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FORMULATION DEVELOPMENT, *IN VITRO* AND *IN VIVO* EVALUATION OF MATRIX TRANSDERMAL SYSTEMS OF GLIBENCLAMIDE

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ABSTRACT

Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence an antidaibetic agent of both therapeutic and prophylatic usage has been subjected to transdermal investigation. Glibenclamde a first generation hypoglycemic agent faces problems like poor solubility with large individual variation and extensive metabolism. In this study, matrix type transdermal drug delivery system of glibenclamide, an antidiabetic drug were prepared by solvent casting method using different polymers like HPMC/PVP/CMC in varied ratios. Dibutylpthalate was used as plasticizer and dimethysulfoxide (DMSO) and propylene glycol was used as permeation enhancers. The prepared tranasdermal patches of glibenclamide were transparent, smooth, uniform and flexible. The cumulative amount of drug release in 6hrs from the four formulations was 74.6%, 98.8%, 97.0%, 84% respectively. On the basis of *ex-vivo* drug release, the skin permeation performance formulation F2 was found to be better than other formulations and it was selected as optimized formulation.

KEYWORDS

Glibenclamide, Matrix type transdermal drug delivery system, Plasticizer-dibutylpthalate, Permeation enhancer, *Ex-vivo* drug release and *Ex-vivo* drug permeation.

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INTRODUCTION

The most common form of delivery of drugs is the oral route. While this has the notable advantage of easy of administration, it also has significant drawbacks-namely poor bioavailability due to hepatic metabolism (first pass) and the tendency to produce rapid blood level spikes (both high and low), leading to a need for high and/or frequent dosing, which can be both cost prohibitive and inconvenient. To overcome these difficulties there is

a need for the development of new drug delivery system; which will improve the therapeutic efficacy and safety of drugs by more precise (i.e. site specific), spatial and temporal placement within the body thereby reducing both the size and the number of doses. New drug delivery system are also essential for the delivery of novel, genetically engineered pharmaceuticals (i.e. peptides, proteins) to their site of action, without incurring significant immunogenicity or biologically inactivation.

Objective

Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentration, hyperglycemia caused by insulin deficiency, often combined with insulin resistance. Gilbenclamide is a potent oral sulfonyl urea hypoglycaemic agent. The drug inhibits ATP sensitive potassium channels in pancreatic beta cells.

The plasma half life is about 4-6 hrs which makes frequent doing necessary to matintain therapeutic drug levels of blood for a long term treatment. Therefore, controlled release transdermal preparation of glibenclamide was prepared to give a sustained effect as compared to the oral conventional multiple oral dosing.

The aim of the present study is to formulate the matrix type transdermal patch of glibenclamide as a model drug with combination of HPMC, CMC, PVP to minimize the dose of drug for lesser side effects. It is found that glibenclamide can be permeated through the skin but its permeation is low. Therefore, its permeation was studied through the freshly excised rat abdominal skin as such in presence of some penetration enhancers.

MATERIALS AND METHOD

Glibenclamide, Hydroxy Propyl methyl Cellulose (HPMC 6cps), Hydroxy Propyl methyl Cellulose (HPMC 15cps), Poly Vinyl Pyrrolidine(PVP), Poly Ethylene Glycol(PEG 4000), Dimethyl Sulphoxide (DMSO), Aluminium chloride, Anhydrous calcium chloride, Methanol, Chloroform.

Construction of standard curve

Preparation of stock solution

10mg of Glibenclamide was accurately weighed and dissolved in a required quantity of methanol and make up to 100ml with Phosphate buffer (100µg/ml).

Sample solutions

Aliquots equivalent to 0.2, 0.4, 0.6, 0.8, 1.2, 1.4, 1.6, 1.8 and 2.ml were drawn from the stock solution and made up to 10ml using Phosphate buffer (pH - 7.4).

Method[1-7]

The absorbance was measured using the sample solutions against region at 226nm. The absorbance values obtained. The calibration curve was plotted by taking concentration on X-axis and absorbance on Y-axis (Table No.2).

Compatibility studies of drug and polymers

In the present study, compatibility studies were carried out to assess any incompatibility between the drug and polymers. The IR studies were carried out to determine whether there is any physical or chemical interaction between drug and polymer. The IR spectrum of plain drug and overlay of physical mixture of drug with polymer were compared. Spectra of the pure drug and the physical mixtures of drug with polymers were taken individually by the potassium bromide pellet method.

Formulation of transdermal patches

In the present study, matrix type transdermal patches of Glibenclamide were prepared by the moulding technique. A flat square-shaped, aluminium foil-coated glass molds having surface area of 25cm² were fabricated for casting the patches (Figure No.1).

Preparation of casting solutions

For HPMC and CMC (F1and F3)

The casting solutions were prepared by dissolving weighed quantities (Table No.1) of polymers in methanol and chloroform. The drug was dissolved in chloroform and added to the above polymer solution along with dimethyl sulfoxide as plasticizer, for formulation F1 and propylene glycol has plasticizer for formulation of F3. Thoroughly mixed to form homogeneous mixtures. The volume was made up to 10ml with methanol. Entrapped air bubbles were removed by applying vacuum.

For HPMC and PVP polymers (F2 and F4)

The casting solutions were prepared by dissolving weighed quantities (Table No.1) of polymers in

methanol and chloroform by heating in water bath. The drug was dissolved in chloroform and added to the above polymer solution along with dimethyl sulfoxide as plastizer, for formulation of F2 and propylene glycol for formulation F4, thoroughly mixed to form a homogenous mixture. The volume was made upto 10ml with methanol. Entrapped air bubbles were removed by applying vacuum.

The patches were removed by peeling and cut into square dimension of 2cm x 2cm (4cm²). These patches were kept in desiccator for 2 days for further drying and wrapped in aluminium foil, packed in self-sealing covers.

Collection and preparation of rat skin

Albino rat was slaughter by exposing to excess chloroform. Hairs from the skin were removed with the help of a razor. Skin was excised from rat with scalpel and the fatty layer was removed by keeping the skin in warm water at 60ºc. After 2min, the fatty layer was peeled off gently and the skin was washed with water and kept for saturation in phoaphate buffer of pH 7.4 for about 15min before it was used for permeation studies.

EVALUATION STUDIES

Physico-chemical parameters

Physical appearance

All the transdermal patches were visually inspected for colour, flexibility, homogeneity and smoothness.

Thickness of the patch

The thickness of the drug loaded patches was measured at three places on a single patch of each formulation using a screw-gauze and the mean values were calculated.

Weight variation

A set of three patches from each formulation having a area of 2cm*2cm (4cm²) were weighed on a digital balance and the mean values were calculated. The tests were performed on films which were dried at 60ºc for 4hrs prior to testing.

Folding endurance

A strip of 2cm*2cm (4cm²) was subjected for folding endurance by folding the patch at the same place repeatedly several times until a visible crack was observed and the values were reported. specific area is to be 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 value of the folding endurance.

Moisture content

The film was weighed and kept in a dessicator containing calcium chloride at 40ºC and dried for at least 24hrs. The film was weighed until it showed a constant weight. The moisture content was the difference between the constant weight taken and the initial weight and was reported in terms of percentage (by weight) moisture content.

Percentage moisture content = [Initial weight-Final weight/ Final weight] ×100

Moisture absorption

The weighed film was kept in a dessicator at room temperature for 24hrs. It was then taken out and exposed to 84% RH using a saturated solution of potassium chloride in a dessicator until a constant weight was achieved.

The % moisture uptake was calculated by using the following formula;

Percentage moisture uptake = [Final weight-Initial weight/ initial weight] ×100

Drug content

The patch (4cm²) was transferred into a graduated flask containing 100 ml of phosphate buffer pH 6.8. The flask was shaken for 4hr in a mechanical shaker. Then the solution was filtered and after suitable dilution with phosphate buffer pH 6.8 the absorbance was measured at 226nm using the placebo patch solution as blank and the drug content was calculated.

***Ex-vivo* skin permeation study**

The *ex-vivo* study of drug permeation through the rat skin was performed using a modified Franz type glass diffusion cell. The modified cell having higher capacity is (27ml) is used to maintain sink condition. This skin was mounted between the donor and receptor compartment of a diffusion cell. The transdermal patch was placed on the skin and covered with aluminium foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer of pH 7.4 containing 0.5% of sodium lauryl sulphate. The hydrodynamic in the receptor compartment were maintained by stirring

with a magnet bead at constant rpm and the temperature was maintained at 32±0.5ºC because the normal skin temperature of human is 32ºC. The diffusion was carried out for 12hr and 1ml sample was withdrawn at an interval of 1hr. The samples were analyzed for drug content spectrophotometrically at 226nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

RESULTS AND DISCUSSION

Compatibility studies of drug and polymers

From the FTIR Studies results, it was concluded that there was no interference in the functional groups between drug and excipients (Figure No.2-4).

Physico-chemical parameters

All the transdermal patches were visually inspected for colour, flexibility, homogeneity and smoothness. The following parameters are present within the limit values and satisfied such us thickness, Weight variation, Folding endurance, Moisture content, **Moisture absorption and** Drug content (Table No.3-4).

Ex-vivo skin permeation study

The *ex-vivo* study of drug permeation through the rat skin was performed using a modified Franz type glass diffusion cell. The formulation (F2) using DMSO as permeation enhancer and DBT as plasticizer showed good drug release (Table No.5).

Table No.1: Composition of Transdermal Films

S.No	Formulations	Polymers	Permeation Enhancer	Plasticizer	Solvent
1	F1	HPMC:CMC	DMSO	DBT	$CHCl_3$: CH_3OH
2	F2	HPMC:PVP	DMSO	DBT	$CHCl_3$: CH_3OH
3	F3	HPMC:CMC	PG	DBT	$CHCl_3$: CH_3OH
4	F4	HPMC:PVP	PG	DBT	CH Cl_3: CH_3OH

Table No.2: Standard plot for Glibenclamide

S.No	Concentration (in µg/ml)	Absorbance
1	2	0.142
2	4	0.286
3	6	0.428
4	8	0.569
5	10	0.720
6	12	0.862
7	15	1.204
8	20	1.546
9	25	1.784

Table No.3: Physicochemical Properties of the prepared Transdermal patches

S.No	Formulation Code	Flexibility	Smoothness	Transparency	Stickiness
1	F1	Flexible	Smooth	Opaque	Non-sticky
2	F2	Flexible	Smooth	Opaque	Non-sticky
3	F3	Flexible	Smooth	Opaque	Non-sticky
4	F4	Flexible	Smooth	Opaque	Non-sticky

Table No.4: Evaluation parameters

S.No	Formulation	Thickness (mm)	Folding endurance	% of moisture absorption	% of moisture loss	Drug content (mg)
1	F1	0.0526±0.005	171.6±7.133	7.26±0.3538	3.72±0.121	4.2
2	F2	0.051±0.0005	176.66±2.356	7.33±0.197	3.62±0.063	4.3
3	F3	0.049±0.0005	164±5.715	7.44±0.367	3.65±0.225	4.4
4	F4	0.0506±0.0005	149.66±2.054	7.236±0.053	3.69±0.225	4.2

Table No.5: Comparison of *ex-vivo* percent drug permeation of formulations

S.No	Time (hrs)	F1	F2	F3	F4
1	1	9.5	20.2	23.5	22.6
2	2	14.55	25.436	27.005	29.6
3	3	27.84	42.89	43.04	34.5
4	4	437.67	60.84	59.65	54.7
5	5	65.8	77.00	67.5	67.5
6	6	74.6	98.82	97.0	84.5
7	24	81.84	99.20	31.60	97.76

Figure No.1: Formulation of Transdermal Patch: Casting Solution in glass mould

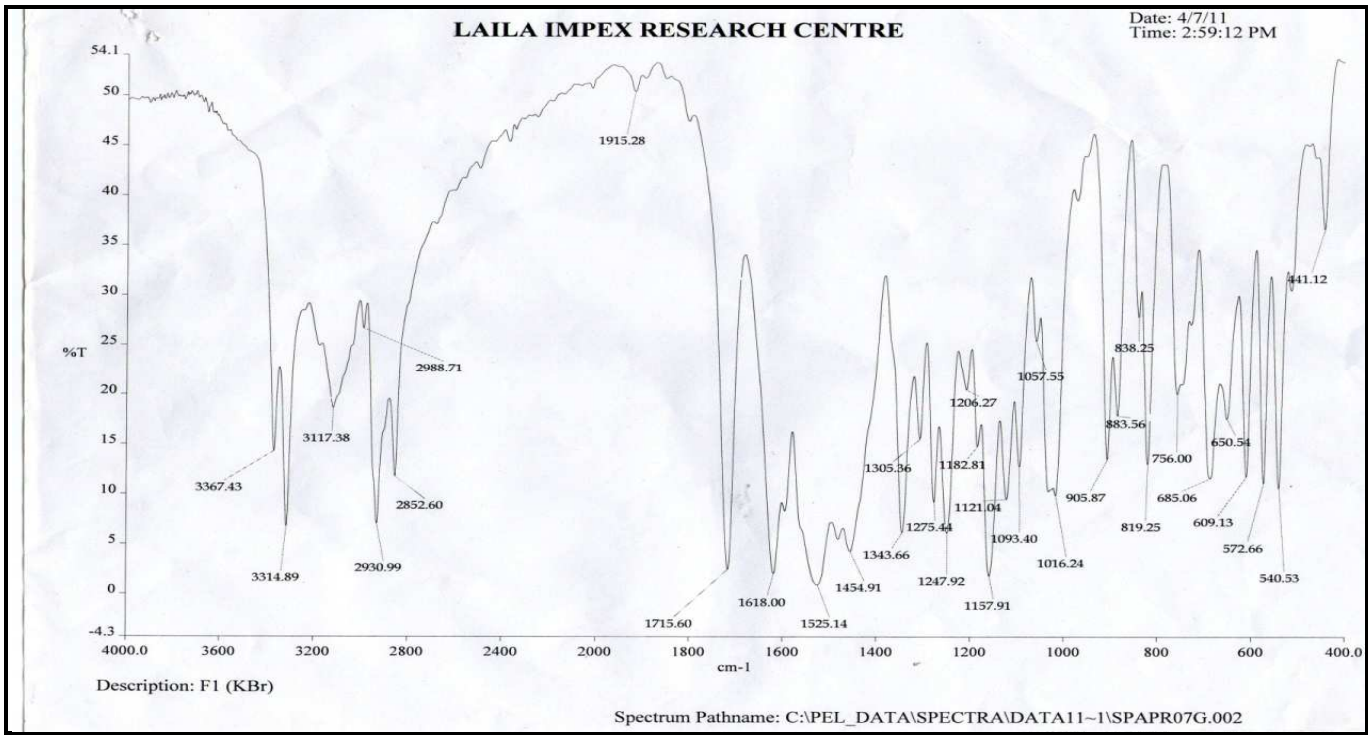

Figure No.2: IR spectra of pure drug

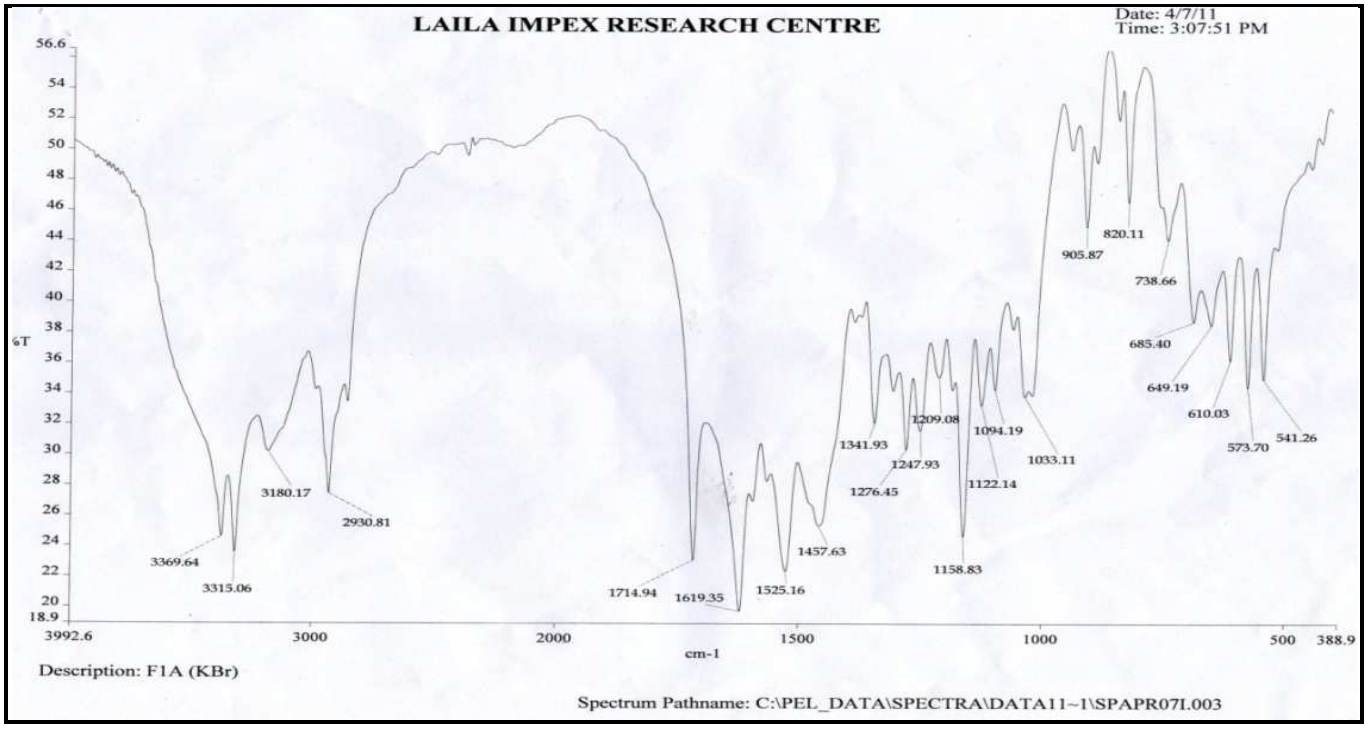

Figure No.3: IR spectra of formulation F2 (HPMC: PVP)

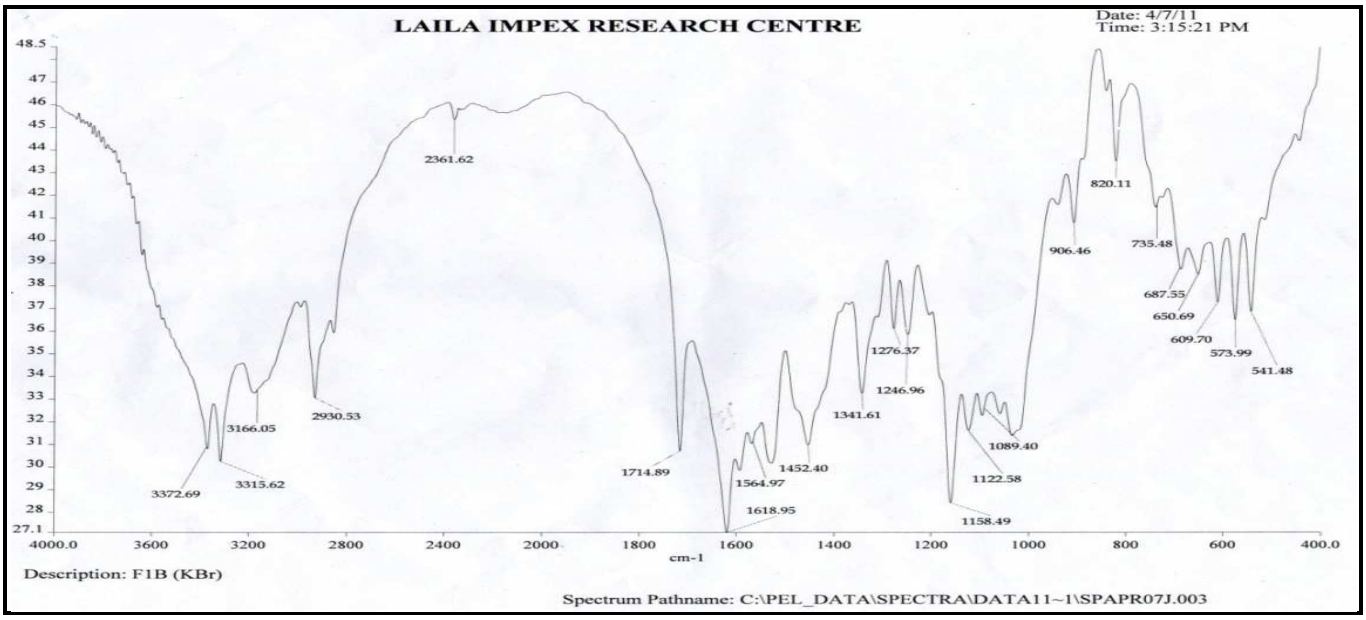

Figure No.4: IR Spectra of formation F1 (HPMC: CMC)

CONCLUSION

All formulations prepared using glibenclamide drug showed good physicochemical properties like thickness, weight variation, drug content, folding endurance, moisture absorbed, moisture loss. The drug release through the transdermal patches of glibenclamide was done with diffusion controlled mechanism. Effect of permeation enhancer has been checked on *ex-vivo* permeation of drug and concluded that the formulation (F2) using DMSO as permeation enhancer and DBT as plasticizer showed good drug release. Hence observations revealed that patches formulated using DMSO and DBT as permeation enhancer and plasticizer showed better drug release characteristics.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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