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DESIGN AND EVALUATION OF TRANSDERMAL SYSTEMS: A REVIEW OF EMERGING APPROACHES

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ABSTRACT

Transdermal Drug Delivery Systems (TDDS) have garnered significant attention as an alternative to traditional routes of drug administration due to their ability to provide controlled and sustained release of the active ingredient while avoiding the hepatic first-pass effect. Repaglinide a short-acting hypoglycemic agent used in the treatment of type 2 diabetes mellitus requires frequent administration due to its low bioavailability and rapid elimination from the body. The present study focuses on the development and optimization of repaglinide-loaded transdermal patches with the aim of enhancing patient adherence to treatment and improving therapeutic efficacy. Utilizing the solvent casting method, various polymers and excipients were employed, and formulation parameters were optimized using a Box–Behnken experimental design. The resulting patches were evaluated based on parameters such as tensile strength, moisture content, and moisture uptake. Further enhancement of drug permeation through the skin was achieved through the incorporation of penetration enhancers, such as Transcutol and Labrasol. In vitro release and permeation studies were conducted using Franz diffusion cells, employing both artificial membranes and porcine ear skin. The obtained results indicate that the developed transdermal system is capable of providing sustained drug release and enhanced bioavailability, thereby positioning it as a promising alternative for the delivery of repaglinide.

KEYWORDS: Transdermal Patchs, BGP-15, Repaglinide.

1. INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are attracting growing interest in the context of administering medications through the skin both to achieve a local therapeutic effect in skin diseases (topical delivery) and for the systemic delivery of drugs into the body. Repaglinide is an oral hypoglycemic agent of the meglitinide class, used for the treatment of NIDDM (non-insulin-dependent diabetes mellitus). It lowers blood glucose levels by stimulating insulin secretion from the pancreas. The objective of the present study was to develop a transdermal dosage form of repaglinide that enhances patient adherence to treatment while also ensuring the prolonged release of the drug to increase its bioavailability.[1] Repaglinide is a rapid-onset, short-acting medication with a mechanism of action analogous to that of meglitinide; however, its duration of action is one hour shorter, its bioavailability is 50% lower, and its absorption in the upper gastrointestinal tract is less efficient. Consequently, the drug must be administered 3 to 4 times daily. These characteristics make repaglinide a suitable candidate for the development of a gastro-retentive dosage form. Gastro-retentive mechanisms which allow a drug to be retained within the stomach for several hours essentially determine the residence time of pharmaceutical agents in this organ. Prolonged retention of a drug in the stomach enhances its bioavailability, minimizes the loss of active ingredient, and improves the solubility of medications that dissolve poorly in acidic environments. Furthermore, proponents of this approach assert that it facilitates the localized distribution of the drug directly within the stomach and the proximal section of the small intestine. Repaglinide lowers blood glucose levels by stimulating insulin secretion from the beta cells of the pancreatic islets. This process is regulated via a specific ion-channel mechanism:

repaglinide blocks potassium ion efflux by acting on ATP-dependent potassium channels located in the beta-cell membranes. Membrane depolarization and the subsequent influx of calcium ions serve as the immediate trigger for insulin release. Repaglinide is a hypoglycemic agent used in the treatment of type 2 diabetes mellitus. During the development of a transdermal dosage form of repaglinide, efforts were undertaken to enhance the drug's solubility.[2]

These patches are designed for application to the skin to deliver a therapeutically effective dose of one or more active ingredients into the systemic bloodstream through the skin. The most fundamental and critical components of transdermal patches are polymers, as they perform a multitude of functions, such as forming the matrix, regulating the rate of drug release, and providing protection, adhesion, flexibility, and permeability.[3,4,5]

The ingredients included in the formulation specifically the selected polymers and excipients exert a significant influence on the physical properties of the patches, as well as on the active ingredient release profile and the suitability of the patches for use. During the composition development process, the properties of the active ingredient (or ingredients) themselves must also be considered as a critical factor requiring careful attention. The polymers most widely utilized in patches include cellulose derivatives (e.g., hydroxypropyl methylcellulose (HPMC)), polyvinylpyrrolidone (PVP), polyvinyl acetate (PVA), polyacrylates and acrylate derivatives, as well as chitosan; however, a range of other available options certainly exists as well.[6,7,8]

Transdermal Patch

A transdermal patch is an adhesive dressing containing a medicinal substance. Such patches are designed to deliver a therapeutically effective dose of a drug through the skin. They ensure the controlled release of the medication into the patient's body. The patch acts as a carrier for the drug, retaining it until the moment of application to the skin. At that point, the adhesive layer securely affixes the patch to the skin's surface. This grants the drug access to the skin, thereby facilitating its penetration. In this manner, localized drug delivery is achieved. A transdermal patch containing a high dose of a drug ensures its entry into the skin, where it remains for an extended period before entering the bloodstream via the process of diffusion.

A transdermal patch containing repaglinide was developed with the aim of ensuring the sustained release of the active ingredient, as well as enhancing its bioavailability and improving patient adherence to treatment. These dosage forms were prepared using the solution casting method. The resulting samples were evaluated based on a range of parameters, including tensile strength, active ingredient content, moisture content, and resistance to repeated flexing. The elimination half-life of repaglinide is 1 hour, and its bioavailability in the body is 56% (due to the hepatic first-pass effect).[9] Diabetes mellitus is a chronic metabolic disorder characterized primarily by hyperglycemia caused by insulin deficiency, and often associated with insulin resistance.[10] Repaglinide belongs to the class of meglitinides medications used to treat non-insulin-dependent diabetes mellitus. Repaglinide is typically prescribed at a dose of 0.5–4 mg, administered 3 to 4 times daily. The melting point of repaglinide is 130–131 °C, and its molecular weight is 452.58.[11,12] It has been demonstrated that, following oral administration, repaglinide induces hypoglycemia. A topical formulation of repaglinide may be beneficial for the patient as it reduces the severity of side effects and avoids first-pass hepatic metabolism.[13,14]

Advantages

1. Unwanted side effects minimized
2. First pass metabolisms of drug avoided.
3. Self-medication is possible

Disadvantages

1. Chances of allergic reactions at the site of applications.
2. Larger molecules size of the drug makes difficulty in absorption.

2. MATERIALS

REP, Glyceryl dibehenate, Poloxamer 188, Chitosan, cetirizine (CTZ), and stearic acid, Acetic acid, Polyoxyethylene (20) sorbitan monooleate (Tween 80), polyoxyethylene sorbitan monolaurate (Tween 20), macrogolglycerol hydroxystearate (Cremophor RH 40), and castor oil polyoxyethylene ether (Cremophor EL), Sorbitan oleate (Span 80), Streptozotocin (STZ) & REP tablets.[15]

Drug Lipid Solubility

The solubility of REP in solid lipids was initially assessed using a previously described method. Briefly, a specific amount of solid lipid was placed into glass vials and melted in a water bath (Isotemp 110; Fisher Scientific, Bloomington, MN, USA) at a temperature 5°C above the lipid's melting point. 10 mg of REP was added to the molten lipid media, and the contents of the vials were immediately subjected to vigorous vortex mixing. Additional portions of the lipid were then added until the REP was completely dissolved and clear, homogeneous mixtures were formed.[16,17]

3. Formulation of Transdermal Patches

Transdermal patches incorporating the drug BGP-15 were prepared using the solution casting method. For this purpose, 12-well plates (2 cm in diameter) were selected. The polymers (PVA and PVP) were accurately weighed and dissolved in 10 mL of an aqueous-ethanol mixture (containing varying volume percentages of ethanol, prepared by diluting 70% ethyl alcohol); the resulting solution was allowed to stand until a clear liquid formed. The active ingredient (10 wt.%) was dissolved in the

aforementioned solution and mixed until a clear mixture was obtained. PEG-400 and propylene glycol were used as plasticizers. The resulting homogeneous solution was cast into the plates and dried at 40°C for predetermined time intervals. The dried patches subsequently underwent comprehensive evaluation.

3.1 Design of Experiment

The manufacturing process for patches was optimized using a Box–Behnken experimental design. During this process, three independent and three dependent factors were evaluated. The independent variables consisted of the amount of PVA (% w/v), ethanol content (% w/w), and drying time (in hours); these parameters were considered critical factors in the manufacturing process that influence product quality. Within the framework of the experimental design, the values of these factors were varied across three levels over the course of 15 runs (formulations); this design scheme accounted for result reproducibility and the significance of each factor's influence on the observed variables. Tensile strength, moisture content, and moisture absorption were selected as the dependent variables. Three-dimensional response surface plots for the dependent factors were generated based on the resulting regression model, with one of the variables held constant at its central level.[18]

3.1.1 Tensile Strength

The tensile strength and tear resistance characteristics of the polymer films were evaluated using a Brookfield CT3 texture analyzer. The instrument is equipped with two grips fitted with force sensors: the lower grip is fixed, while the upper one is movable. Film strips measuring 1 × 1 cm were secured between the grips, after which a load was gradually applied until the film ruptured.[19]

3.1.2 Moisture Content

The moisture content of the patches was analyzed using a KERN DAB moisture analyzer. The initial mass of the patches was accurately weighed, after which the instrument heated them to 120 °C. The water content was measured by the instrument, and the moisture level of the films was calculated based on the initial mass and expressed as a percentage.[20]

3.1.3 Moisture Uptake

The moisture absorption of the patches was studied using a climatic chamber. The patches were kept in the chamber at room temperature and 80% relative humidity for 48 hours. The initial mass of the patches was determined beforehand by weighing, and after 48 hours, they were weighed again.[21]

3.2 Penetration Enhancement

After determining the most optimal formulation, Composition 4 was further combined with penetration-enhancing excipients with the aim of increasing the bioavailability of BGP-15. In accordance with recommendations from Gattefosse, Transcutol and Labrasol were selected as such excipients. During the preparation of the dosage form, Labrasol, Transcutol, or a 1:1 mixture thereof was incorporated into the patch composition at a concentration of 0.1%.[22]

3.3 In Vitro Permeation Studies

In vitro permeability studies were conducted using Franz diffusion cells modified such that the artificial cellulose acetate membrane was replaced by pre-prepared fragments of porcine ear skin. A phosphate buffer with a pH of 5.5 was selected as the acceptor phase, with a volume of 7 mL per cell. Porcine ears were obtained from a slaughterhouse. Skin sections 1 mm in thickness were harvested from the inner thinner and more intact side of the ears, after which they were frozen at −18 °C until the time of the experiment. The harvested skin samples were thawed and rehydrated in a saline solution supplemented with sodium azide (0.01% w/v) at 25 °C for 30 minutes to preserve functional activity. After washing with saline solution free of sodium azide, the skin layer was used in place of the membrane for the *in vitro* experiment (study of active ingredient release).[23]

3.4 In Vitro Release of the Active Ingredient

In vitro drug release was investigated using a Franz diffusion cell. During the experiment, a synthetic cellulose acetate membrane was placed between the donor and acceptor phases. Sampling from the acceptor phase was performed at predetermined time intervals. Transdermal patches were applied to the membrane (with a pore size of 0.45 μm) to serve as the donor phase; a buffer solution with a pH of 5.5 (simulating skin pH), with a volume of 7 mL per cell, was selected as the acceptor phase. The surface area of the cell was 17.66 cm^2. The solubility of BGP-15 in this medium is 28 mg/mL; thus, theoretically, it is capable of dissolving 196 mg of BGP-15. The transdermal patches contained 50 mg of BGP-15; consequently, this medium could dissolve more than three times the amount of the active substance. Prior to the start of the experiment, the membrane was impregnated with isopropyl myristate to simulate the lipophilic properties of the skin. The temperature of the acceptor phase was maintained at 32 °C to simulate the temperature of the skin surface.[24]

4. RESULT

4.1 Design of Experiment

4.1.1 Tensile Strength

Drying time did not exert a significant influence on tensile strength; consequently, only the relationship between PVA and the solvent was investigated. The graph indicates that increasing the PVA concentration resulted in a linear increase in the patch's tensile strength, while the 3D surface clearly demonstrates the linear nature of the dependence on PVA content. Regarding the solvent, a nonlinear relationship was observed in this instance, which is well described by an exponential trend. Within the concentration range of 20–40% (by mass), a slower increase in tensile strength was noted,

whereas a further increase in the ethanol content of the solvent mixture led to an accelerated growth of this parameter.

4.1.2 Moisture Content

The moisture content of the developed patches did not depend significantly on the solvent used; however, as the obtained results indicate, this parameter was significantly influenced by the PVA concentration and the drying time. Increasing the PVA concentration led to an increase in moisture content, though this increase ceased to be linear once a certain polymer concentration was reached. Extending the drying time contributed to a reduction in moisture content for up to 24–30 hours; subsequently, however, no significant changes in the nature of the curve were observed.

4.1.3 Moisture Uptake

The investigated factors (PVA concentration, ethanol concentration, and drying time) had no influence on moisture absorption during the preparation of the composition. No significant differences were observed. The average moisture absorption of the patches was 22.05 ± 4.06% (by mass).

4.2 Penetration Enhancers

According to the results of an experiment designed using the Box–Behnken scheme, Composition No. 4 containing 67% PVA and 20% ethanol, with a drying time of 24 hours was identified as the most optimal formulation. Consequently, this composition was subsequently supplemented with excipients specifically, penetration enhancers with the aim of enhancing the bioavailability of BGP-15. Transcutol and Labrasol were selected as the penetration enhancers.

4.3 In Vitro Drug Release

The graph illustrates the amount of BGP-15 that diffused through an isopropyl myristate-impregnated cellulose acetate membrane from various transdermal patches both those containing and those lacking penetration enhancers. Formulations containing Labrasol, or a combination of Labrasol and Transcutol, demonstrated higher active ingredient release rates. The best result was achieved using the combination of Transcutol and Labrasol, with the amount of diffused drug reaching 37.19%. The second most effective result was obtained using a patch formulated with Labrasol, where the amount of diffused drug was 29.58%. The lowest release rates were recorded for patches manufactured with Transcutol or those containing no auxiliary penetration-enhancing agents.

CONCLUSION

This study successfully demonstrated the feasibility of developing transdermal patches containing repaglinide, utilizing an optimized approach to formulation design. The solution-casting method, combined with statistical experimental design, enabled the production of patches possessing the requisite mechanical and physicochemical properties. The incorporation of penetration enhancers into the formulation significantly enhanced the drug's permeability across the skin barrier. *In vitro* studies confirmed the sustained release of the drug and its effective diffusion across biological membranes, thereby demonstrating the potential of this dosage form to overcome limitations associated with oral administration—such as low bioavailability and the need for frequent dosing. Overall, the developed transdermal drug delivery system represents a promising strategy for improving therapeutic outcomes and enhancing patient adherence in the management of type 2 diabetes mellitus. Further *in vivo* studies are recommended to validate the clinical efficacy of this system.

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