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Regular Article

Effect of polymeric activity on transdermal patches of Glipizide

Subash. S. Pillai*[1], K.L.Senthil Kumar[1], T.Panneerselvam[2], A.R.Shabaraya[2], T.K.Muneer[3]

[1]Department of Pharmaceutics, Prist University, Thanjavur, Tamilnadu, India
[2]Department of Pharmacy, Srinivas College of Pharmacy, Valachil, Mangalore, Karnataka
[3]Department of Pharmaceutics, M.S.R. College of pharmacy; Bangalore, Karnataka, India
Corresponding author email- subashpillai79@rediffmail.com

An effort was made to formulate transdermal patches of Glipizide which is a potent antidiabetic drug by using different ratio of polymers like hydroxy propyl methyl cellulose, ethyl cellulose and Eudragit. Eight batches of transdermal patches were prepared by solvent casting technique in which the best formulation was found out. The polymers such as HPMC, Ethyl cellulose, Eudragit were incorporated with Glipizide in various proportions, out of which the best formulation on the ratio (HPMC: EC: Eudragit - 2:2:1) with the drug was determined. The prepared transdermal patches were uniform in shape and white in color which was calculated for physicochemical characteristics, in-vitro release profile, and *in-vivo* evaluation on mice. Higuchis plot studies revealed that the predominant mechanism of drug release was diffusion.

Key words: Glipizide, Polymers, solvent casting technique, Fabrication, Plasticizer, Transdermal diffusion, diabetic mellitus.

Substantial efforts have been focused on the development of new drug delivery system. Transdermal dosage form create new dimension in the era of controlled drug delivery system. Transdermal drug delivery systems are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose (Jain 2003). Transdermal drug delivery systems have an advantage of targeting, reliability, ease of administration. Glipizide is an effective oral antidiabetic drug. Single dose produced provoke a brisk release of insulin from pancreases by acting on the so called sulfoxyl urea receptors on the pancreatic Beta-cell membrane (AlSaidan 2004). The aim was to study the polymeric effect on Transdermal films of Glipizide with the following objectives (Florance 1994). To reduce frequency of administration. To avoid first pas metabolism. To reduce dose of Glipizide. To reduce the oral side effects of Glipizide. The molecular weight of drug is 445.5 and the melting point (208°c) and its Bioavailability through skin (85 to 90%), protein binding (90%) were the various important criteria which should be considered Glipizide for Transdermal drug delivery systems (Rim 2005). The drug input can be terminated simply by removing the patch.

Materials and Methods

The present work was carried out to prepare and evaluate transdermal patches of Glipizide. It was carried out as follows. Casting of plain transdermal patches (Riciere 2001). Preparation of drug incorporated polymeric films. Physicochemical evaluation of transdermal patches. Percentage moisture absorption, percentage moisture loss, swelling index, time taken for swelling, water vapors

transmissions rate, thickness, weight uniformity, folding endurance (Cevc 2003). *In-vitro* diffusion studies of transdermal patches. *In-vitro* studies on animals.

Standard curve for Glipizide

Primary stock solution: - Glipizide of 100mg was accurately weighed and dissolved in water to obtain 100ml of solution with a concentration of l000mcg/ml.

Secondary stock solution: - 1ml of primary stock solution was diluted to 100ml with water to get a concentration of 10mcg/ml from the secondary stock solution Aliquots ranging from 1ml to 8ml were pipette out and dilute to 10ml with water to get the concentration range of 1mcg/ml to 8mcg/ml. The absorbance were measured at 269nm.

Standard curve value for Glipizide

Concentration (mcg/ml)	Absorbance
1	0.002
2	0.010
3	0.014
4	0.020
5	0.026
6	0.032
7	0.034
8	0.036

Solvent casting technique

The films were prepared by the method of solvent casting technique (Merkle 1989). Fabrication of drug reservoir films with hydroxy propyl methyl cellulose, Ethyl cellulose and Eudragit. Accurately weighed quantity of hydroxy propyl methyl cellulose, hydroxyl ethyl cellulose and Eudragit of composition of different formulations get mixed with 10mg of Glipizide (Vavrova 2005). Then add 2.5ml of distilled water. Then it was poured over the mercury surface in a petridish and allowed to dry at room temperature (Nicoli 2001). The same procedure was repated with different composition of polymers with Glipizide.

PHYSICO-CHEMICAL EVALUATION

Percent moisture absorption

The percent moisture absorption test was carried out to check the physical stability of the transdermal films at high humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 1.00cm diameter films were cut out and weighed accurately then the films were placed in dessicator containing saturated solution of aluminum chloride keeping the humidity inside the dessicator at 79.5% after 3 days the films were removed ./weighed and percentage moisture was calculated . Average percentage moisture absorption of three films was found.

Percentage moisture loss

This test was also carried to check the integrity of films at dry condition. Three l.cm diameter films were cut out and weighed accurately and kept in a dessicator containing fused anhydrous calcium chloride. After 72 hours the films were removed and weighed. Average percentage moisture losses of three films were found out. Percentage moisture loss= [(initial weight -final weight)] /initial weight)*100.

Swelling index

Three films are taken from each batch and it is put in pH6.6 phosphate buffer and the weight in moisture every three minutes till the weight becomes constant.

Water vapour transmission rate

For water vapour transmission rate glass vials of equal diameter were used as transmission cells. These transmission cells were washed thoroughly dried in an oven. About 1 gm of anhydrous calcium chloride was taken in the cells and the polymer films were fixed over the brim with the help of the solvent. The cells were accurately weighed. Then allow to Kept in a closed desecrator containing saturated

solution of potassium chloride to maintain humidity of 84% RH. The cells taken weighed after 6,12, 24,36,48,72 hours of storage. The amount of water vapour transmitted were found out using the formula.

Water vapour transmission rate = Final weight-Initial weight / Time x area

Water vapour transmission rate usually expressed as the number of grams of moisture/hr/sq.cm. from the data obtained water vapour transmission calculated.

Thickness

Thickness of the film was measured at six different points using a screw guage and average thicknesses of three films were found out.

Weight of film

Each film was weighed individually and average weight of three films were found out.

Folding endurance

It was determined by repeatedly folding a small strip of films at the same place till it broke. The number of times, the films could be folded at the same place without breaking gave the value of folding endurance.

Drug content

A film size of 1 cm diameter was cut and dissolved in phosphate buffer. After adding suitable reagent and dilution, optical density was found out at 269 nm. Average during content of three transdermal, films were determined.

***In-vitro* drug release evaluation**

Here, dissolution test apparatus USP (paddle type) was employed throughout the study. The medium employed was 0.1N HCL at 37°C room temperature. The dissolution was carried out at an RPM maintained was at 100 with in a stipulated interval ofl5min. A film of size diameter was cut and introduced in to the cylinder filled with equal quantity of 0.1N HCL as the medium. Sample of 10ml were withdrawn at every 15min duration for continues two hours. The volumes of sample withdrawn were replaced by the same volume of dissolution medium. Filter the above sample and then taken 5ml from each sample and made at 50ml with the medium. The withdrawn samples were analyzed by using visible UV spectrophotometer 269nm using reagent blank (Brown 1998).

***In-vivo* studies**

Acute and long term hypoglycemic activity, biochemical and histopathologic studies, skin irritation and pharmacokinetic studies in mice (Carmichael 1994).

Skin Irritation test (Visual and histopathological evalution of skin (Benowitz 1992))

The mice were divided into 5- groups (n=6) on the previous day of the experiment the hair on the back side area of mice was removed. The animals of group I was served as normal, without any treatment. One group of animals (group II, control) was applied with marketed adhesive type (official adhesive type in USP). Transdermal system (blank, without drug and drug loaded) were applied into nude skin of animals of 3 and 4 groups AO.8% v/v aqueous solution of formation was applied as a standard irritant (Group V) (Prausnitz 2004). The formation solution each day upto 7 days and finally the application sites were graded according to a visual scoring scale, always by the same investigator.

The erythema scale was as follows:-

0, none; 1, slight; 2, well defined; 3, moderate; and 4, scar formation. The edema scale was; 0, none; 1, slight; 2, well defined; 3, moderate; and 4, severe. After visual evaluation of skin irritation the animals were sacrificed and skin samples were processed for histological examination (6)

Results and Discussion

In the present study, the transdermal patches of Glipizide were prepared by using different polymers such as hydroxy propyl methyl cellulose K100m, Ethyl cellulose and Eudragit L100 by solvent casting method. *Invitro* dissolution study of drug along with different combination of polymers that is hydroxy propyl methyl cellulose, Ethyl cellulose, Eudrgit has been preformed. The higher rate and percentage of release of drug in film containing less concentrations of Eudragit i.e., in batch B4 (HPMC: Ethyl cellulose: Eudragit (2:2:l) has been performed. As the percentage of Eudragit was reduced the rate of release of drug was increased. Hence moreover, the batch shows the best moisture of films and the graph representing the best sustained drug release. Film with batch code B4 shows better stability and suitability.

Composition of polymers with drug

Batch Code	Polymers			Solvent	Plasticizer
	HPMC K100M %	EC%	EUDRAGIT L 100%	Acetone ml	Glycerin (%W/W)
B1	1	1	1	2.5	30
B2	2	1	1	2.5	30
B3	1	2	1	2.5	30
B4	2	2	1	2.5	30
B5	1	1	2	2.5	30

***In-vitro* drug release for batch 1 -5**

Time	Square root of time	Cumulative drug release (%)				
		Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
5	2.236	9.48	13.55	16.8	24.2	17.71
10	3.162	15.95	18.97	24.52	33.18	19.53
15	3.873	22.84	24.84	32.25	45.66	25.88
20	4.472	29.74	35.68	37.69	57.77	37.24
25	5	32.33	39.747	44.51	64.29	44.05
30	5.477	33.62	42.006	50.41	73.6	49.5

Conclusion

The formulation containing 2 parts of HPMC, 2 parts of Ethyl cellulose and 1 part of Eudragit, has shown best release in concentration independent manner. Higuchi's plot revealed that predominant mechanism of drug release in diffusion. Hence the formulation achieved the objectives of present study such as reducing the dose, improving bio-availability by avoiding first pass metabolism and it may have better patient compliance.

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