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FORMULATION AND EVALUATION OF TRANSDERMAL PATCHES OF GLIZPIZIDE

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ABSTRACT

Drug Delivery through skin would provide a useful alternative to oral delivery, which has numerous side effects. Therefore, the present investigation was aimed to develop sustained release transdermal therapeutics system containing Glipizide with varying ratios of HPMC & PVPK30 using solvent evaporation technique. Ten different formulations were prepared keeping the concentration of Glipizide constant as 45mg in each formulation. The films were developed and evaluated for thickness, weight variation, percent moisture absorption, percent moisture loss, folding endurance, drug content and *in vitro* drug dissolution studies. Finally, on the basis of best release one of the formulations was selected for further kinetic studies which exhibited that release rate followed Fickian's diffusion law. The selected formulation showed no sign of irritation when studied using mice skin. Finally, it was concluded that Glipizide transdermal patch could improve the bioavailability of the drug by avoiding its first pass metabolism.

KEYWORDS: Transdermal Drug Delivery, Glipizide, HPMC, PVPK30

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INTRODUCTION

Glipizide is an oral blood- glucose- lowering drug of the sulfonyl urea class. Glipizide has been in extensive use to treat non insulin dependent diabetes mellitus and acts by increasing the release of endogenous insulin as well as its peripheral effectiveness. It has been associated with sever and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heart burn, anorexia and increased appetite after oral therapy, compliance problem can arise[1]. Transdermal drug delivery system *viz* transdermal patches offers many advantages over oral route of administration. Such systems not only reduces the load that the oral route commonly places in the digestive tract and liver but also enhances patient compliance and reduces harmful side effect of a drug caused from temporary over dose.[2,3] Such system posses added advantages, as they control the area of application of drug, amount, release kinetics and application time of the drug[4]. The Glipizide is a suitable drug candidate for design into an effective transdermal system when would eliminates its first pass metabolism, ensure more uniform plasma levels, reduces side effects like gastric irritation and hence aid in patient compliance. Therefore, the objective of current investigation was to formulate and evaluate transdermal patches of Glipizide.[5]

MATERIALS AND METHODS

Pure Glipizide was obtained from M/S Stadmed Private Limited, Kolkata. The other chemicals were obtained from authenticated manufacturers i.e Hydroxy methyl cellulose (Leo Chem. Mumbai), Polyvinyl pyrrolidone (Otto chemika, Mumbai), Polyethylene glycol (Leo chem., Banglore) Dimethyl sulphoxide (Thomas Baker (chemicals) ltd., Mumbai), Methanol (Rankem laboratories, New Delhi), Chloroform (Bharat instruments and chemicals, Hissar).Franz diffusion cell (Bharat instruments and chemicals, Hissar), Micrometer (Mitutoyo, Japan). All other chemicals used were of analytical grade.

Preformulation Studies

Before preformulation of drug substances into a dosage form, it is essential that it should be chemically and physically characterized. Preformulation studies furnish the information required to define the drug nature and also gives information regarding framework for the drug combination with pharmaceutical excipients in dosages form fabrication.

Physico- chemical characterization studies

Physico- chemical studies are usually associated with great precision, accuracy and in case of a new drug substance would include melting point, solubility and partition coefficient.

Melting point determination

The melting point of pure drug (Glipizide) was observed using Differential Scanning Calorimetry (DSC) of pure drug was carried out by heating the samples from 40^0C to 300^0C at the rate of 10^0C per minute using Differential Scanning Calorimeter.

Solubility analysis [6]

The equilibrium solubility studies or saturation solubility of Glipizide were carried out in phosphate buffer saline pH 7.4, methanol, chloroform. An excess amount of Glipizide was added to each 10 mL solvent (PB pH 7.4, methanol, chloroform) taken in 50 mL conical flasks separately and then placed in a mechanical shaker at room temperature for 24 hrs. At the end of 24 hrs, samples were filtered through the whatmann filter paper no. 42. The aliquots of the filtered samples were suitably diluted and analyzed at their respective wavelengths. Solubility of drug in each solvent was calculated using eqn.

Solubility = Sample abs. × dilution factor / Slope of std curve. × 1000

Partition coefficient[7]

The partition coefficient of the drug (Glipizide) was determined by taking equal volume of n-octanol and aqueous phase in a separating funnel. A drug solution of 1mg/ml was prepared in pH 7.4. 25 ml of this solution was taken in a separating funnel and shaken with an equal volume of n-octanol/ water for 2 hrs

and allowed to stand for 24 hours. Then aqueous phase was separated, centrifuged for 10 minutes at 2000 rpm. The aqueous phase was assayed before and after partitioning using U.V spectrophotometer at wavelength 276.5 nm to get partition coefficient. Triplicate readings were taken and the average was calculated

Preparation of transdermal patches[8]

Matrix type transdermal patches composed of different ratios of HPMCK4M, PVPK30, HPMCK15M with drug (Table 1) were prepared by solvent evaporation technique in a glass ring. The bottom of the ring was wrapped with aluminium foil by adhesive and placed in a petridish of area 26.28 cm^2. A fixed volume of (10 mL) of polymeric solution with drug, plasticizer and penetration enhancer was poured on to the petridish to facilitate the evaporation of solvent at a controlled rate over the drying period of 24h at room temperature. The dried films were removed and cut into 2 cm^2 area and kept in a desicator until used.

Evaluation of transdermal patches

A) Physical Characterization [9]

Thickness

The thickness of the film was measured at three different points using a micrometer and average thickness was observed.

Weight variation

Five films from each batch were weighed individually and average weight was calculated.

Percentage moisture absorption

The films were weighed accurately and placed in the dessicator at room temperature for 24 hrs and then exposed to 84% RH using a saturated solution of potassium chloride. The films were weighed repeatedly until they showed a constant weight.

Percentage moisture loss

The films were weighed accurately and kept in a dessicator containing anhydrous calcium chloride, after 3 days the films were taken out and weighed.

Folding endurance

Folding endurance was determined by repeatedly folding the film at the same place till it get broken down. The folding endurance value could be obtained by determining the number of times of films folded at the same place without breaking.

B) Drug Content [10]

The film was dissolved in 5 mL of casting solvent (chloroform**:** methanol), subsequently diluted with pH 7.4 phosphate buffer (upto 10 mL) and stirred for 30 minutes. The resulting solutions were further diluted with pH 7.4 phosphate buffer and filtered. A blank was prepared in the same manner using drug free patches to neglect the absorption of formulation components. After filtration, the drug content was determined spectrophotometrically at 276.5 nm

C) In vitro drug release[10]

The in-vitro release profile is an important tool that predicts in advance how a drug will behave *in vivo*. *In-vitro* studies were performed using a frenz diffusion cell with a receptor compartment capacity of 22mL. The receptor compartment was filled with phosphate buffer saline pH7.4 and the cellophane membrane was mounted between the donor and receptor compartment of the diffusion cell. The prepared transdermal film was placed on the cellophane membrane. The whole assembly was kept on a magnetic stirrer and the solution was stirred continuously at 600 rpm using a magnetic bead at 37±1°C. The 2 mL of sample was withdrawn at different time interval and replaced with an equal volume of diffusion medium. Sample were analysed spectrophotometrically at 276.5 nm for the determination.

Kinetic Release of dissolution studies

The release kinetics was found out by using zero order, first order, Higuchi and Peppas model. The results were shown in table 4 and fig. 2- 5.

Skin irritation studies[11,12]

The selected formulation (F3) was tested for its potential to cause skin

irritation/sensitization in mice. The procedure used for skin irritation study was as follows

Procedure

- The mice were divided into two groups (each group having 6 mice).
- On the previous day of the experiment, the hairs of the dorsal portion of the mice were removed physically with the help of hair removal cream and the skin was cleared with rectified spirit.
- The animals of group I serves as control group, standard without any treatment.
- The animals of the group II served as the test group "a" and treated with placebo patch (without drug, 2.0×2.0 cm^2).
- The animals of group III served as the test group "b" and treated with transdermal patches of Glipizide (2.0×2.0 cm^2).
- After 24 hrs of exposure, each patch was removed with the help of alcohol swab and the test site was rinsed with tap water.
- After 24 hrs of application, the application sites were examined and scored for signs of erythema according to the Draize dermal scoring criteria.
- The erythema scores were given from 0-4 depending upon the degree of erythema according to table 6.
- The studies was approved by ethics committee of Lord Shiva College of Pharmacy, Sirsa

RESULTS AND DISCUSSION

The solubility of Glipizide was found to be 0.257 mg/ mL 0.839 mg/mL, 0.099mg/mL in PBS, methanol, chloroform respectively and partition coefficient value was 0.30±0.002. The melting point of pure drug (Glipizide) was found to be 205.74 ^oC shown in fig. 1 and table 2. Transdermal patches of Glipizide were prepared by solvent evaporation technique employing aluminium foil as substrate. Different formulations of HPMCK4M / PVPK30 and HPMCK15M / PVPK30 were prepared containing Glipizide to the desired the optimum drug release via the most suitable choice of polymeric blends among the formulation. Thickness of transdermal patches (F1-F7) was measured by micrometer. The thickness of the films varied between 0.206±0.002 mm to 0.218±0.004 mm as shown in table 3. Low standard deviation values in the film thickness measurements ensure physical uniformity of the prepared patches by solvent casting technique. Folding endurance of the formulated transdermal patches was measured manually and results were summarized in table 3. The results of the moisture absorption studies for different formulations are shown in table 3. The percentage moisture uptake in the formulation F5, HPMCK4M: PVPK30 in (6:4 ratio) has shown the highest value which may be due to higher polydispersity index and solubility parameter of HPMCK4M and PVPK30 as compared to HPMCK15M. Parallel results were obtained when Anitha *et al*(2011) studied transdermal patches containing Glibenclamide and Atenolol. Overall, the moisture content values in all cases favours that the developed formulations are well protected from microbial contamination and also favours reduction in bulkiness of films. The results of percentage moisture loss are shown in table 3. The percentage moisture loss in the formulation F5 HPMCK4M: PVPK30 in (6:4) ratio shows higher values of moisture loss due to the presence of higher concentration of PVPK30 which revealed its high hydrophilicity than other polymers. The drug content uniformity of formulation, F1 to F10 was determined by UV spectrophotometric method. The results of drug content varies between 96.88±0.003% to 98.90±0.003% as shown in Table 4 which indicated that the process employed to prepare patches in the study was capable of producing patches with uniform drug content and minimal patch variability.

***In vitro* dissolution studies**

The *in vitro* dissolution studies were conducted to investigate the effect of polymer(s) (HPMCK4M & PVPK30) on the release rate of Glipizide patches. Release of a drug from a transdermal drug delivery system mainly involves diffusion factor and drug polymer affinity that control release of drug from formulation. Maximum release (84.44%) was observed with formulation F3 (HPMCK4M**:** PVPK30 in 8:2 ratio). The addition of polymers HPMC and PVP into the formulation tends to enhance release rate of formulation. This may be attributed to the

leaching of the soluble component which ultimately leads to the pore formation and thereby tends to decrease in the mean diffusion path length of drug molecule to release into the dissolution medium and hence higher dissolution rate. However as in formulation F5 and F10 the cumulative %drug release (59.073 and 55.309) was found to be quite less may be due to excess amount of PVPK30. Owning to its a high viscosity leading to drug diffusion may be hampered From the results it is clear that release rate was decreased due to deposition of high concentration of PVPK30 in diffusion rivulets in the matrix patches.

Skin irritation study

Results of skin irritancy study are shown in table 7, which revealed that neither blank patch nor patch containing Glipizide caused any noticeable signs of erythema on mice skin throughout the period of 24 h. Hence, the formulated transdermal patches were found to be free from skin irritation and compatible with the studied mice animal skin.

Table 1
Composition of transdermal patches

S.No.	Batch Code	Polymeric ratio*		Drug (mg)	Plasticizer (PEG400) %of polymer wt.**	Penetration enhancer (DMSO) % of polymer wt.***	Casting solvent Chloroform: Methanol
		HPMCK4M: PVPK 30	HPMCK15M :PVPK30				
1	F1	10:0	__	45	36	12	1:1
2	F2	9:1	__	45	36	12	1:1
3	F3	8:2	__	45	36	12	1:1
4	F4	7:3	__	45	36	12	1:1
5	F5	6:4	__	45	36	12	1:1
6	F6	__	10:0	45	36	12	1:1
7	F7	__	9:1	45	36	12	1:1
8	F8	__	8:2	45	36	12	1:1
9	F9	__	7:3	45	36	12	1:1
10	F10	__	6:4	45	36	12	1:1

Polymeric weight in mg: 250
****Density of PEG 400 is 1.13 g/mL therefore amount used 0.081mL***
*****Density of DMSO is 1.1004 g/mL therefore amount used0.027mL***

Table 2
Characteristics of differential scanning calorimetry of Glipizide

S.No.	Formulation	Weight of sample taken(mg)	Area of peak mJ	Onset of endotherm(degrees)	Peak of endotherms(degrees)	End set of endotherm(degrees)	Peak heightwW
1	Glipizide	6.0	342.751	202.21	205.74	207.57	14.891

Table 3
Physico chemical properties of Glipizide transdermal patches

S.No	Formulation Code	Thickness	Weight variation	Folding endurance	% Moisture absorption	% Moisture loss
1	F1	0.206±0.002	49.24±0.43	251±1.72	4.512±0.375	4.12±0.015
2	F2	0.210±0.002	52.48±0.23	230± 2.51	3.547±0.165	6.29±0.036
3	F3	0.212±0.003	51.93±0.54	253±4.51	3.178±0.256	7.21±0.01
4	F4	0.215±0.005	52.02±0.71	272±7.94	2.631±0.138	9.20±0.015
5	F5	0.218±0.004	55.02±0.54	286±5.03	4.78±0.264	10.12±0.024
6	F6	0.207±0.008	48.57±0.48	220±3.46	1.42±0.068	4.25±0.076
7	F7	0.209±0.002	51.53±0.23	270±6.89	2.148±0.436	8.45±0.054

Table 4
Drug Content of transdermal patches of Glipizide

S.No	Formulation Code	Polymeric ratio		% Drug Content
		HPMCK4M: PVPK30	HPMCK15M: PVPK30	
1	F1	10:0	__	97.67±0.003
2	F2	9:1	__	98.68±0.003
3	F3	8:2	__	98.82±0.008
4	F4	7:3	__	96.98±0.220
5	F5	6:4	__	97.93±0.005
6	F6	__	10:0	98.35±0.009
7	F7	__	9:1	98.02±0.002
8	F8	__	8:2	96.88±0.003
9	F9	__	7:3	97.78±0.004
10	F10	__	6:4	98.90±0.001

Table 5
Kinetic analysis of dissolution data of best formulation (F3)

Zero Order	Slope(K)	3.2385
	Intercept	28.4
	r^2	0.6813
First Order	Slope(K/2.303)	-0.01303
	K	-0.030
	Intercept	1.8241
	r^2	0.730
Higuchi's model	Slope(K)	17.541
	Intercept	11.579
	r^2	0.8774
Korsemeyer-Peppas model	Slope(n)	0.4783
	Intercept(log K)	0.1338
	K	1.3611
	r^2	0.9597

Table 6
Draize scoring criteria

S. No.	Erythema formation	Score assigned
1	No erythema	0
2	Very slight erythema	1
3	Well defined erythema	2
4	Moderate to severe erythema	3
5	Severe erythema	4

Table 7
Skin irritation scores following transdermal patch application of Formulation F3

Animal Code	Group I (Control)	Group II (test "a" group)	Group III (test "b" group)
	Erythema	Erythema	Erythema
I	0	0	0
II	0	0	0
III	0	0	0
IV	0	0	0
V	0	0	0
VI	0	0	0

1 Group I was standard, received no treatment (Control group)
2 Group II was test group, treated with placebo patch (test "a" group)
3 Group III was test group, treated with drug loaded patches of formulation F3

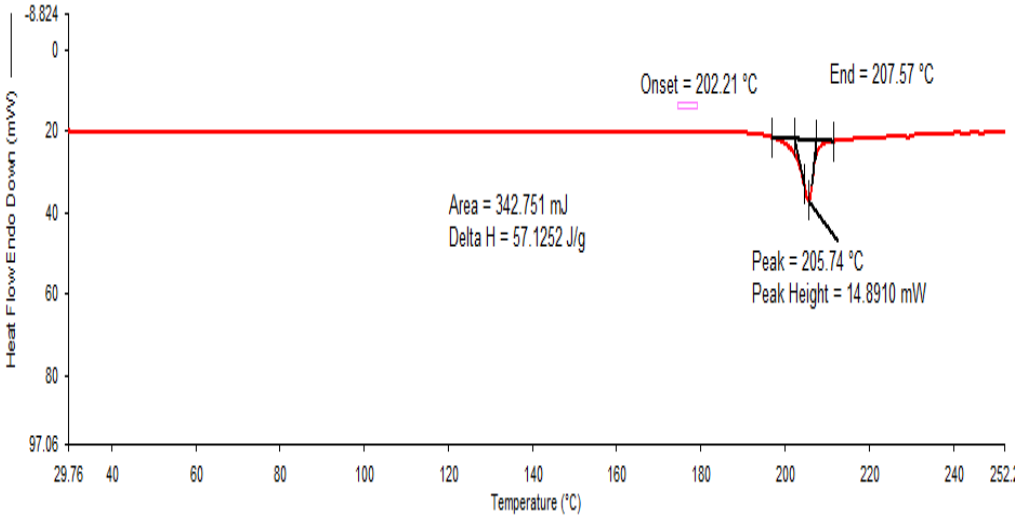

Figure 1
DSC of Glipizide

Figure 2
Percent drug release vs time plot of selected formulation F3 showing zero order kinetics

Figure 3
Log % drug remained vs time plot of selected formulation F3 showing first order kinetics

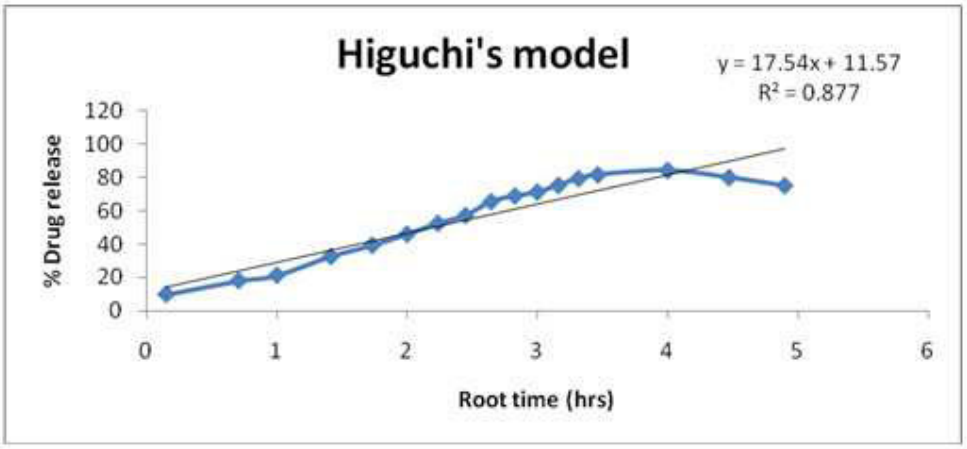

Figure 4
Percent drug release vs square root of time plot of formulation F3 showing Higuchi's model

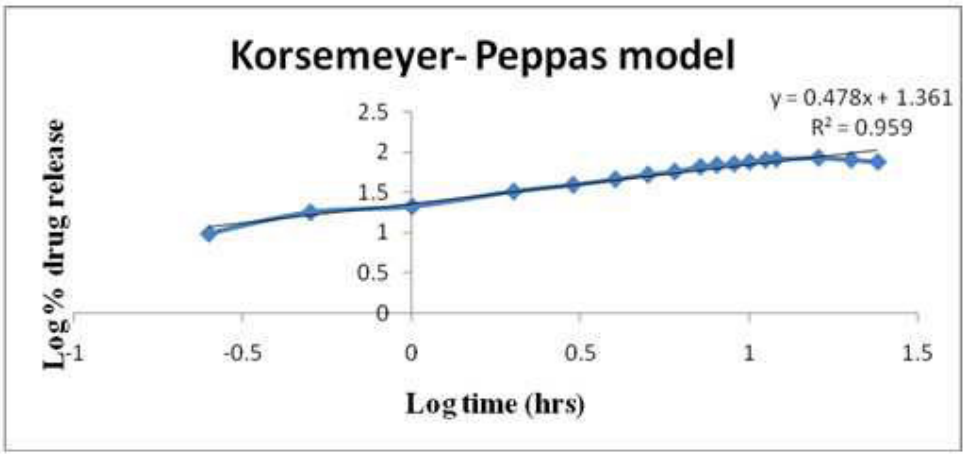

Figure 5
log % drug release vs log time plot of formulation F3 showing Korsemeyer - Peppas model

CONCLUSION

The transdermal drug delivery system is mainly suited for the drugs that preferably undergo hepatic first pass metabolism along-with the short elimination half life of less than five hours. Glipizide transdermal patches were prepared using HPMCK4M, PVPK30 and HPMCK15M. Among all the patches F3 showed optimum sustained release characteristics following Fickian type of diffusion. Hence it can be concluded that HPMCK4M/ PVPK30 (8:2) with 36% PEG400 plasticizer may be suitable for development of transdermal drug delivery system of Glipizide. Also, *in-vivo* studies carried out using mice skin exhibited no irritation on the skin. Further *in-vivo* studies have to be performed to co-relate with *in-vitro* release data for the development of suitable sustained release patches for Glipizide.

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