OPTIMIZATION OF POLYMER BASED TRANSDERMAL PATCHES FOR ENHANCED DELIVERY OF POORLY WATER-SOLUBLE DRUGS

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Abstract

The development of polymer based transdermal patches offers a promising approach for the enhanced delivery of poor water soluble drugs, addressing the limitations of conventional oral dosage forms, such as poor bioavailability and extensive first pass metabolism. The goal of this research is to optimize transdermal patches for the regulated and effective distribution of medications that are not particularly water soluble by choosing the right polymers and creating an adequate drug matrix. A range of hydrophilic and lipophilic polymers, such as Polyvinyl Alcohol (PVA), Ethyl Cellulose, and Hydroxypropyl Methylcellulose (HPMC), were assessed for their ability to penetrate the skin and release drugs. In order to increase the drug's solubility and permeability across the skin barrier, the formulation procedure included the use of solvents, plasticisers, and penetration enhancers. For the transdermal patches to maintain constant quality and function, their physical characteristics such as thickness, homogeneity, medication content, and folding endurance were assessed. To evaluate the release kinetics, cumulative drug release was tracked over time in in vitro drug release experiments utilising a Franz diffusion cell. The results indicated that the patches formulated with HPMC and Ethyl Cellulose exhibited a more sustained release profile, with zero order kinetics, compared to other formulations. Permeation studies using excised rat skin demonstrated a significant enhancement in the transdermal flux of the drug, with formulations containing HPMC showing the highest flux rates. The stability of the developed patches was assessed under accelerated storage conditions, and the formulations were found to be stable, with no significant degradation of the drug or change in physical properties. The study demonstrates that optimizing the combination of polymers, excipients, and penetration enhancers can efficiently enhance the administration of medications that are not very soluble in water.

Keywords: Polymer Optimization, Drug Delivery, Skin Permeation, Transdermal Patches, PVA etc

1. Introduction

The pharmaceutical industry has persistently pursued better methods of medication administration to circumvent the drawbacks of conventional oral formulations. A lot of people still prefer to take their medications orally; however it often faces significant drawbacks, including poor bioavailability, extensive first pass metabolism, and the need for frequent dosing. These challenges are especially prominent for poor water soluble drugs, which have limited absorption and systemic availability when administered orally. Hence, there has been a surge in research into alternative drug delivery methods, with a focus on transdermal drug delivery (TDD) systems. These systems have many benefits, such as better patient compliance, continuous drug release, and avoiding first pass metabolism. The term "transdermal drug delivery" describes the method by which medicinal substances are introduced into the bloodstream via the skin. This technique has garnered a lot of interest

because to its capacity to deliver macromolecules like peptides and proteins over long periods of time, as well as small molecule medications, in a non-invasive and easy alternative to conventional oral administration. Transdermal drug administration has many benefits. It may avoid the gastrointestinal system, which means patients are more likely to take their medication as prescribed. Another advantage is that the drug can be released gradually, under controlled conditions, so the therapeutic effects can last longer. However, while transdermal drug delivery holds great promise, its application for the delivery of poor water soluble drugs presents significant challenges. Poor solubility is a major issue for many drugs, especially in the context of transdermal delivery. The skin, as an effective barrier, limits the permeation of drugs into systemic circulation, making it difficult to deliver hydrophobic, poorly soluble compounds through this route.

The Challenge of Poor water soluble Drugs

Poor water soluble drugs, also known as class II drugs based on the Bio pharmaceutics Classification System (BCS), present one of the most persistent challenges in pharmaceutical formulations. These drugs have low solubility in aqueous environments but exhibit high permeability through biological membranes. As a result, they face significant absorption limitations when administered orally, leading to poor bioavailability. To overcome this, various formulation strategies, such as the use of surfactants, co-solvents, and solid dispersion techniques, have been explored for oral delivery. However, these methods do not always yield satisfactory outcomes, particularly when the drug is intended to be delivered over a long period, as in the case of chronic disease management or hormone replacement therapies. The transdermal route offers a potential solution to the limitations of oral administration for poor water soluble drugs. Unlike oral drug formulations, transdermal systems can provide continuous, controlled drug release, which is particularly beneficial for maintaining therapeutic drug levels. Also, transdermal patches may be a good way to increase the bioavailability of medications that aren't very water soluble as they avoid the liver and intestines (first pass metabolism). To be successful, transdermal administration must first overcome a number of hurdles, the most significant of which being the stratum corneum, the skin's outermost layer and a highly effective barrier to drug absorption.

Skin Penetration and Permeation Enhancers

The stratum corneum, a protective layer of dead skin cells that acts as a barrier against the outside world, is the main obstacle to the efficient transdermal administration of medications. The stratum corneum's lipophilic nature impedes the permeation of hydrophilic and poor water soluble drugs. Consequently, improving skin permeability is essential for transdermal medication delivery system optimization, particularly for poorly soluble substances. In order to boost medication penetration, permeation enhancer's excipients that momentarily

break down the epidermal barrier are often used as a means of getting beyond this barrier. There are two types of penetration enhancers: chemical and physical enhancers. Surfactants, alcohols, terpenes, and fatty acids are chemical enhancers that increase drug permeability by interacting with the stratum corneum's lipid bilayer and changing its structure. Physical enhancers, on the other hand, include techniques such as microneedles, iontophoresis, and ultrasound, which create transient channels or facilitate drug movement across the skin. The selection of appropriate permeation enhancers is a critical aspect of the optimization of polymer based transdermal patches. Permeation enhancers must be compatible with the drug and the formulation components while being safe for use on the skin. Additionally, the enhancer's effect on the skin's barrier function must be carefully balanced to avoid irritation or toxicity.

Role of Polymers in Transdermal Patch Formulation Polymers play a crucial role in the formulation of transdermal patches by controlling drug release, enhancing stability, and providing the necessary mechanical strength for the patch. The choice of polymer is pivotal in optimizing the transdermal delivery of poor water soluble drugs.

2. Literature Review

A review of literature is a comprehensive analysis of existing research and scholarly works relevant to a specific topic. It identifies gaps, evaluates methodologies, and synthesizes findings to provide context and support for new research. It helps establish a foundation and justifies the significance of the current study.

Anju Nirwana (2023) A transdermal patch containing dimenhydrinate was created for the trial in order to distribute medication and penetrate skin. This is crucial because of the drug's short elimination half-life and first pass metabolic problems. Dependability was shown by the statistically significant results of the patches, which had a p-value of less than 0.05. This demonstrates the efficacy of novel formulations. According to the study, penetration enhancers increase the permeability of patch dimenhydrinate. This implies that drug formulation has an impact on systemic circulation and skin penetration. Transdermal patch safety was assessed using rabbit skin irritation tests. Human safety testing of the patch is required utilising DD Solver to predict kinetics and quantify drug release data.

Manisha Bharadwaj (2022). The hydrolysis of hesperidin that is insoluble in water is investigated. Solid dispersions enhanced the solubility and release of hisperidin, which was necessary for therapy. The study uses natural polymers to create solid dispersions. It is biocompatible and biodegradable and aids in the release of medications. The process of hot melt extrusion hardens paper. The manufacturing of drugs may be improved via continuous solid dispersion synthesis. Compatibility is determined by FT-IR and DSC, which aids in drug polymer research and formulation stability. This thorough study demonstrates

how solid dispersion predicts biological activity and distributes medications.

Poonam Sawhaney (2021) investigated if applying a lotion containing 0.1 percent triamcinolone actinide to human skin beforehand might reduce the incidence and severity of persistent skin irritation associated with testosterone transdermal movement (TTD). Triamcinolone acitonide 0.1 percent salve pretreatment at evaluation 1 was linked to more 0 (no erythema), equal instances of sensitive human skin being bothered, and less instances of mild erythema (near with no pretreatment). The findings of this evaluation shown that pretreatment with 0.1 percent triamcinolone actinide cream may reduce the likelihood of human skin exacerbations at application sites and their recurrence in patients using TTD structures.

Rajendra Kumar Gupta (2020) Human skin irritation caused by an exploratory testosterone transdermal structure (System I) was broken down in strong people and replaced by a mechanically open testosterone transdermal (System II). In stage 1 of the assessment, Structure I was repeatedly coordinated over a period of more than 14 days to resemble human skin on the backs of 26 individuals. Over the course of 14 days, Fragment 2 examined the human skin irritation caused by the dependable use of Systems I and II in 17 people under 65 and 16 men 65 and over. Both transdermal methods produced the same amount of erythema, regardless of how active or prepared the subjects were. Even though more settled men do not have a lower event of human skin responses, repeated use of System I to an area that closely resembles human skin produced average non joined aggravation in this investigation, suggesting that application site turn may not be necessary. When the two methodologies are broken down, System I cause significantly less application site unsettling influence than System II.

Akhtar Jahan (2019) According to studies, water insoluble medications may be transported by nano sponges. This novel technique improves the bioavailability and solubility of drugs. Nano sponges were enhanced by Central Composite Design and statistical design. It investigated the effects of stirring rate and ethyl cellulose ratio on entrapment and particle size. Nano sponges filled with drugs stabilized by polyvinyl alcohol and ethyl cellulose. More trapping and smaller particles are needed for the dispersion of medications. FTIR, SEM, zeta potential, and entrapment were used to assess the nano sponges. These methods demonstrated the chemical and physical characteristics of nano sponges, pointing to drug delivery. Insoluble medications may be transported via enhanced nano sponges. There is a wealth of creative Nano medicine research and development. Effective formulation and optimization of nano sponges demonstrates their promise as a delivery system for medications that are not very soluble in water and the need of statistical design.

Nidhi Goyal (2019) examines drug penetration of a manufactured patch utilising a Franz dispersion cell and a layer of human dead body skin. This test showed that the cornea had a significant impact on the

medication outflow from the fix. The human skin stream is more noticeable when the corneum is removed than when the stratum corneum is present. Additionally, they ensured that heat and a damp epidermis promote drug retention via the human skin.

3. Research Methodology

This section outlines the research methodology adopted for optimizing polymer based transdermal patches for the enhanced delivery of poor water soluble drugs, specifically Danazol. A Quantitative Experimental Research Methodology was used to conduct this study. This methodology will allow for systematic experimentation to develop, optimize, and evaluate the formulation of transdermal patches in a controlled and measurable manner. This methodology enables precise measurement and statistical analysis of the effects of various factors on the drug release and skin permeation processes. The methodology begins with the formulation of transdermal patches, where independent variables such as the type and concentration of polymers (e.g., HPMC, Ethyl Cellulose, PVA), plasticizers, permeation enhancers, and solvents are manipulated. These variables are adjusted to assess their influence on the drug release rate and skin permeability of Danazol. The dependent variables include parameters like the cumulative drug release, permeation flux, drug content uniformity, and stability of the patches. In this experimental setup, a control group of transdermal patches will be used to establish a baseline for comparison. Data is collected through in vitro studies, including Franz diffusion cell testing, to measure drug release profiles and skin permeation. Statistical methods in order to ascertain the impact of different formulation parameters on medication delivery efficiency, statistical methods such as analysis of variance and regression are used. The optimization process aims to identify the most effective formulation, enhancing Danazol's bioavailability and therapeutic efficacy through transdermal delivery. The study is designed to systematically investigate various formulation and optimization strategies, focusing on the development of transdermal patches capable of improving the bioavailability and therapeutic outcomes of Danazol, a poor water soluble drug. The methodology comprises several stages, including the selection of materials, preparation of patches, evaluation of physicochemical properties, in vitro release studies, and in vivo testing. The approach used aims to optimize the formulation of transdermal patches to enhance drug delivery, improve skin permeation, and ensure stability.

4. Results and Discussion

The optimization of polymer based transdermal patches for enhanced delivery of poor water soluble drugs, specifically Danazol, was conducted using various polymers, plasticizers, and permeation enhancers. The research focused on the preparation, evaluation, and optimization of these patches to achieve a controlled and sustained release of Danazol, improving its systemic absorption. The experimental results are discussed below, including the

formulation characteristics, to determine the best formulation parameters; we conducted in vitro drug release profiles, skin penetration experiments, and statistical analyses. A variety of polymers, such as polyvinyl alcohol (PVA), hydroxypropyl methylcellulose (HPMC), and ethylene cellulose (EC), were used to create the transdermal patches. To increase the patches' flexibility and processability, plasticisers including glycerin (GL) and diethyl phthalate (DEP) were added. To improve the drug's skin penetration, penetration enhancers such as oleic acid (OA) and dimethyl sulfoxide (DMSO) were used. Physical characteristics such thickness, weight, consistency of medication content, folding endurance, and mechanical strength were assessed for each formulation.

Studies on drug release in vitro were carried out using Franz diffusion cells, with dialysis membrane as a model for human skin. The release of Danazol from the patches was evaluated over a period of 24 hours. To find out how the medication was released, researchers evaluated the cumulative percentage of release at various time intervals and fitted the data to several kinetic models.

Researchers used Franz diffusion cells and skin samples taken from pigs to study skin permeation. The permeation flux, lag time, and cumulative amount of drug permeated were measured over a period of 24 hours.

1) F1 (HPMC + DEP + OA) and F2 (HPMC + GL + DMSO) exhibited the highest skin permeation rates, with 1.50 mg/cm² and 1.38 mg/cm², respectively, after 24 hours. These formulations, with HPMC and permeation enhancers like DMSO, significantly enhanced the drug's ability to permeate through the skin.
2) F3 (EC + DEP + OA) and F4 (EC + GL + DMSO) showed moderate permeation rates, with 1.42 mg/cm² and 1.10 mg/cm² at 24 hours, respectively. Ethyl Cellulose based patches, while slower than HPMC, still exhibited substantial permeation.
3) F5 (PVA + DEP + OA) had the lowest permeation rate, with 1.05 mg/cm² after 24 hours, which could be attributed to the more compact and rigid nature of PVA, limiting drug diffusion.

The experimental results indicate that the polymer type, plasticizer, and permeation enhancers play a crucial role in the performance of transdermal patches for poor water soluble drugs like Danazol.

5. Figures and Tables

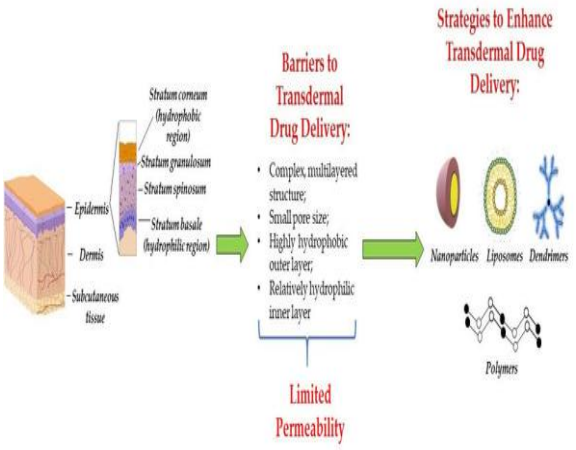

Figure: 1 (Transdermal Drug Delivery System)

S.No.	Natural Polymers	Synthetic Elastomers	Synthetic Polymers
1	Gelatin	Neoprene	Polyethylene
2	Gum Arabic	Polysilazane	Polystyrene
3	Methyl Cellulose	Silicone Rubber	Acetyl Copolymer
4	Arabino Galactan	Chloroprene	Polyvinyl Chloride
5	Starch	Hydrin Rubber	Polyester

Table: 1 (Classification of Natural and Synthetic Polymers)

6. Conclusion

Enhancing the distribution of Danazol and other weakly water soluble medicines with polymer based transdermal patches could greatly increase medication bioavailability and therapeutic effectiveness. To improve the transport of the weakly water soluble medication Danazol, this research aimed to formulate, evaluate, and optimize transdermal patches utilising various polymers, plasticisers, and permeation enhancers. In vitro drug release and permeation tests were part of the experimental design that showed how important the formulation factors and polymer choice were for drug delivery performance. Results showed that medication release rate and transdermal patch penetration properties were significantly affected by polymer matrix type and concentration. When utilised at optimal quantities, polymers like ethyl cellulose and hydroxypropyl methylcellulose (HPMC) showed encouraging results regarding medication release and penetration. Additionally, the use of plasticisers and permeation enhancers increased the drug's capacity to penetrate the skin, improving Danazol's systemic absorption. All things considered, this study effectively shows that transdermal patches made of polymers are a viable method for improving the administration of medications like Danazol that are not highly soluble in water. The study concludes with important findings that may be used to improve the design and development of transdermal patches for medication administration and opens the door to more studies in this area. In cases when oral administration is difficult or not successful, this method has great potential for improving the therapy by increasing the bioavailability and therapeutic effects of medications that are not very water soluble, such as Danazol. The outcomes of this study may serve as a foundation for developing more efficient and patient friendly pharmaceutical formulations, contributing to advancements in pharmaceutical sciences and drug delivery technologies.

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