RESEARCH ARTICLE

Preparation and characterization of transdermal patches of repaglinide for the treatment of diabetes

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ABSTRACT

Transdermal patch type delivery system bearing repaglinide was developed for topical drug delivery. Repaglinide was identified and characterized by infrared, ultraviolet spectroscopy, solubility, and partition coefficient studies. The transdermal patches were prepared by solvent evaporation technique. The homogeneous dispersion of drug was mixed with different blends of polymers in (1:1) mixture of ethyl alcohol (95%) and dichloromethane. Natural permeation enhancers camphor, menthol, and 1, 8 cineole were selected for further study. The patches were evaluated for physicochemical parameters such as moisture content, moisture uptake, folding endurances, thickness, weight variation, and surface pH. The moisture content and moisture uptake varied to a small extent in all the formulations. However, there was an increase in moisture content and uptake with an increased concentration of hydrophilic polymer, hydroxypropyl methylcellulose (HPMC) K4M in matrix patches. The optimized batch of HPMC K4M and EC 8:1 was selected to study the effect of different natural permeation enhancers, i.e., camphor, menthol, and 1, 8 cineole. All the patches with HPMC K4M:EC (8:1) showed controlled and sustained release. Formulation F5 containing 10% camphor was found to release the highest quantity of drug, 422.01 μg/cm^2 of patch in 24 h. From the present study, it can be concluded that the transdermal patch type delivery system may be a suitable device through the topical delivery of repaglinide. When HPMC K4M polymer was used in high concentrations; it showed controlled release pattern.

Keywords: Diabetes, hyperglycemia, percutaneous, permeation enhancer, repaglinide, transdermal drug delivery system

Introduction

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action, or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys, and nerves, as well as an increased risk for cardiovascular disease. The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy. The disadvantages of the conventional drug delivery systems necessitate the need to deliver a drug into newer system. Hence, the transdermal delivery approach has drawn the interest for the delivery of antidiabetic drugs. These systems are so designed that the drug can be delivered at a predetermined and controlled rate.[1] The main aim of drug delivery system is to efficiently deliver the drugs to the tissue organ.

Transdermal therapeutic systems are defined as self-contained discrete dosage form which when applied to the intact skin deliver the drug(s), through the skin at controlled rate to the systemic circulation. This system also offers added advantages such as being user-friendly, painless, minimized inter- and intra-patient variability, ease of self-administration, and leading to better patient compliance.

Repaglinide is a lipophilic drug was drug of choice used for lowering the blood glucose level by stimulating insulin secretion. After oral administration, peak plasma concentration of repaglinide is reached within 1 h. It possesses low oral bioavailability (56%) due to hepatic first pass metabolism and has a short biological half-life of <1 h, thus originates the need of an alternative route of administration which can bypass the above shortcoming and also involve attainment and maintenance of drug concentration in the body within a therapeutic effective range.

The present study was designed to develop a suitable matrix patch type transdermal drug delivery system for repaglinide employing various ratios of ethyl cellulose and hydroxypropyl methylcellulose (HPMC) K4M[2] using camphor, menthol, and 1, 8 cineole different

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natural permeation enhancers. The aim of this study was to compare the effect of different permeation enhancers in terms of *in-vivo* and *in-vitro* skin permeation of the drug and to find out the best possible ratio of hydrophilic and lipophilic polymeric combination, which might be chosen for further studies to find out the best natural permeation enhancers with concentration.

Materials

Repaglinide was received as a gift sample from Healthy Life Pharma Pvt. Ltd.; HPMC, EC, and K4M were purchased from Otto Chemise Pvt. Ltd., and acetone, dichloromethane, propane 2-ol, cyclohexane, chloroform, hexane, carbon tetrachloride, glacial acetic acid, and ethanol were received as gift sample from Karnataka Fine Chem.

Methods

Preformulation studies

Preformulation studies were performed to quantify the drug and polymer before formulation. Solubility may be defined as spontaneous interaction of two or more substances to form homogeneous dispersion. The solubility of the repaglinide was studied in various aqueous and nonaqueous solvents 10 mg of drug was taken in 10 ml of each solvent at room temperature in screw-capped test tube and sonicated for 10 min. The partition coefficient directly influences the permeability of drug across various membranes. The study has been designed to determine partition coefficient of drug in 1-octanol:distilled water. 10 mg of drug was added to 50 ml of distilled water in a stoppered bottle and shaken at 370°C in water bath shaker (GFL 10 & 3, Germany) overnight. The pure drug, repaglinide, and a mixture of (1:1) ratio with the polymers, HPMC K4M, and EC were mixed separately with infrared grade KBr in the ratio of 100:1. Pellets were prepared by applying 6 metric ton of pressure in a hydraulic press. The pellets were scanned over a wave number range of 4000-400/cm in Shimadzu (Model - 8400 S), Japan Fourier transform infrared (FTIR) instrument.

Preparation of transdermal patch

The matrix type transdermal films of repaglinide were prepared by homogeneous dispersion using different ratios of HPMC K4M and EC polymers in 8:1, 4:1, and 2:1 ratios were increased to the total weight of 540 mg. HPMC K4M and EC were dissolved in 15 ml ethanol at room temperature and 50 mg of the drug was dissolved in 15 ml dichloromethane in separate beaker and this solution added with stirring in solution of HPMC K4M and EC to obtain uniform solution, dibutylphthalate 5% w/w of dry polymer was used as a plasticizers. Backing membrane was cast by pouring and then evaporating 4% aqueous solution of polyvinyl alcohol (PVA) in glass molds covered on one side with aluminum foil, at 60°C for 3 h. The uniform dispersion (3 ml each) was cast on the PVA backing membrane. Now, the polymeric solution of the drug was poured onto the glass mold (2.9 cm internal diameter) and dried at room temperature in dust free environment. A release liner (wax paper) on either side of the film was applied to complete the transdermal drug delivery systems (TDDS).[3] The films were stored in airtight container at ambient conditions for 7 days before use. Then, out of the three polymers combination, the best was chosen for further study using three different natural penetration enhancers menthol, 1, 8 cineole, and camphor. These enhancers were used as 5% and 10%

Characterization of formulation

Thickness of patch

The thickness was measured using a screw gauge. Each patch was measured for thickness at three different point concentrations of total weight of the dry polymer. The dry patches were kept in desiccators until use.[4]

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place until it broke. The number of times the film can be folded at the same place without breaking was the folding endurance value.[4]

Weight variation

Weight variation was studied by individually weighing 10 randomly selected patches.

Content uniformity

A film was cut into small pieces, dissolved into 10 ml of methanol and diluted into 100 ml with the phosphate buffer (pH 7.4), and shaken continuously. Then, the filtered solution of the drug was estimated spectrophotometrically at 239 nm after dilution as performed for each formulation.

Percentage moisture content

The films were weighed individually and kept in the desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight.[4]

Percentage moisture uptake

A weighed film was kept at room temperature for 24 h and was taken out and exposed to 84% relative humidity (a saturated solution of aluminum chloride) in a desiccator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to the initial weight.[4]

Surface pH

Patches of a particular diameter size about 2 cm were taken and were placed in 10 ml of 30% methanolic isotonic phosphate buffer pH 7.4. They were allowed to swell for 2 h, and pH was measured using pH electrode.

In-vitro drug release studies

The dissolution studies of patches are crucial because one needs to maintain the drug concentration on the surface of the stratum

corneum consistently and keep it substantially higher than the drug concentration in the body, to achieve a constant rate of drug permeation. The *in-vitro* drug release studies were performed using USP dissolution apparatus (Disso DA-6D, Mumbai, India). The release rate determination is one of the most important studies to be conducted for all controlled release delivery systems. A circular patch with an area of 6.60 cm^2 containing 5 mg of drug was used for the study. All dissolution studies were performed at 37 ± 2°C, 50 rpm, in 30% methanolic IPB pH 7.4. Samples were withdrawn at predetermined time intervals up to 12 h and analyzed at 239 nm spectrophotometrically.[5]

In-vitro skin permeation studies

In-vitro release profile is an important tool that predicts in advance how the drug will behave *in-vivo*.[6] Thus, we can eliminate the risk of hazards of drugs because of direct experimentation in the living system. *In-vitro* skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs.[7] When the active agent (drug) is released from the matrix in such a way that the rate of release of the drug remains constant, the release kinetics of the drug are believed to follow a zero-order kinetics.[8]

The *in-vitro* skin permeation of repaglinide from the selected TDDS through depilated mouse abdominal skin was conducted using a modified Keshary-Chein diffusion cell.[7] *In-vitro* skin permeation studies were performed using a Keshary-Chein cell with a receptor compartment capacity of 30 ml. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with 30% methanolic isotonic phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 32±0.5°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 239 nm. The receptor phase was replenished with an equal volume of 30% methanolic isotonic phosphate buffer pH 7.4 each sample withdrawal.[4]

Result and Discussion

Solubility profile

Solubility of repaglinide was determined in different solvent including acetone, dichloromethane, propane 2-ol, cyclohexane, chcl3, hexane, ccl4, glacial acetic acid, ethanol, phosphate buffer pH 1.0, phosphate buffer pH7.4, and phosphate buffer pH 9.0. During the study it was found that drug molecules possess slight solubility in water, and freely soluble in acetone hence drug can be a hydrophobic in nature.

The partition coefficient of repaglinide was 3.80 (reported log P 3.97). It showed that drug lipophilic in nature. Drug excipient studies were performed by FTIR. All the drug and excipients were shown compatibility with each other as shown in Figures 1 and 2.

Characterization of formulation

Uniform thickness was shown by formulation F3 and F7OF (0.42 mm). The maximum folding endurance was shown by F3 formulation HPMC K4M:EC 2:1 which shown that in above combination EC is responsible for the strength. The average weight varies from 25.1 ± 0.6 mg (F1) to 26 ± 1 mg (F8 and F9). Formulations F5 and F6 show more uniformity of content of (5.0 ± 0.01 mg). F1 showed most moisture content (4.50 ± 1.2%). F1 (5.52 ± 1.1%) shows the more of moisture uptake then others. Formulations F5 and F6 show pH 6.5 that was more resembles with skin pH as shown in Table 2.

Table 1: Solubility profile of repaglinide in different solvent systems

Solvents	Solubility
Acetone	+++++
Dichloromethane	++++
Propane 2-ol	++++
Cyclohexane	++
CHCl3	++++
Hexane	+
CCl4	++
Glacial acetic acid	++++
Ethanol	++++
Phosphate buffer pH 1.0	+
Phosphate buffer pH 7.4	+++
Phosphate buffer pH 9.0	++++

++++++: Freely soluble, ++++: Soluble, +++: Slightly soluble, ++: Turbid, +: Insoluble

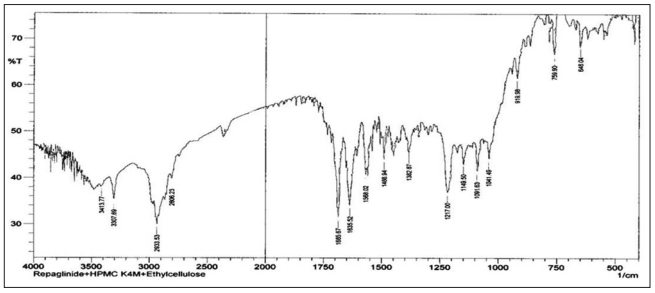

Figure 1: Fourier transform infrared of hydroxypropyl methylcellulose K4M, EC, and repaglinide

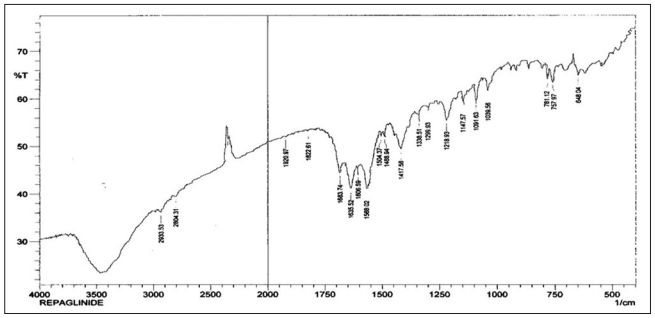

Figure 2: Fourier transform infrared of pure drug repaglinide

Table 2: Physicochemical evaluation*

Formulation code	Folding endurance	Weight variation (mg)	Thickness (mm)	Content uniformity (mg)	Moisture content %	Moisture absorb %	Surface pH
F1	21±3	25.3±0.6	0.35±0.002	5.4±0.01	4.50±1.2	5.52±1.3	6.40±0.6
F2	23±2	24.9±0.7	0.41±0.04	5.1±0.05	3.51±1.1	4.41±1.1	6.43±0.7
F3	25±2	25.3±0.6	0.42±0.01	5.2±0.02	2.99±1.7	3.20±1.8	6.42±0.3
F4	20±2	24.8±0.8	0.40±0.05	5.3±0.03	4.41±1.1	4.02±1.2	6.48±0.2
F5	22±2	25.8±0.6	0.37±0.01	5.01±0.01	4.02±1.2	4.71±1.1	6.50±0.1
F6	20±3	22.8±0.8	0.41±0.02	5.1±0.03	3.81±1.9	3.70±1.5	6.48±04
F7	22±3	23.8±0.7	0.42±0.03	5.3±0.02	4.09±1.2	5.32±1.3	6.49±0.6
F8	21±1	26±1.00	0.40±0.0	5.2±0.01	3.90±1.1	2.61±1.1	6.41±0.7
F9	21±2	26±1.00	0.39±0.03	5.01±0.01	3.69±1.1	4.52±1.2	6.49±0.3

*All values are expressed as mean±SD (n=6)

In-vitro drug release studies

All the patches with HPMC K4M:EC (8:1) showed controlled and sustained release. Formulation F5 containing 10% camphor was found to release the highest quantity of drug, 422.01 µg/cm^2 of drug in 24 h. All the seven formulations with and without permeation enhancers - F1 (without permeation enhancer), F4 and F5 (camphor - 5%, 10%), F6 and F7 (menthol 5%, 10%), F8 and F9 (1, 8 cineole 5%, 10%) appeared to follow similar patterns of drug release profiles, i.e., initially apparent zero-order and then first-order release kinetics. Initially, for first few hours, the drug release, kinetic patterns followed zero-order drug release profiles and with the enhancement of time the release profiles gradually changed into the concentration dependent first-order release kinetics.

The effect of permeation enhancers often depends on their applied concentrations.[9] The mechanism of action of permeation enhancers[8] is by (i) disruption of the highly ordered structure of SC lipids, (ii) interactions with intracellular proteins, or (iii) improvement in partitioning of the drug, coenhancers, or cosolvent into the stratum corneum. It is reported that terpenes enhance diffusion of drugs by extracting lipids from stratum corneum,[4,5] which results in reorganization of lipid domain and barrier disruption.[6,7]The mechanism of barrier disruption may be due to the competitive hydrogen bonding of oxygen containing monoterpenes with ceramide head groups, thereby breaking the interlamellar hydrogen bonding network of lipid bilayer of stratum corneum and new polar pathways or channels are formed.[10]

The formulation F5 with 10% Camphor was found to show the best percentage cumulative drug release of 422.01 µg/cm^2 in 24 h, due to its higher fluidizing activity among the terpenes containing essential oils. Menthol produces local vasodilation and could distribute preferentially into the intercellular spaces of stratum corneum and the possible reversible disruption of the intercellular lipid domain[11] and 1, 8 cineole improved the skin permeation of hydrophilic drugs better than other terpenes and repaglinide is hydrophobic in nature. Menthol was the most effective permeation enhancer than the 1, 8 cineole as shown in Figure 3.

In-vitro skin permeation studies

In-vitro release profile is an important tool that predicts in advance how the drug will behave *in-vivo*.[6] Thus, we can eliminate the risk of hazards of drugs because of direct experimentation in the living system. *In-vitro* skin permeation experiments are known for their value for studying the rate and mechanism of percutaneous absorption of drugs.[7] When the active agent (drug) is released from the matrix in such a way that the rate of release of the drug remains constant, the release kinetics of the drug are believed to follow a zero-order kinetics.[8]

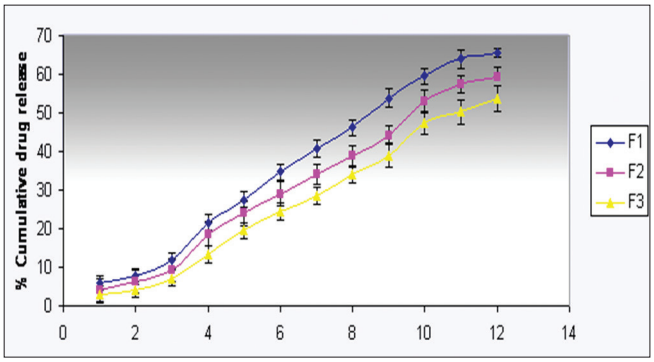

Figure 3: *In-vitro* release profile of hydroxypropyl methylcellulose K4M: EC patches

The *in-vitro* skin permeation of repaglinide from the selected TDDS through depilated mouse abdominal skin was conducted using a modified Keshary-Chein diffusion cell.[7] *In-vitro* skin permeation studies were performed using a Keshary-Chein cell with a receptor compartment capacity of 30 ml. The excised rat abdominal skin was mounted between the donor and receptor compartment of the diffusion cell. The formulated patches were placed over the skin and covered with paraffin film. The receptor compartment of the diffusion cell was filled with 30% methanolic isotonic phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 32 ± 0.50°C. The samples were withdrawn at different time intervals and analyzed for drug content spectrophotometrically at 239 nm. The receptor phase was replenished with an equal volume of 30% methanolic isotonic phosphate buffer pH 7.4 each sample withdrawal[4] as shown in Figure 4.

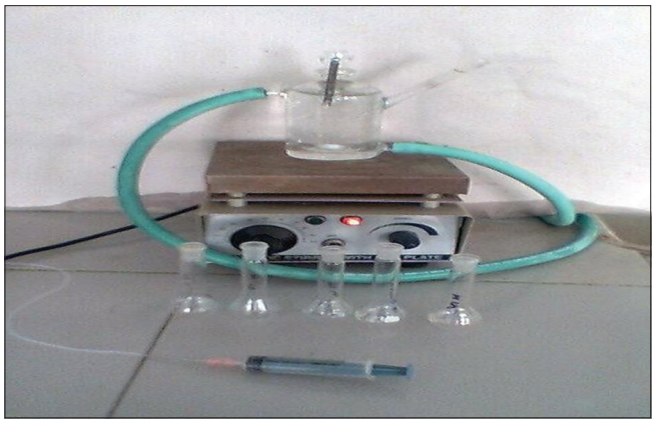

Figure 4: *In-vitro* skin permeation studies using modified K-C cells

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