67.3	Polyisobutylene	252.40 mg
		Total wt.	375.00 mg

Table 2: Necessary Weights for Transdermal System (kg)

Component	Year 1	Year 2	Year 3
Ethinyl Estradiol	11.6	23.2	36.2
Norelgestromin	115.8	231.7	362.3
Polyvinyl pyrrolidone	1158.0	2317.0	3623.0
Propylene glycol monolaurate	579.0	1158.5	1811.5
Oleic Acid	29.3	58.7	91.8
Polyisobutylene	3898.0	7796.0	12194.0

Pressure-sensitive adhesives are the common form of adhesive used in transdermal systems. They are permanently tacky at room temperature, and they are easily applied with light pressure. Pressure-sensitive adhesives do not require solvents for activation [3]. Three major pressure-sensitive adhesives are polyisobutylenes, acrylics, and silicones. Polyisobutlyene is the adhesive used in this patch due to its exceptional adhesion in high moisture environments and its low cost [3]. Polyisobutylene has a surface tension of 30-32 dyne/cm. This is lower than the critical surface tension of skin, which is 38-56 dyne/cm, depending on humidity and temperature.

Skin penetration enhancers assist the diffusion of a particular drug into the skin. In other words, the addition of enhancers increases the mass flux of a drug across the desired surface area. The driving force for the drug in the absence of penetration enhancers is the concentration gradient between the patch and the skin. The enhancer used in this patch is crospovidone, which draws water to the surface of the skin. This in turn causes swelling, which provides more surface area for diffusion.

Excipients are ingredients within a drug product that are considered inactive, from a pharmacological perspective. In the case of Ortho Evra®, which is the patch that combines ethinyl estradiol and norelgestromin, there is one excipient used. The excipient used is propylene glycol monolaurate, which acts as an emollient.

Manufacturing

The formulation presented in Table 1 will be manufactured using the following steps:

1. Weighing of raw materials.
2. Mixing of ingredients and solvent.
3. Coating of mixture on patch backing.
4. Evaporating solvents and curing the matrix.

5. Lamination of the release liner.
6. Cutting individual patches followed by pouch lamination.
7. Boxing pouched patches.

It has been determined that the coating process will require one line operating for approximately 66% of the first year to produce 16.1 million patches. A second line will be added for production of 32.2 million patches during the second year of operation, which will only require run time during 66% of the year for both lines. The 48.3 million patches produced during the third year will be accomplished by running two lines for the entire year. Due to the high rate of production for the cutting/pouching line and the boxing line, only one of each of these units is required, even at the full-scale production of 48.3 million patches. It was assumed that one year will consist of 250 working days at one shift for production per day. A second shift will be incorporated for cleaning, maintenance, and packaging.

The economics of this process were evaluated under the assumption that the manufacturing facility would be located in South America, specifically Brazil. Appropriate labor, utility, and warehouse costs were used in the design. It has been determined that the cost of manufacturing one patch is between $0.28 and $0.30 depending on employee salaries. The current U.S. pharmacy price for Ortho Evra® is $15 per patch. Since this product is a generic drug, it was assumed that its price will be half of Ortho Evra® at the pharmacy. The mark up at the pharmacy is assumed to be twice the price for which it was purchased. Therefore, the estimated manufacturer's patch price will be $3.75. Selling the patches for $3.75 per patch yields a net present value of $684 million after production for 10 years and after startup of the second line. A price of $1.00 per patch yields a net present value of $142 million. Table 3 presents the manufacturing cost summary for the process. The product sales in Table 3 were calculated by charging $1.00 per patch. Utility costs resulted from electricity usage. The yearly rental cost of the manufacturing facility is $249 thousand. The building space required for the equipment and storage was costed as a rental charge. Table 4 illustrates the investment summary. As the investment summary illustrates, the first coating line, one mixer, the cartoner, the cutter/poucher, the incinerator and the hexane tank are to be purchased during the first year. The second coating line and a second mixer are to be purchased during the second year. The overall layout of the facility is shown in Figure 1.

Table 3: Manufacturing Cost Summary

Product Sales	1st Year	2nd Year	3rd Year
Estranor	$ 16,100	$ 32,200	$ 48,300
Raw Material Costs			
Ethinyl Estradiol	$ 256	$ 512	$ 768
Norelgestromin	$ 219	$ 437	$ 656
Polyvinyl Pyrrolidine	$ 37	$ 75	$ 112
Propylene Glycol Monolaurate	$ 589	$ 1,177	$ 1,766
Oleic Acid	$ 0.06	$ 0.11	$ 0.17
Polyisobutylene	$ 15	$ 30	$ 44
Hexane	$ 7.8	$ 16	$ 23
Backing	$ 67	$ 134	$ 201
Laminate	$ 95	$ 190	$ 285
Methane	$ 7.0	$ 14	$ 21
Pouches	$ 190	$ 380	$ 570
Boxes	$ 67	$ 134	$ 201
Totals	$ 1,549	$ 3,098	$ 4,648
Utilities	$ 73	$ 146	$ 219
Com	$ 4,232	$ 6,517	$ 9,036
Values expressed in $ thousands			

Table 4: Investment Summary

	1st Year	2nd Year
Dryers	$ 848	$ 848
Other Coating Equip	$ 30	$ 30
Cutter/Poucher	$ 300	$ -
Cartoner	$ 200	$ -
Mixers	$ 10	$ 10
Hexane Tank	$ 21	$ -
Incinerator	$ 270	$ -
Total	$ 1,680	$ 889
Values in $ thousands		

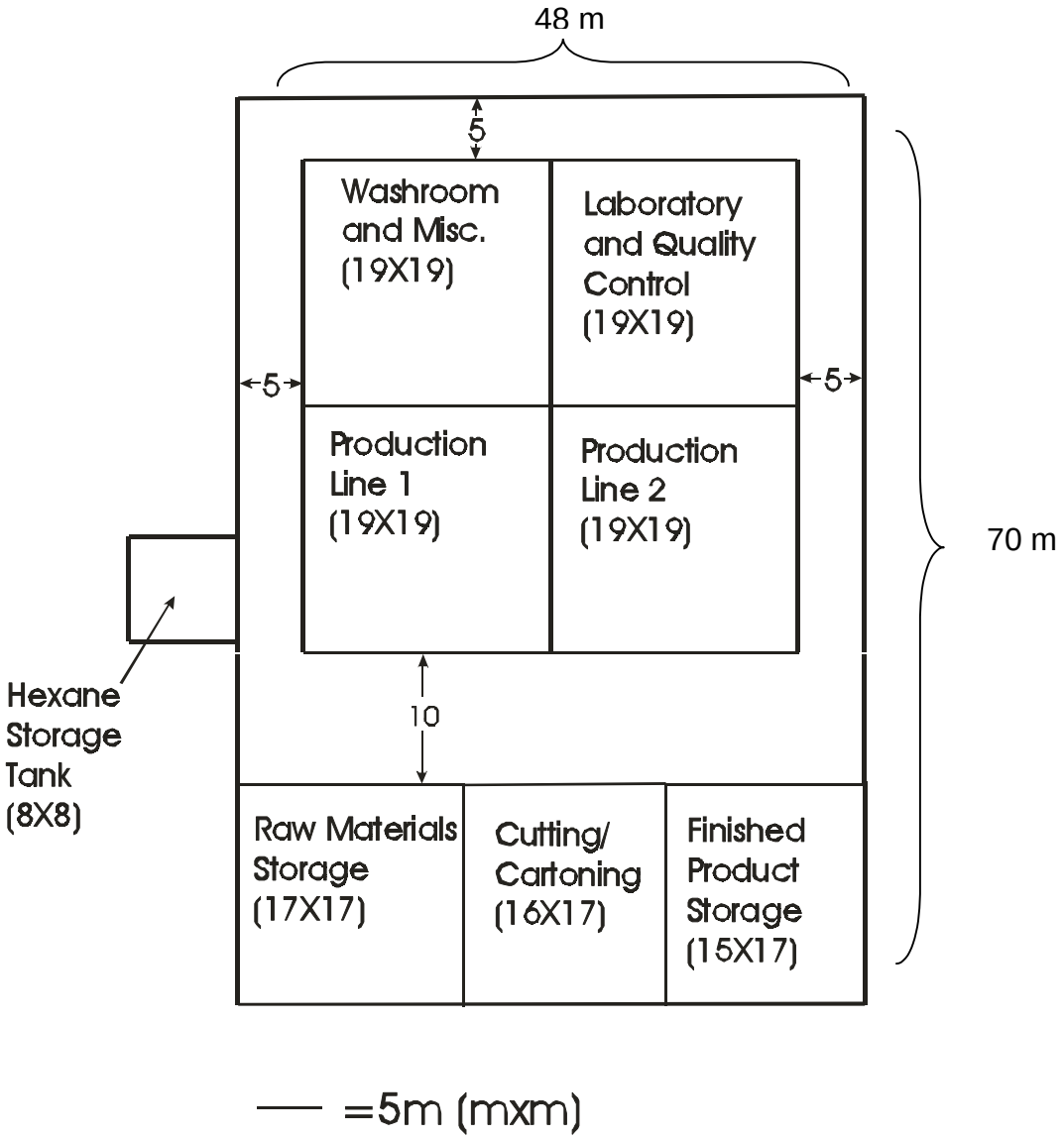

Figure 1: Diagram of the Production Facility Layout

Mathematical Modeling

In the design of a transdermal patch, the dose is a key factor to consider. The drug is delivered from the patch to the body through the process of diffusion through the skin, so determination of the diffusional flux is essential in designing a patch that delivers the desired amount of drug. A mathematical model may be derived for the transdermal system. The flux of a given drug from a transdermal system into the body can be modeled as:

$$j = \frac{C_o}{k_1 M_1} \qquad (1)$$

where C_o *is* the concentration of the drug in the patch, k_1 is the inverse of the resistance to diffusion of the drug provided by the stratum corneum, which is the rate limiting layer of skin, and M_1 is the partitioning coefficient of the drug between the patch and the skin.

A pharmacokinetic model was also developed and can be used to predict the concentration of the active ingredients in the blood. Equations 2 and 3 are used with the parameters in Table 5 to model each active ingredient,

$$\frac{dC_1}{dt} = \frac{-k_1 C_1}{V_1} \tag{2}$$

$$\frac{dC_2}{dt} = \frac{k_1 C_1 - k_2 C_2}{V_2} \tag{3}$$

where C_1 is the concentration of an active ingredient in the patch, k_1 is the elimination rate constant from the patch, V_1 is the volume of the patch, C_2 is the concentration of the active ingredient in the blood, k_2 is the elimination rate constant from the blood, and V_2 represents the volume of blood in which the drug is distributed.

Table 5
Parameters for Mathematical Model for Ethinyl Estradiol and Norelgestromin

Parameter	Ethinyl Estradiol	Norelgestromin
k_1 (mL/h)	0.00122	0.000853
V_1 (mL)	1	1
k_2 (mL/h)	1725	7750
V_2 (mL)	20000	132000

Multi-Scale Design

The design project presented in this report has included almost all levels of engineering thought. The project involved investigation on many scales, ranging from the molecular scale to process design scale. The project requires understanding the value of being able to apply previously obtained knowledge in new and unfamiliar ways. The project also requires learning to self educate on complex thought processes.

The process of learning began at the molecular scale. The initial research was completed by investigating how various molecules are used for medicinal purposes. Once the main

molecule was identified, the next step was to understand the other components of the transdermal system. The four main components were determined to be active ingredients, adhesives, enhancers, and excipients. The active ingredients were discussed on the molecular scale. The enhancers and excipients were researched, and their size and functionality allowed for them to be researched on the nano scale. The final components were the adhesives. The adhesive and the properties that are needed for the patch to remain on the skin were the next steps in research. The adhesion properties require analysis on the colloid scale.

Once the components of the patch were determined, it was necessary to identify how the drug enters the skin and is distributed throughout the body. The research was done on the microscopic scale. The skin diffusion was evaluated using transport phenomena concepts. For example, development of a model of the active ingredient's path though the skin into the bloodstream followed a resistance in series model for mass transfer. The pharmacokinetics, what happens to the active ingredient once it reaches the bloodstream, was modeled as stirred tanks in series with an accompanying reaction.

The next step in the project was to understand how to mix the components of the patch together. The solution is highly viscous, and the active ingredients are in relatively small quantities. The mixing was examined on the macroscopic scale, and the properties of solution required introduction of concepts obtained from a fluid mechanics course. The viscosity of the solution was lowered to obtain high quality of mixing. Hexane was introduced as the solvent to allow the solution to be well mixed. The hexane in the solution was then removed using solvent recovery and an incinerator. The design of the incinerator required separation process and economic considerations.

The final step was performed at the design scale. The design of the process was initiated by research on the equipment needed to take the well-mixed solution and obtain a packaged patch. The equipment and the economics were examined and the optimization began. Once the optimization was completed, the facility to produce the patch was designed. The storage of the equipment, raw materials, and products were examined, and dimensions for the facility were then developed. The process was designed and the distribution of the patch was examined. The target market and sales estimation were established and then the economics of the process were completed.

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