Research Article

Fabrication and Characterization of Glibenclamide Transdermal Patches

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ABSTRACT

The purpose of the present investigation was to prepare Glibenclamide transdermal patches and to study the effect of different polymer combination and polymer ratios on physiochemical parameters including *in-vitro* drug release profile. Matrix type Glibenclamide transdermal patches were prepared using Ethyl Cellulose (EC) and Hydroxy propyl methyl cellulose (HPMC) in different ratios. Propylene glycol was used as a plasticizer and tween 80 used as permeation enhancers which were prepared by solvent casting method. The prepared formulations were evaluated for various parameters like Thickness, Weight variation, Folding endurance, Moisture absorption, Moisture loss, Drug content, Drug permeation, Drug–polymer interactions. *In- vitro* drug release studies were performed by using Franz diffusion cells. Variations in drug release profile were observed among various formulations. The FT-IR studies revealed no interaction between drug and polymers. The present work also concentrates on comparision between the effect of hydrophillic and hydrophobic polymers on the physicochemical parameters of the transdermal patches.

Keywords: Glibenclamide, ethyl cellulose, HPMC, Transdermal patches.

INTRODUCTION

Transdermal drug delivery is one of the most promising methods for drug delivery. Increasing numbers of drugs are being added to the list of therapeutic agents that can be delivered to the systemic circulation via skin.[1] The main advantages of this system are that there is controlled release of the drug and the medication is painless. In this system the drug is mainly delivered to the skin with the help of a transdermal patch which adheres to the skin.[2] The transdermal drug delivery system has potential advantages of avoiding hepatic first pass metabolism, maintaining constant blood level for longer period of time resulting in a reduction of dosing frequency, improved bioavailability, decreased gastrointestinal irritation that occur due to local contact with gastric mucosa and improved patient compliance.[4] Glibenclamide is a potent oral sulfonylurea hypoglycaemic agent. It is currently available for treating hyperglycemia in Non insulin dependent Diabetes Mellitus (NIDDM-type-2). Plasma half life is 4-6hrs.[3] Which make frequent dosing necessary to maintain therapeutic blood level. Therefore controlled released Transdermal patch of Glibenclamide was prepared to give controlled effect as compared to conventional multiple oral dosing. It is highly accepted that membrane controlled transdermal systems have the distinct advantage that the drug release rate, which is regulated by permeation through the rate controlling membrane, remain relatively constant as long as drug loading in the reservoir is maintained at high level.[5] Hence, the proposed work involves the fabrication and evaluation of transdermal drug delivery systems containing Glibenclamide.

MATERIALS AND METHODS

The following chemicals were obtained from different sources and used as received. Glibenclamide was a kind gift sample from Glenmark Pharmaceuticals Ltd. EC, HPMC, Tween 80 and glycerine were obtained from S.D Fine chemicals, Mumbai. All other chemicals and reagents used were of analytical grade. Double-distilled water was used throughout.

Formulation of Transdermal Patch of Glibenclamide

A series of transdermal patches with different proportions and combinations of HPMC, and EC were dissolved / dispersed in 10 ml of water in a beaker and allowed to swell by keeping it aside for 5 minutes. Propylene glycol was incorporated as a plasticizer at a concentration of 20% w/w of dry weight of polymers. Tween 80 (1ml) was added to the polymer solution as permeation enhancer. Glibenclamide 10 mg was dispersed in 5 ml water in another beaker. The drug solution was added to the polymer solution and was mixed thoroughly with the help of a magnetic stirrer. The whole solution was transferred into the petridish and kept for 24 hours. Inverted funnel was placed over to avoid sudden evaporation. After drying, the films were observed and checked for possible imperfections upon their removal from the petridish. Patches with any imperfections, entrapped air, differing in thickness, or weight (or) content uniformity were excluded from further studies.

Table 1: Shows the quantities of different ingredients in the formulation.

Code	Glibenclamide (mg)	HPMC (mg)	EC (mg)	Tween 80	Glycerin	Water (ml)
F1	10	400	-	1 drop	2 drops	15 ml
F2	10	300	100	1 drop	2 drops	15 ml
F3	10	200	200	1 drop	2 drops	15 ml
F4	10	100	300	1 drop	2 drops	15 ml
F5	10	-	400	1 drop	2 drops	15 ml

Experimental Methods

Preparation of standard calibration curve of glibenclamide

Standard calibration curve of Glibenclamide was prepared with a known concentration of drug in between 2-10 µg/ml using UV spectrophotometer (LabIndia) at λmax 229 nm using phosphate buffer pH 7.4 as solvent.

Evaluation of the prepared formulation I

Physicochemical evaluation

Physical appearance

All the transdermal systems were visually inspected for color, clarity, flexibility and smoothness.

Folding Endurance

Folding endurance of the film was determined manually by folding a small strip of the film (4×3 cms) at the same place till it breaks. The maximum number of folding operation done at the same place of the film without breaking, gives the value of folding endurance, where the cracking point of the films were considered as the end point.

Thickness of the films

The thick nesses of the patches were determined using Digital Screw Gauge micrometer (Mitutoyo, Japan) at three different places and mean thickness was calculated.

Weight uniformity:

The dried patches were weighed individually on electronic balance (Sartorius UK). The average of 3 observations was calculated.

Drug content

Transdermal systems of specified area (5.088 cm2) was cut into small pieces and taken into 50 ml volumetric flask, then the volume was made up to 50ml with phosphate buffer saline pH 7.4 and further dilutions were made from this solution. Similarly, a blank was carried out using a drug free patch. The solutions were filtered and absorbances were read at 220nm by UV spectrophotometer.

Tensile Strength & Percentage Elongation

Tensile strength of the film was determined with Universal Strength Testing Machine (Hounsfield, Slinfold, Horsham, U.K.). It consisted of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (4 × 1 cm2) was fixed between these cell grips and force was gradually applied till the film broke. The tensile strength of the film was taken directly from the dial reading in kg. The values are shown in table 10. Tensile strength is expressed as follows

***In-vitro* diffusion studies**

Diffusion studies were carried out for the prepared formulations by Franz diffusion cell using dialysis membrane with 7.4 pH phosphate for a period of 24 hours. The donor chamber was exposed to air and receiver chamber had 7.4 pH Phosphate buffer with dialysis membrane in between. 1ml of solution from receiver chamber was withdrawn every 1 hour for 24 hours, and the aliquot of 1 ml was replaced. The withdrawn solution was analysed by UV at 229 nm.

RESULTS AND DISCUSSION

Construction of calibration curve of Glibenclamide in phosphate buffer saline of pH 7.4

Glibenclamide shows absorption maxima at 229 nm in phosphate buffer saline of pH 7.4. The spectrophotometric determination shows linearity range of 5 to 25µg/ml.

The linear regression analysis was done on absorption data points. A straight line equation y= 0.0512x+0.0072 was generated for the calculation of amount of drug.

Physical parameters

The physicochemical evaluation of formulated patches shows that they were found to be uniform in their weight and thickness with low SD values.

The weights of the patches are in between 0.524gm to 0.785gm. The resulted thickness of the patches formulated is in between 0.093 mm to 0.113 mm

The folding endurance measures the ability of patch to withstand rupture. The results were in between 100 to 207. And formulation found to maintain their integrity with general skin folding when used. The results were tabulated in the table: 2.

Tensile strength and elongation

The tensile strength of the patches was found to vary with the nature of the polymer. F4 formulation possessed high tensile strength when compared to other

formulations. The tensile strength results were in between 0.305kg/mm2 to 0.498kg/mm2 and the elongation were in between 12.45mm to 26.56mm. The results are expressed in the table no: 3.

Table 2: Data showing physical parameters of Glibenclamide TDDS patches

S. No	Formulation	Folding endurance	Thickness (mm)	Weight variation (gm)
1	F1	100±9.0	0.108±0.078	0.599
2	F2	150±11.6	0.113±0.032	0.621
3	F3	200±7.3	0.093±0.011	0.785
4	F4	207±6.0	0.116±0.019	0.675
5	F5	169±8.76	0.123±0.029	0.524

Drug content

Homogeneous uniform drug distribution is one of the important characteristics of a transdermal patch that ensures the uniform reproducible controlled release of the drug from the patch. The results revealed that the drug content was almost uniform in the range of 90.76 to 97.07 in all the patches with low SD value. The results are shown in table no: 3.

In-vitro diffusion studies of Glibenclamide TDDS patches

In vitro release studies revealed that release of glibenclamide across dialysis membrane from F1 and F2 formulation showed only 63.90% and 55.23% at the end of 24h, respectively. The flux was calculated from the slope of linear graph, and it was found to be 39.09 and 32.27µg/cm2/h, respectively. It was proved from the above result that there was a lower flux and lower diffusion rate through the dialysis membrane. However, *in vitro* release of glibenclamide across dialysis membrane from formulation F3, F4 and F5 were 83.10%, 93.98% and 81.12% respectively at the end of 24h. The flux for the formulation of F3, F4 and F5 was 50.45%, 53.75%, 48.93% µg/cm^2/hr, diffusion coefficient was 0.79, 0.83, 0.70cm^2/hr. It was clear from the above results that the F4 formulation shows the prolonged release of drug from the patches.

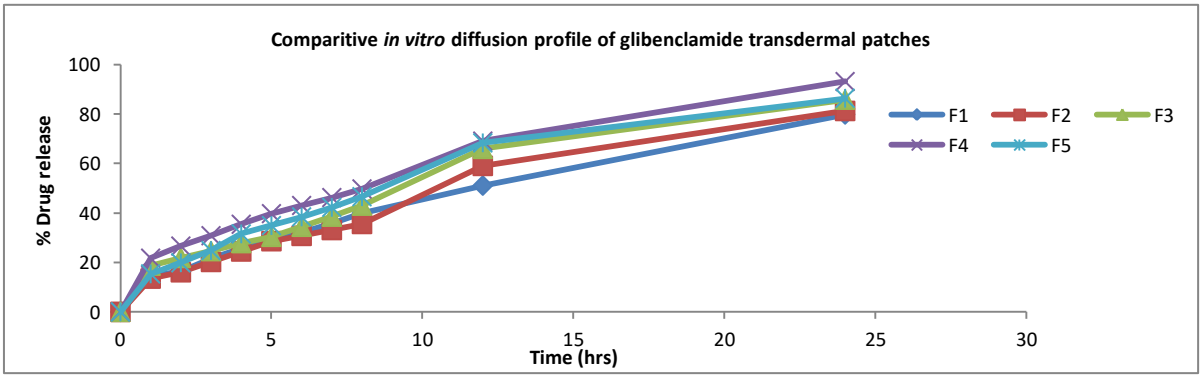
In the formulation of F4, containing HPMC and EC in the ratio of 1:3, showed 93.98% glibenclamide release at the end of 24h study. The reason for high release from HPMC and EC could be explained by the hydrophilic nature of the polymers which could affect the release of drug from the patches because of swelling and hydration of the patches. The physicochemical properties of the formulation F4 depicted suitable formulation for the transdermal delivery. Therefore, F4 formulation was selected as an optimized formulation. The results are expressed in table no: 3.

Release kinetics

To know the mechanism of drug release, the data were fitted to models representing zero-order, first-order, higuchi and Korsmeyer-Peppas. It was found that the release of Glibenclamide from the transdermal patch follows zero-order kinetics.

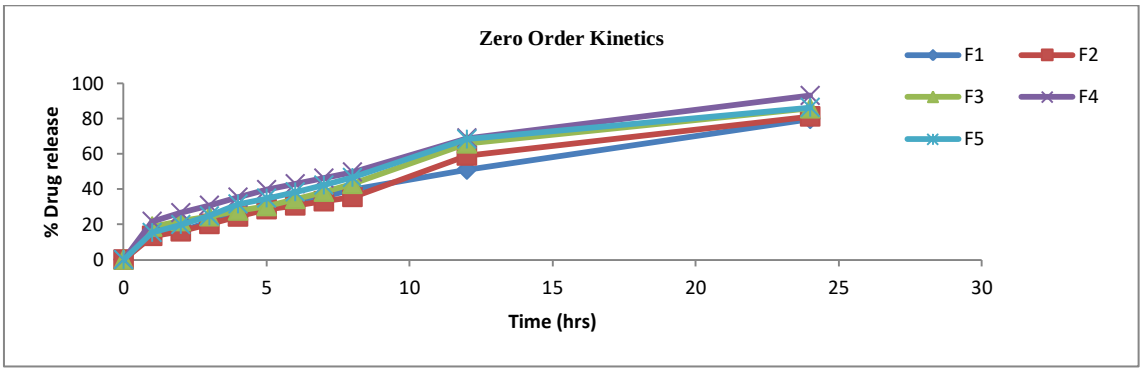
Table 3: Data obtained from tensile strength, elongation, drug content and % drug release for Glibenclamide TDDS patches

S. No.	Formulation	Tensile strength (kg/mm^2)	Elongation (mm)	Drug content	% Drug Release
1	F1	0.305+0.0100	19.49+1.086	91.89±0.0597	63.90
2	F2	0.375+0.0134	22.35+1.704	90.76±0.0595	55.23
3	F3	0.424+0.0122	17.48+1.151	94.09±0.635	83.10
4	F4	0.498+0.0093	26.56+0.700	97.07±0.402	93.98
5	F5	0.312+0.0126	12.45+0.855	95.23±1.270	81.12

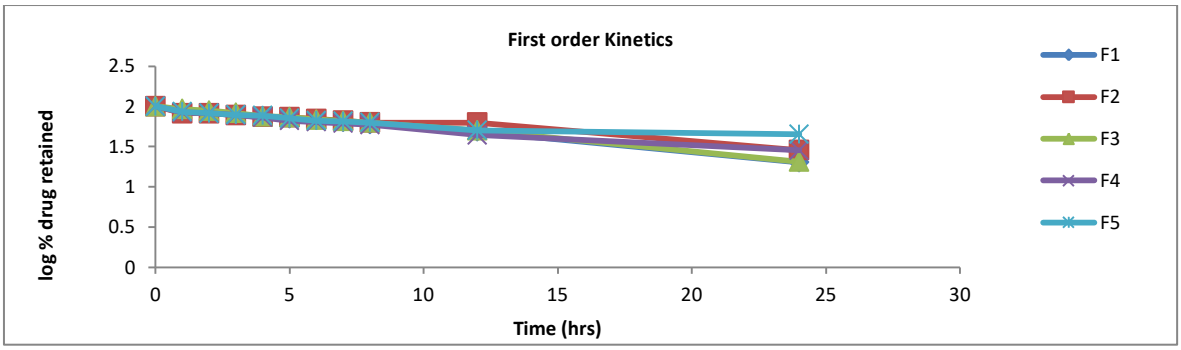


Graph 1: Comparitive *in-vitro* diffusion profiles of Glibenclamide trandermal patches

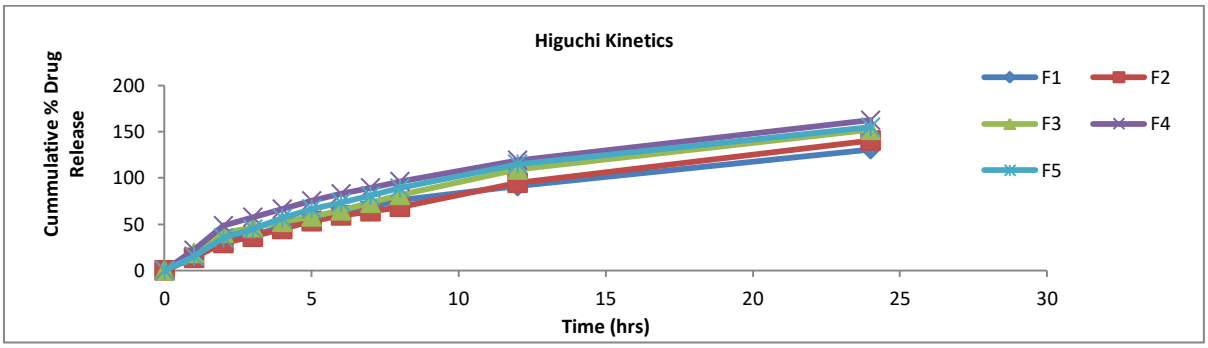
The coefficient of determination (R2) was found to be much closer to 1 for the Korsmeyer-Peppas equation. Slope values (n>1.0) suggest that the drug permeation from transdermal patches followed the super case II transport mechanism, possibly owing to chain disentanglement and swelling of hydrophilic polymer. The values were plotted in graph 2-5.



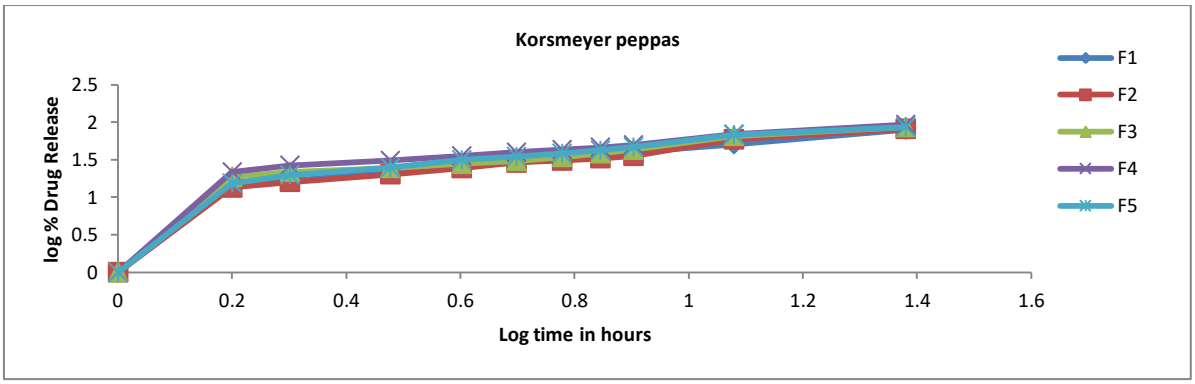
Graph 2: Zero Order Kinetics



Graph 3: First Order Kinetics



Graph 4: Higuchi Kinetics



Graph 5: Korsmeyer Peppas Kinetics

CONCLUSION

From the above physicochemical evaluation and *in vitro* studies it was concluded that preformulation studies of glibenclamide were found in accordance with the reported literature limits. The formulated transdermal patches of combinations of HPMC and EC showed good physical properties Thickness, folding endurance and drug content were found to be uniform and reproducible with low SD values compared to patches with hydrophillic and hydrophobic polymers alone. All the optimized patches formulated were stable at room temperature. F4 showed highest release during in vitro drug permeation studies through dialysis membrane. The release of glibenclamide appears to be dependent on hydrophilicity of the matrix. Moderately hydrophilic matrices showed best release. The predominant release mechanism of drug through the fabricated matrices was believed to be by diffusion mechanism. The release of glibenclamide from the optimized formulation F4 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled.

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