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DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEM OF A MODEL ANTIDIABETIC AGENT

Pandya Narendra*[1], Patel Manvi[1], Bhaskar V.H.[1], Patel K.R.[2]

[1]Department of Pharmaceutics, M.P. Patel College of Pharmacy, Jeevanshilp Campus, Kapadwanj, Gujarat - 387620, India.
[2]Department of Pharmaceutics, Shri B.M.Shah College of Pharmaceutical Education and Research, Modasa, Gujarat - 383315, India.

ABSTRACT

The aim of the present investigation was to prepare Glipizide transdermal patches of matrix type using the Eudragit RL 100 and Eudragit RS 100 by the mercury substrate method. The systems were evaluated for various *in vitro* parameters (Thickness, Folding endurance, Moisture content, Moisture uptake, Flatness, Water vapor transmission rate, Drug content, Drug permeation, Drug–polymer interactions and Scanning lectron morphology). Drug content of the patches was found to be more than 98%. *In vitro* permeation studies were performed by using Franz diffusion cells. Variations in drug permeation profile were observed among various formulations. The SEM of the patch showed the formation of pores on the surface after *in vitro* permeation studies. The drug–polymer interaction results suggested no interaction between drug and polymers was observed. From all the formulations, formulation M 3 was selected as the best formulation and formulation was stable for period of 90 days stability study.

Keywords: Transdermal drug delivery, Matrix patch, Membrane controlled Patch, Glipizide, Eudragit, *In vitro* skin permeation studies.

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*Corresponding author.
M.P. Patel College of Pharmacy, Jeevanshilp Capus, Kapadwanj, Gujarat - 387620, India

.E-mail address: speed_5naren@yahoo.co.in

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INTRODUCTION

Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms. Transdermal drug delivery offers controlled release of the drug into the patient, it enables a steady blood-level profile resulting in reduced systemic side effects and sometimes, painless and offer multi-day dosing. It is generally accepted that they offer improved patient compliance. Although transdermal drug delivery patches have a relatively short regulatory history compared to other, more traditional dosage forms, the technology has a proven record of FDA

approval. Since the first transdermal patch was approved in 1981 to prevent the nausea and vomiting associated with motion sickness, the FDA has approved, throughout the past 22 years, more than 35 transdermal patch products, spanning 13 molecules[1]. The transdermal route is ideally suitable for drugs that need to be administered for diseases those are chronic in nature and required a steady state drug concentration throughout the treatment[2]. The present study is an attempt to develop a transdermal system capable of delivering the selected anti-diabetic drug in the desired therapeutic concentration for prolong period.

The objectives of the present study are as follows: To design and develop transdermal therapeutic system of a model antidiabetic drug, Glipizide, using matrix devices. To estimate the physicochemical properties and drug release profile of the formulations, To choose the best transdermal drug delivery system based on the above evaluations. And finally, to subject the most satisfactory formulation(s) to accelerated stability studies.

MATERIALS AND METHODS

Materials

Glipizide was received as gift samples from Micro Labs, Bangalore. Eudragit RL 100 and Eudragit RS 100 were obtained as gift samples from Roehm Pharma, Germany. All the other chemicals used were of analytical grade.

Methods

Preformulation Parameters

Determination of solubility of Glipizide in phosphate buffer pH 7.4: The solubility studies were performed in phosphate buffer solution, pH 7.4, by adding excess amounts of drug in each case and keeping the excess amounts of drug containing phosphate buffer flasks on a rotary shaker for 24 hrs. After 24 hrs, solutions were analyzed spectrophotometrically at 276 nm, which was the absorption maxima determined earlier and drug concentrations were calculated.

Drug partition coefficient: N-octanol and pH 7.4 phosphate buffers were presaturated with each other for 24 hrs before experiment. To the pre-equilibrated buffer (10 ml), known quantity of drug was dissolved. 10 ml of octanol was added to equal volume of drug solution in a separating funnel. The system was kept for 24 hrs with intermittent shaking. Finally, buffer layer was separated, clarified by centrifugation and assayed.

Drug–excipient interaction study: The FTIR study was carried out using Perkin Elmer Spectrum GX at Organic Chemistry Unit, IISc, Bangalore, to check compatibility of glipizide with selected polymers.

Preparation of Matrix Type Transdermal Patches

The polymer and drug were weighed and dissolved in 5 ml of chloroform along with di-n butyl phthalate (30% w/w of polymers) and oleic acid (0%, 5% & 7.5% w/w of polymers) . The solution was poured on mercury placed in a glass petri dish of 18 cm^2 area and dried at room temperature for 24 hrs. (The solvent was completely evaporated in 24 hrs whereas di-n-butyl phthalate and oleic acid remained in drug-polymer matrix). Aluminum foil was used as the backing membrane that was cast by pouring and then evaporating 4%w/v solution of PVA at 60ºC for 6 hrs (See Table 1)[3,4,5].

Evaluation of Transdermal Patches

Thickness: The thickness of patches was measured at three different places using an Absolute Digimetic (Mitutoyo) from Medreich Lab, Bangalore[6].

Folding endurance: This was determined by repeatedly folding one film at the same place until it broke. The number of times the film could be folded at the same place without breaking / cracking gave the value of folding endurance[6].

Percentage of moisture content: The films were weighed individually and kept in desiccator containing activated silica at room temperature for 24 hrs. 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[7].

Percentage of moisture uptake: A weighed film kept in a desiccator at room temperature for 24 hrs was taken out and exposed to 84% relative humidity (a saturated solution of Aluminium chloride) in a desicator 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 initial weight[7].

Flatness: Longitudinal strips were cut out from the prepared medicated patches, the lengths of each strip were measured, and then the variation in the lengths due to the non-uniformity in flatness was measured. Flatness was calculated by measuring

constriction of strips and a zero percent constriction was considered to be equal to a hundred percent flatness.

Constriction (%) = $(L_1 – L_2)/L_2$ x 100

Where, L_1 initial length of each strip; L_2 final length[4,5]

Water vapor transmission (WVT) rate: The film was fixed over the brim of a glass vial, containing 3 g of fused calcium chloride as desiccant, with an adhesive tape. The vial was weighed and kept in desiccator containing saturated solution of potassium chloride to provide relative humidity of 84%. The vial was taken out and weighed at every 24 hrs intervals for a period of 72 hrs. The water vapor transmission rate was calculated from the plots of amount of water vapor transmitted versus time[8].

Drug content analysis: The patches (n = 3) of specified area were taken into a 100 ml volumetric flask and dissolved in methanol and volume was made up with phosphate buffer pH 7.4. Subsequent dilutions were made and analyzed by UV spectrophotometer at 276 nm[9].

***In Vitro* skin permeation study**: The *in vitro* skin permeation experiments were conducted using a Franz diffusion cell (receptor compartment capacity: 100 ml; surface area: 3.799 cm^2). Full thickness skin from dorsal region of Swiss albino mice, whose hair had been removed by razor, was used as membrane. The mice were sacrificed by cervical dislocation and dissected skin was used immediately. The receiver compartment was filled with 100 ml of phosphate buffer, pH 7.4. The transdermal patch was firmly pressed onto the centre of the mouse skin and then the skin was mounted on the donor compartment. The donor compartment was then placed in position such that the surface of dermis side skin just touches the receptor fluid surface. The whole assembly was kept on a water bath maintained at 37 ± 0.5ºC. The samples were withdrawn at different time intervals up to 24 hrs and analyzed for drug content. Receptor phase was replenished with an equal volume of buffer solution at each time interval[10].

Data analysis: The steady-state flux (*J*) of glipizide was calculated from the slope of the linear portion of plots of cumulative amount in the receptor solution versus time.

J is mathematically expressed as follows:

$$J = \frac{dQ/dt}{A}$$

Where, dQ/dt is the cumulative amount permeated per unit time and *A* is the diffusion surface area.

The apparent permeability coefficients (Papp) were calculated according to the following equation:

$$P_{app} = \frac{dQ/dt}{C_s A}$$

Where, Cs is the concentration of glipizide in the donar compartment.

Enhancement ratios were calculated according to the following expression:

$$ER = \frac{J_{(enh)}}{J_{(ctrl)}}$$

Where, *J* (enh) is the enhanced steady state flux and *J* (ctrl) is the flux of drug without the presence of enhancer[10,11,12].

Differential scanning calorimetry (DSC): The physicochemical compatibility between glipizide and polymers used in the patches was studied by using differential scanning calorimetry (DSC; Shimadzu DSC-60 Calorimeter, Tokyo, Japan) [13].

Scanning electron morphology (SEM): The external morphology of the transdermal patches was analyzed using a scanning electron microscope (JSM 6100 JEOL, Tokyo, Japan). The samples placed on the stubs were coated finely with gold palladium alloy and examined under the microscope[14].

Stability Studies

The selected formulations were packed in amber- colored bottles, which were tightly plugged with cotton and capped with aluminium. They were then stored at 25ºC / 60% RH, 30ºC / 65% RH, & 40ºC / 75% RH for 3 months and evaluated for their drug content and permeation study.

RESULTS & DISCUSSION

In the Present study Phosphate buffer, pH 7.4 was used as *in vitro* study fluid and the solubility of glipizide in pH 7.4 buffer was found to be 0.257 mg/ml. The logarithmic value of the partition

coefficient (log *P*) was found to be 0.363 ± 0.006. The results indicated that the drug has sufficient lipophilicity, which fulfilled the requirements of formulating it into a transdermal patch. Drug – polymer interaction were studied using FTIR analysis showed 1689.39, 1651.31, 1527.92, 1160.19, 1034.08 and 903.58 wave numbers as major peaks for glipizide. There were no changes in the major peaks of glipizide in the presence of Eudragit RL 100 and RS 100.

In case of Matrix type of patches, six different formulations were made out of which three were made using Eudragit RL 100 and three with Eudragit RS 100. Di-n butyl phthalate (30% w/w of polymer) and different concentration of oleic acid was used (Table 1). The physicochemical characteristics and the permeation characteristics were different in the patches studied. The patches prepared were thin, flexible and transparent with almost uniform thickness within the range of 85.833 µm to 95.591 µm. Folding endurance test results indicated that the patches would not break and would maintain their integrity with general skin folding when applied.

The moisture content of the prepared formulations was low (1.842% to 5.759%), which could help the formulations remain stable and reduce brittleness during long-term storage. The moisture uptake of the formulations was also low (3.483% – 7.361%), which could protect the formulations from microbial contamination and reduce bulkiness. Thus, these formulations can maintain a smooth and uniform surface when applied onto skin. The flatness study showed that all the formulations had the same strip length before and after their cuts, indicating 100% flatness. Thus, no amount of constriction was observed; all patches had a smooth, flat surface; and that smooth surface could be maintained when the patch was applied to the skin. Good uniformity of drug content among the batches was observed with all formulations and ranged from 95.896% to 98.47%. The results indicate that the process employed to prepare patches in this study was capable of producing patches with uniform drug content and minimal patch variability.

In the *in vitro* drug diffusion studies the cumulative amount of drug (Glipizide) permeated per cm^2 from different matrix patches of Eudragit RL and Eudragit RS 100 with di- n butyl phthalate and different concentrations of oleic acid showed variable permeation patterns. The process of drug permeated in the most of the controlled/sustained release devices including transdermal patches is governed by diffusion. When this matrix patch is exposed to an *in vitro* study fluid, thermodynamically compatible with the polymer, the fluid is absorbed into the polymer matrix and this initiates polymer chain dissolution process in the matrix. Polymer chain dissolution from the matrix surface involves two distinguishable steps. The first step involves changes in entanglement of individual drug molecules at the matrix surface, which depends on the rate of hydration. The second step involves the transport of this molecule from the surface across the skin, adjacent to the matrix patch, initially to the surface and then to the bulk of the *in vitro* study fluid. Molecular diffusion through polymers is an effective, simple and reliable means of attaining sustained/controlled release of a variety of active agents.

The formulations made with Eudragit RL 100 (M1 to M3) showed greater drug permeation (256.254 µg to 412.748 µg) than that of Eudragit RS 100 (M4 to M6) (225.787 µg to 350.377 µg). This permeation can be attributed to the greater permeable nature of RL 100 polymer, which is due to a higher content of hydrophilic quaternary ammonium groups than RS 100 polymer. Also among the Eudragit RL 100 and RS 100 formulations, the amount of drug permeation was found to increase with the increase in the concentration of permeation enhancer oleic acid. The result revealed that oleic acid increased the diffusion of drug through the skin that agrees with the reported mechanism by which oleic acid enhanced the permeability of drug. Oleic acid was reported to function by partitioning into the lipid regions of stratum corneum, disrupting the structure and lipid fluidity of the stratum corneum. For all the formulations, enhancement factor was calculated taking the formulation without enhancer as control and enhanced steady state flux. Enhancement factor upto 1.586 was observed with formulation M3.

Among the different formulations of matrix type (M1 to M6), the formulation M3 containing Eudragit RL 100 and 7.5% oleic acid was selected as best formulation, after considering its low percentage moisture content (5.458%), percentage moisture uptake (7.258%), water vapor transmission rate (4.138%), better % drug content (98.210%) and maximum (412.748 µg/cm^2/hr) drug permeated through the skin at the end of 24 hrs. The drug permeation profile was also found to follow zero order kinetics, which was evidenced by the straight line graph with regression 0.99. When graph was plotted between time and percentage drug permeated. (Figure 1)

The DSC analysis of glipizide alone showed a sharp endothermic peak at 207.5 °C corresponding to its melting point. The DSC analysis of formulation M3 demonstrated negligible change in the melting

point of glipizide (200.50°C), which indicated that the polymer do not interact with the drug.

Figures 2 and 3 showed the SEM of M3 formulation's films before and after the *in vitro* drug permeation experiments respectively. The films prior to *in vitro* permeation studies showed uniform smooth surface. After the permeation studies, the surface became rough and pore were formed on the surface of the patches. This best formulation M3 was subjected to accelerated stability studies for 90 days at 25ºC/60% RH, 30ºC/65%RH, & 40ºC/75% RH for % drug content and permeation profile performed every 30 days and showed negligible change in % drug content and permeation profile.

CONCLUSION

In the present study, an attempt was made to deliver a novel antidiabetic drug, Glipizide through transdermal route in the form of transdermal patches. Among the different formulations of matrix type (M1 to M6), the formulation M3 containing Eudragit RL 100 and 7.5% oleic acid was selected as best formulation, after considering its low percentage moisture content (5.458%), percentage moisture uptake (7.258%), water vapor transmission rate (4.138%), better % drug content (98.210%) and maximum (412.748 µg/cm^2/hr) drug permeated through the skin at the end of 24 hrs. The drug permeation profile was also found to follow zero order kinetics. The patches were thin, flexible and transparent. The SEM of the formulation M3 showed the formation of pores on the surface after *in vitro* permeation studies. The drug–polymer interaction results suggested no interaction between drug and polymers was observed. The best formulation M3 showed negligible change in % drug content and permeation profile for a period of 90 days study. Based on the *in vitro* characterization, it was concluded that glipizide could be administered transdermally through the matrix type TDDS.

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TABLES AND FIGURES

TABLE 1: Formulation of Matrix Type Transdermal Patches

Formulation Code	Eudragit (% w/v)	Di-n-Butyl Phthalate (% w/w of Polymer)	Oleic Acid (% w/w of Polymer)
M1	RL 100 (8%)	30%	------
M2	RL 100 (8%)	30%	5%
M3	RL 100 (8%)	30%	7.5%
M4	RS 100 (8%)	30%	-----
M5	RS 100 (8%)	30%	5%
M6	RS 100 (8%)	30%	7.5%

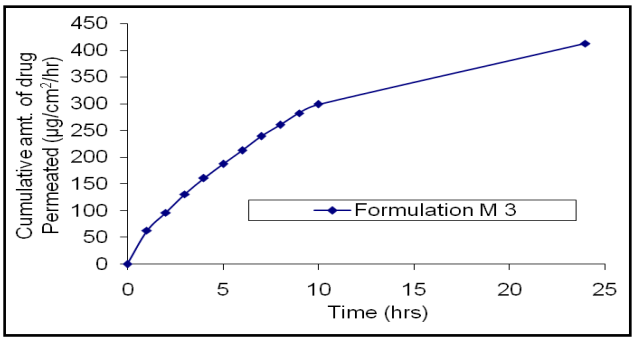

Figure: 1 *In Vitro* Drug Permeation of Glipizide in Formulations M3

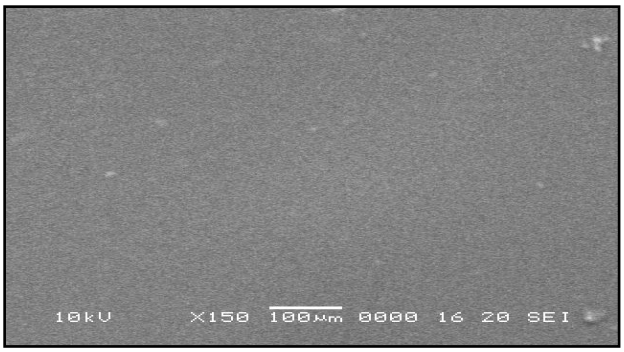

Figure 2: SEM of Glipizide Matrix Patch before Permeation

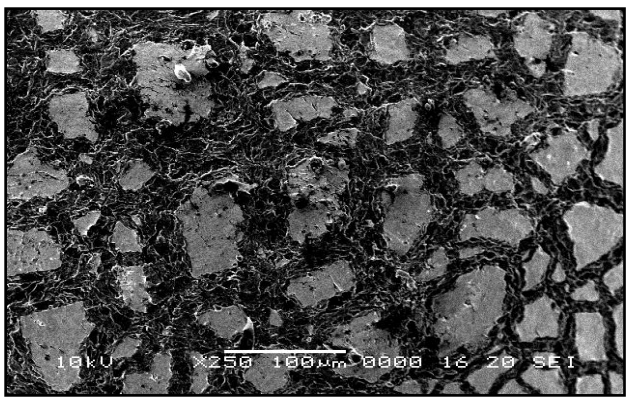

Figure 3: SEM of Glipizide Matrix Patch After Permeation