Research Article

Design and Development of Glipizide Matrix Transdermal Patches with Eudragit RLPO Polymer

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ABSTRACT

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. The present study is an attempt to develop a transdermal system of selected anti-diabetic drug using different polymers like Eudragit RLPO and different solvents like Acetone, Methanol, and Chloroform by mercury substrate method. Glipizide appears to lower the blood glucose acutely by stimulating the release of insulin from the pancreas, an effect dependent upon functioning of beta cells in the pancreatic islets. The present study thus indicates that the polymer and solvent used has significant influence on the water vapour transmission, drug diffusion and permeability of the films. The Eudragit RLPO films prepared with acetone has high permeability than other films.

Keywords: Transdermal patches, glipizide, Eudragit RLPO Polymer, water vapour transmission.

INTRODUCTION

Recently there has been a growing recognition that the benefits of intravenous infusion can be closely duplicated without its hazards, by using the intact skin as the port of drug administration to provide continuous drug delivery into the systemic circulation[1]. This is known as the transdermal administration and the drug delivery systems are known as “transdermal therapeutic systems” or popularly as “transdermal patches”. Transdermal therapeutic systems[2] are defined as self contained, discrete dosage forms which, when applied to the intact skin, deliver the drug, through the skin at controlled rate to the systemic circulation. Transdermal drug delivery systems[3] are adhesive drug containing devices of defined surface area that deliver a predetermined amount of drug to the surface of intact skin at a programmed rate. These systems provide drug systemically at a predictable rate and maintain the rate for extended periods of time thus eliminating numerous problems associated with oral dosing including product stability, bioavailability and the peaks and troughs of pulse dosing. Glipizide is rapidly and completely absorbed from the gastrointestinal tract. It is extensively bound to plasma proteins and half-life of approximately 3-4 hrs. It is metabolized in the liver and excreted in the urine largely as inactive metabolites. Glipizide undergoes variable and extensive first pass metabolism before entering into systemic circulation and varies with species. The transdermal administration of drugs, which undergoes first pass metabolism, can improve the bioavailability, reduces the dosing frequency compared to the oral route.

MATERIALS AND METHODS

MATERIALS

Glipizide - Natco Pharma; Hyderabad , Eudragit RLPO- Natco Pharma; Hyderabad , Acetone- Qualigens; Mumbai , Methanol- S. D. fine-chem Ltd.; Mumbai, Chloroform- S. D. fine-chem Ltd.; Mumbai , n-dibutyl phthalate- Ranbaxy Laboratories; New Delhi .

Preparation of Eudragit RLPO Films

The polymer is weighed and dissolved in 10 ml of solvent along with 10mg of drug and plasticizer n- dibutyl phthalate (30% w/w of polymers) is added. The solution was poured in a Glass bangle (6.2 cm diameter) on mercury placed in a glass Petri dish and dried at room temperature for 24 hrs. The solvent was completely evaporated in 24 hrs whereas n-dibutyl phthalate and drug remained in drug-polymer matrix. The rate of evaporation was controlled by inverting a funnel over the Petri plate. After 24 hours the dried films were taken out and stored in desiccators.

EVALUATION OF TRANSDERMAL FILMS

1. Physical Appearance

The free films prepared were evaluated for physical appearance by visual observation.

2. Thickness uniformity

The thickness of the films was measured by a 'dial caliper'. The mean of the five observations were calculated.

3. Folding Endurance[4]

The folding endurance was measured manually for the prepared films. A strip of film (2x2 cm) was cut evenly and repeatedly folded at the same place till it broke. The number of times the film could be folded at the same place without breaking gave the exact value of folding endurance.

4. Water vapour Transmission (W.V.T) Rate[5]

For the study vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1.0 g of Calcium chloride was taken in the cell and the polymeric films measuring 3.14 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight is recorded, and then kept in a closed desiccator containing saturated solution of KCl (about 200 ml.). The humidity inside the desiccator was measured by a hygrometer, and it was found to be in between 80 – 90 % RH. The cells were taken out and weighed after.

From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula.

Water vapour transmission rate

$$(W.V.T) = WL/S$$

Where,

W= Water vapour transmitted in gms.

L= Thickness of the film in cm.

S= Exposed surface area in cm^2

5. Drug Diffusion Study[6]

Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 15 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. Magnetic stirrer was set at 100 rpm and whole assembly was maintained at 37 $\pm$ 2 ^0C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 3 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a U V spectrophotometer at 262 nm.

6. Permeability Coefficient[7]

From the drug diffusion data the Permeability Coefficient for various films was calculated using the equation

$Pm = K_{app}\ H/A$

Where, K_{app}= Diffusion rate constant (mg/h) calculated from the slope of the linear drug (d/p) diffusion profiles.

H = Thickness of the film (cm)

A = Surface area of the film (cm^2)

7. Diffusion flux[8]

Diffusion flux was determined by using the equation

$$\text{Flux (J)} = dm/s.dt$$

Where s = surface area

dm/dt = rate of permeation.

RESULT AND DISCUSSION

Studies have been carried out on transdermal formulations of Glipizide to reduce its frequency of administration. The films were formulated with Eudragit RLPO. The films were prepared by employing three solvents - Acetone, Methanol and Chloroform. The films prepared with polymer alone were found to be brittle. To prevent brittleness a plasticizer, dibutyl phthalate was tried at various concentrations ranging from 33-40% (w/w) of the polymer. Dibutyl phthalate at a concentration of 40% (w/w) of the polymer was found to give good flexible films.

All the films prepared were evaluated for uniformity of thickness, folding endurance, water vapour transmission and drug diffusion and permeability characteristics. Thickness and folding endurance measurements of films prepared in various solvents are given in table 2. The film thickness measurements ensured uniformity of thickness in each film. The method of casting on mercuric surface was found to be given reproducible results with regard to film thickness. The folding endurance was measured manually and folding endurance values indicates good handling properties of films. Water vapour transmission studies indicated that all the films prepared were permeable to water vapour. Water vapour transmission through the films followed zero order kinetics. The results are given in table 3, 4 and fig.1.

Water vapour transmission values indicating that the Eudragit RLPO films were more permeable to water vapour. The rate of water vapour transmission was decreased in the order of films in various solvents is as follows: Acetone> Methanol> Chloroform.

Drug diffusion was studied by using Franz diffusion cell. All the films were found to be permeable to Glipizide and the results are

given in table 6, 8 and fig.2, 3. The correlation coefficient values (r) were reported in Table 6 and fig 2. These values revealed that the diffusion profiles follow zero order kinetics. The diffusion exponent of release profiles (slope) has a value of 1.056-1.071 (n>1), which indicates super case II transport diffusion. Permeability coefficient values (Pm) of the films towards the Glipizide was calculated from the drug diffusion data and the results were given in table 7. The rate of permeability coefficient was decreased in the order of films in various solvents is as follows: Acetone> Methanol> Chloroform. Permeability coefficient values (Pm) of Glipizide was high when compared to the Permeability coefficient values of, Eudragit RLPO films prepared with Acetone shown high Permeability when compared to other films.

CONCLUSION

The films were formulated with eudragit RLPO and by employing three solvents acetone, methanol, and chloroform. Eudragit RLPO films were more permeable to water vapour ,the rate of water vapour transmission was decreased in the order of films in various solvents is as follows Acetone> Methanol> Chloroform. The drug diffusion follows zero order kinetics. The diffusion exponent of release profiles (slope) has a value of 1.056-1.071 (n>1), which indicates super case II transport diffusion. Eudragit RLPO films prepared with Acetone shown high Permeability when compared to other films.

Table 1: Composition of Eudragit RLPO films

Ingredients	F1	F2	F3
Glipizide	10mg	10mg	10mg
Eudragit RLPO(mg)	800mg	800mg	800mg
n-Di butyl phthalate(ml)	0.32ml	0.32ml	0.32ml
Acetone (ml) upto	10ml	----	----
Methanol (ml) upto	----	10ml	----
Chloroform(ml) upto	-----	**----**	10ml

Table 2: Mechanical properties of prepared transdermal films

Polymer	Formulation	Casting solvent	Thickness (µm)	Folding endurance
Eudragit RLPO	F1	Acetone	38.0	303
	F2	Methanol	41.4	292
	F3	Chloroform	42.8	282

Table 3: Water vapour transmission values of transdermal films

Time	Amount of water vapour transmitted (g) Eudragit RLPO		
	F1	F2	F3
0	0	0	0
18	0.394	0.347	0.272
36	0.691	0.647	0.540
54	0.959	0.839	0.813
72	1.039	0.953	0.942

Table 4: Water vapour transmission values of transdermal films

Formulation	Water vapour transmission Q gm/cm ^{2} .24 h
F1	3.782
F2	3.511
F3	3.205

Table 5: Diffusion data of glipizide

TIME (hrs)	Amount of glipizide diffused(µg)		
	F1	F2	F3
0	0	0	0
0.5	0.916	0.750	0.525
1	1.816	1.492	1.026
1.5	2.788	2.293	1.542
2	3.819	3.124	2.117
2.5	4.902	4.013	2.712
3	6.063	4.945	3.349

Table 6: Diffusion characteristics of glipizide through Eudragit RLPO films prepared with various solvents

Formulation	Correlation coefficient values (r)		Zero order rate constant(k)values (mg/h)	Diffusion exponent value (n)
	Zero order	Peppas model		
F1	0.9989	0.9995	2.011	1.055
F2	0.9990	0.9996	1.642	1.052
F3	0.9989	0.9993	1.108	1.033

Table 7: Permeability coefficient values of glipizide through Eudragit RLPO films prepared with various solvents

Formulation	Permeability coefficient Pm x 10^4 mg/cm. H
F1	4.70
F2	4.30
F3	3.59

Table 8: Diffusion flux profiles of glipizide through Eudragit RLPO films prepared with various solvents

Avg time	F1	F2	F3
0	0	0	0
0.25	153.75	140.53	128.34
0.75	156.82	143.49	130.75
1.25	155.41	139.98	130.92
1.75	160.48	134.62	126.39
2.25	157.49	140.84	128.37
2.75	171.48	143.38	127.05

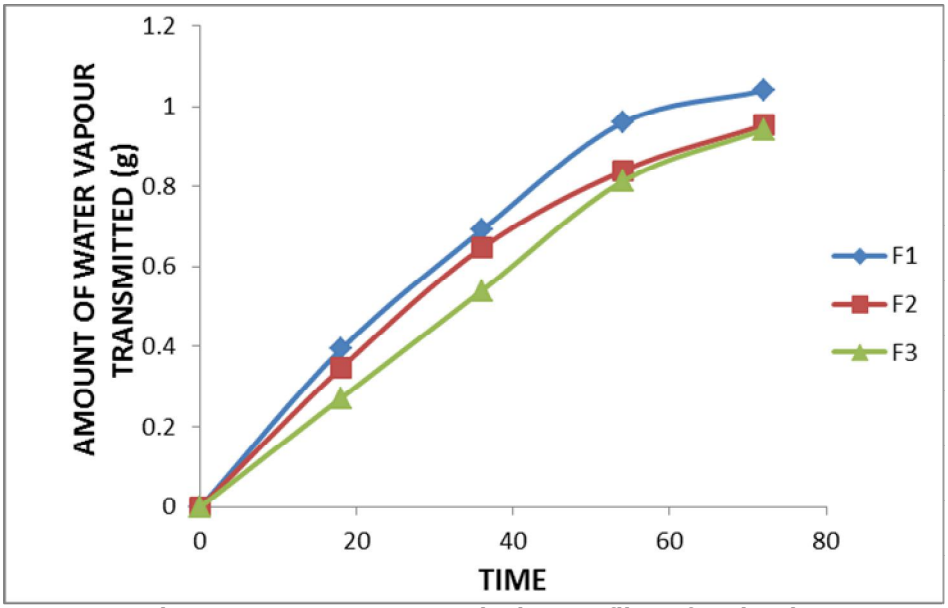

Fig. 1: Water vapour trasmission profiles of eudragit rlpo films casted with various solvents

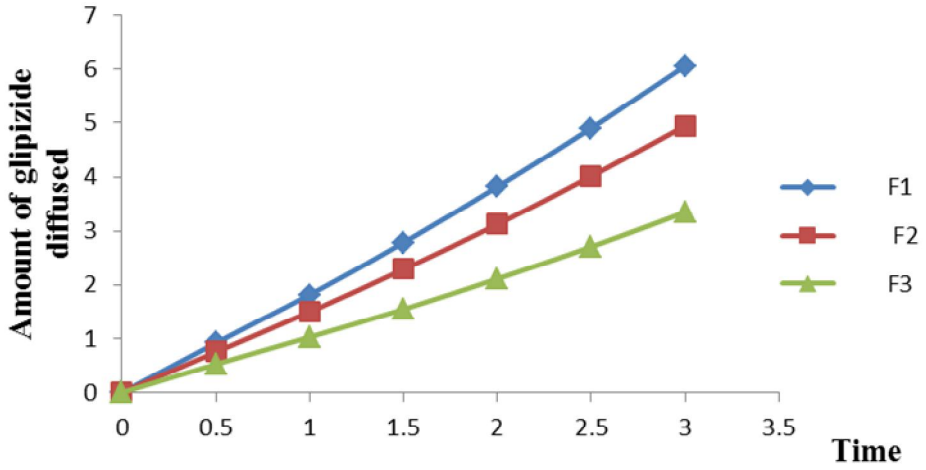

Fig. 2: Diffusion data of glipizide amount of glipizide diffused (µg)

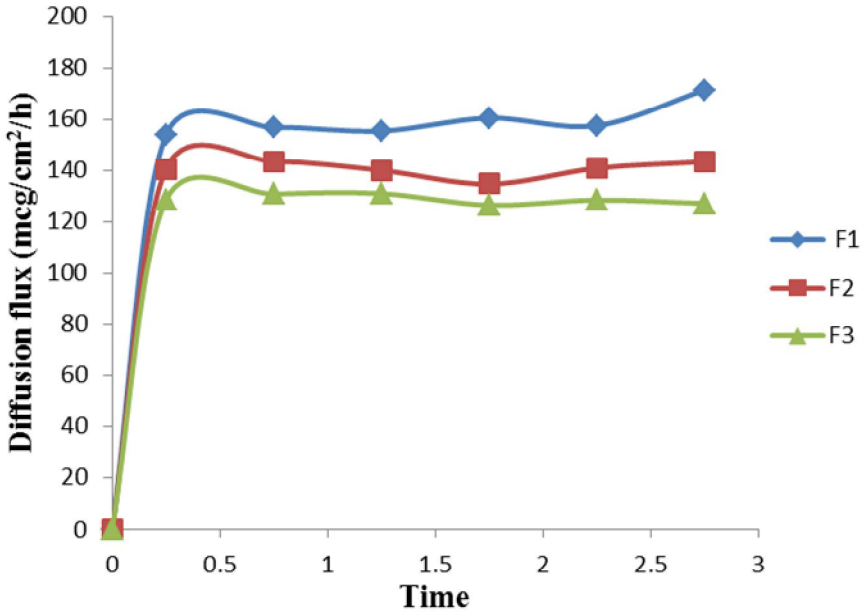

Fig. 3: Diffusion flux profiles of glipizide through eudragit rlpo films prepared with various solvents

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