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FORMULATION AND EVALUATION OF GLIMEPRIDE TRANSDERMAL PATCHES USING SYNTHETIC POLYMERS

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ABSTRACT
One of the thrust areas in drug delivery research is transdermal drug delivery systems (TDDS) due to their characteristic advantages over oral and parenteral drug delivery systems. Development of functional delivery systems is a challenging task. Transdermal drug delivery involves the transport of drug across the skin. Optimal physiochemical properties are required in drug candidates for delivery via transdermal patches. Traditional transdermal patches can be divided into two categories – reservoir-based and matrix-based, according to their physical structure. Transdermal drug delivery offers advantages like patient compliance, avoidance of firstpass metabolism, and large surface area of skin over which to deliver the drug, quick termination of dosing, etc. However, only a few drug products with optimum characteristics have been successfully marketed to deliver a drug through the skin. This study concentrates on matrix-based transdermal drug delivery systems, formulated using glimepride and polymers in different ratios. The release of glimepride 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 glimepride from the optimized formulation F4 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled.

KEYWORDS: Transdermal patches, Matrix-based, Reservoir-based, Patient Compliance, Optimal physiochemical properties.

INTRODUCTION
Transdermal drug delivery systems (TDDS), also known as patches, are dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. In order to deliver therapeutic agents through the human skin for systemic effects, the comprehensive morphological, biophysical and physicochemical properties of the skin are to be considered. Transdermal delivery provides a leading edge over injectables and oral routes by increasing patient compliance and avoiding first pass metabolism respectively1. Transdermal delivery not only provides controlled, constant administration of the drug, but also allows continuous input of drugs with short biological half-lives and eliminates pulsed entry into systemic circulation, which often causes undesirable side effects. Thus various forms of Novel drug delivery system such as Transdermal drug delivery systems, Controlled release systems, Transmucosal delivery systems etc. emerged. Several important advantages of transdermal drug delivery are limitation of hepatic first pass metabolism, enhancement of therapeutic efficiency and maintenance of steady plasma level of the drug. Transdermal formulation maintain drug concentration within the therapeutic window for prolonged period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration. Glimepride is the first III generation sulfonyl urea against Diabetes mellitus-II. Though glimepride has100% oral absorption, due to high first pass metabolism it has a low and variable bioavailability. The drug is given in 4mg twice a day and hence there is less patient compliance. The physicochemical properties of glimepride i.e., slight water solubility, low molecular weight (490.62), high first pass metabolism and its suitable elimination half-life (t1/2=5 h), make it a suitable candidate for administration by transdermal route. As Glimepride has first pass metabolism, transdermal patches were designed with an objective to increase its bioavailability. Controlled release formulation was developed with polymers HPMC (Hydroxy propyl methyl cellulose), EC (Ethyl cellulose) in various proportions which released the drug over an extended period of 24 hours giving an

advantage of once a day dosing. Tween 80 was used as permeation enhancer and glycerine as plasticizer.

MATERIALS AND METHODS

The following chemicals were obtained from different sources and used as received. Glimepride 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 GLIMEPRIDE

A series of transdermal patches composed of 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. Glycerine was incorporated as a plasticizer at a concentration of 15% w/w of dry weight of polymers (61.2 mg approximately equals 2 drops). Tween 80(1 drop) was added to the polymer solution as permeation enhancer. Glimepride 8 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. A clean petridish was placed over a flat surface. The whole solution was poured 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: Quantities of different ingredients in the formulation.

Code	Glimepride (mg)	HPMC (mg)	EC (mg)	Tween 80	Glycerin	Water (ml)
F1	8	400	-	1 drop	2 drops	15 ml
F2	8	300	100	1 drop	2 drops	15 ml
F3	8	200	200	1 drop	2 drops	15 ml
F4	8	100	300	1 drop	2 drops	15 ml
F5	8	-	400	1 drop	2 drops	15 ml

EXPERIMENTAL METHODS

Preparation of standard calibration curve of glimepride

Standard curve of Glimepride was prepared with a known concentration of drug in between 2-10 µg/ml using UV spectrophotometer (LabIndia) at λmax 220 nm.

Evaluation of the prepared formulation

I. Physicochemical evaluation

1. Physical appearance

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

2. 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.

3. Thickness of the films

The thickness of the patches was measured at three different places by using a Digital Screw Gauge micrometer (Mitutoyo, Japan) and mean thickness was calculated.

4. Weight uniformity

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

5. 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 absorbance were read at 220nm by UV spectrophotometer.

6. 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.

Tensile Strength = Applied force/ cross sectional area %

7. *In-vitro* diffusion studies

Diffusion studies were carried out for the prepared patches by Franz diffusion cell with 7.4 pH phosphate buffer using dialysis membrane 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 220 nm.

RESULTS AND DISCUSSION

I. Construction of calibration curve of Glimepride in phosphate buffer saline of pH 7.4.

Glimepride shows absorption maxima at 220nm 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= 0.0402x+0.0062 was generated for the calculation of amount of drug.

1I. Physical parameters

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

The weights of the patches are in between 0.589gm to 0.902gm. The resulted thickness of the patches formulated is in between 0.092 mm to 0.118 mm.

The folding endurance measures the ability of patch to withstand rupture. The results were in between 50 to 241. and formulation found to maintain their integrity with general skin folding when used. The results were tabulated in the table: 2.

Table No 2: Data showing physical parameters of Glimepride TDDS patches

S. No	Formulation	Folding endurance	Thickness (mm)	Weight variation (gm)
1	F1	80±10.1	0.118±0.029	0.603
2	F2	50±12.2	0.103±0.023	0.612
3	F3	217±7.50	0.083±0.011	0.863
4	F4	227±6.39	0.100±0.017	0.637
5	F5	179±8.08	0.097±0.028	0.592

III. 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 0.575kg/mm^2 to 0.324kg/mm^2 and the elongation were in between 32.45mm to 15.48mm. The results are expressed in the table no: 3.

Table No 3: Data obtained from tensile strength and elongation for Glimepride TDDS patches

S. No.	Formulation	Tensile strength (kg/mm^2)	Elongation (mm)
1	F1	0.385+0.0100	20.49+1.086
2	F2	0.575+0.0134	23.35+1.704
3	F3	0.424+0.0122	15.48+1.151
4	F4	0.474+0.0093	24.56+0.700
5	F5	0.324+0.0126	32.45+0.855

IV. 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 96.36 to 89.48 in all the patches with low SD value. The results are shown in table no: 4.

Table No 4: Data obtained from drug content for Glimepride TDDS patches.

S. No.	Formulation	Drug content
1	F1	90.77±0.0597
2	F2	89.45±0.0595
3	F3	91.48±0.635
4	F4	96.36±0.402
5	F5	93.72±1.270

V. *In-vitro* diffusion studies of Glimepride TDDS patches.

Invitro release of glimepride across dialysis membrane from F1 and F2 formulation showed only 61.90% and 52.11% at the end of 24h, respectively. The flux was calculated from the slope of linear graph, and it was found to be 37.09 and 30.27µg/cm^2/h, diffusion coefficient was 0.59×10^{-2} and 0.48×10^{-2} cm^2/h respectively. It was evident from the above result that there was a lower flux and lower diffusion rate through the dialysis membrane. However, at the end of 24h, *invitro* release of glimepride across dialysis membrane from formulation F3, F4 and F5 were 81.09%, 91.16% and 74.83% respectively. The flux for the formulation of F3, F4 and F5 was 48.57%, 51.75%, 44.93% µg/cm^2/hr, diffusion coefficient was 0.77, 0.81, 0.71cm^2/hr. It was revealed from the above results that the F4 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 91.16% glimepride release at the end of 24h study. The flux and diffusion coefficient was found 51.03µg/cm2.h and 0.081cm^2/h respectively.

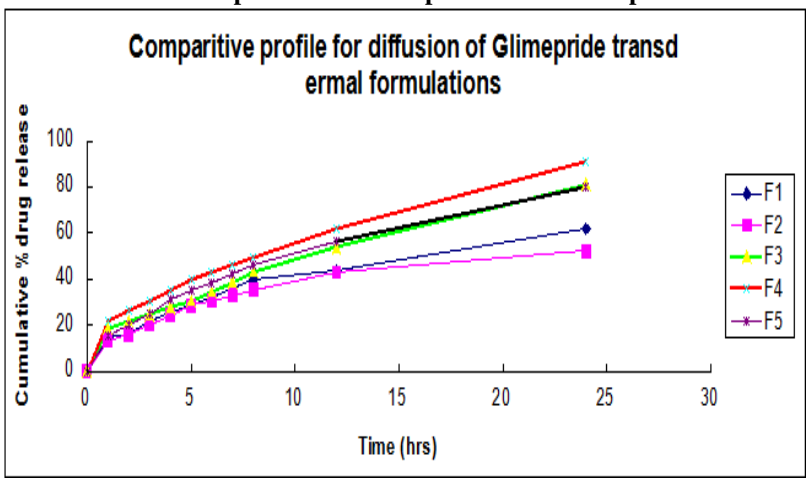
The reason for high release from HPMC and EC could be explained by the hydrophilic nature of the polymers which could affect the release of drug from the patches because of swelling and hydration of the patches. The physicochemical properties of the formulation F4 depicted suitable formulation for the transdermal delivery. Therefore, F4 formulation was selected as an optimized formulation.

The results are expressed in table no: 5.

Table: 5 *In vitro* profile of formulations.

Formulation Code	% Drug Release
F1	61.90
F2	52.11
F3	81.04
F4	91.16
F5	79.84

Graph 02: Comparitive *in-vitro* diffusion profiles of Glimepride trandermal patches



VI. Release kinetics

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

Table No 6: Drug release kinetics data for the optimized formulation F4.

	RELEASE KINEITCS				
	ZERO	FIRST	HIGUCHI	Hixson Crowell	PEPPAS
	1	4	2	5	3
	R(C vs T)	Time vs Log % Remaining	R(C vs√(T))	Time vs (Q1/3-Qt1/3)	Log T vs Log C
Slope	3.5642	-0.004	17.084	0.025	0.385
Correlation	0.9393	-0.9582	0.9949	0.9428	0.9928
R^2	0.9401	0.9181	0.9656	0.8888	0.9698

CONCLUSION

From the above experimental results it was concluded that preformulation studies of glimepride were found in accordance with the reported literature limits. The formulated TDD 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. 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 glimepride 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 glimepride from the optimized formulation F4 follows zero order kinetics and the mechanism of drug release was concluded as diffusion controlled.

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