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FORMULATION CHARACTERIZATION AND EVALUATION OF TRANSDERMAL PATCHES OF GLIMEPIRIDE

Pabbiniddi Veera Lakshmi*[1] and Chepuri Prasanthi[2]

[1]School of Pharmaceutical Sciences and Technologies, Jntuk Kakinada.
[2]Sri Siddhartha College of pharmacy Nuzvid.

***Corresponding Author: Pabbiniddi Veera Lakshmi**
School of Pharmaceutical Sciences and Technologies, Jntuk Kakinada.

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ABSTRACT
Transdermal drug delivery systems (TDDS), are the dosage forms designed to deliver a therapeutically effective amount of drug across a patient's skin. The aim of the present study was to formulate, characterize and evaluate transdermal patches of glimepiride by solvent casting method employing natural polymers like sodium alginate and xanthan gum. The prepared formulations were evaluated for different physicochemical characteristics like Weight Variation, Folding Endurance, thickness uniformity, %Moisture uptake, %Drug Content & %Drug Release. The drug release characteristics of the formulation were studied in-vitro by using Franz diffusion cell. The in-vitro drug release plot showed that the drug release followed zero order kinetics & Higuchi model, which was evidenced from the regression values. Based on the drug release and physicochemical values, formulation EF4 was considered as an optimized formulation which shows higher percentage of drug release (70.13±0.26% at 24 hour) with diffusion mediated mechanism. Korsmeyer-Peppas exponential plots shows fairly linear and it is well supported by their regression coefficient values & slope values (n) which suggest that drug was released by Super Case-II transport.

KEYWORDS: Glimepiride, Transdermal drug delivery systems, Solvent casting method.

INTRODUCTION
Glimepiride is a third generation oral antidiabetic sulphonylurea drug frequently prescribed to patients of type 2 diabetes. However, its oral therapy is encountered with bioavailability problems due to its poor solubility leading to irreproducible clinical response, in addition to adverse effects like dizziness and gastric disturbances. [1] As a potential for convenient, safe and effective antidiabetic therapy, the rationale of this study was to develop a transdermal delivery system for glimepiride. [2] Transdermal drug delivery is one of the best approaches to resolve the problems of low solubility and low bioavailability. TDDS when topically administered medication in the form of patches, delivers the drug at a predetermined rate through the skin into the systemic circulation.[3]

Mechanisms of Transdermal Permeation through skin: For a systemically-active drug to reach a target tissue, it has to possess some physico-chemical properties which facilitate the sorption of the drug through the skin and also the uptake of the drug by the capillary network in the dermal papillary layer. Various events governing percutaneous absorption are shown in Figure 1.[4]

The rate of permeation, dQ/dt, across various layers of skin tissues can be expressed as.

$$\frac{dQ}{dt} = P_s(C_d - C_r) \text{ - - - - - (1)}$$

Where, C_d and C_r are, respectively, the concentrations of skin penetrate in the donor phase (stratum cornea) and the receptor phase (systemic circulation); and P_s is the overall permeability coefficient of the skin.[5]

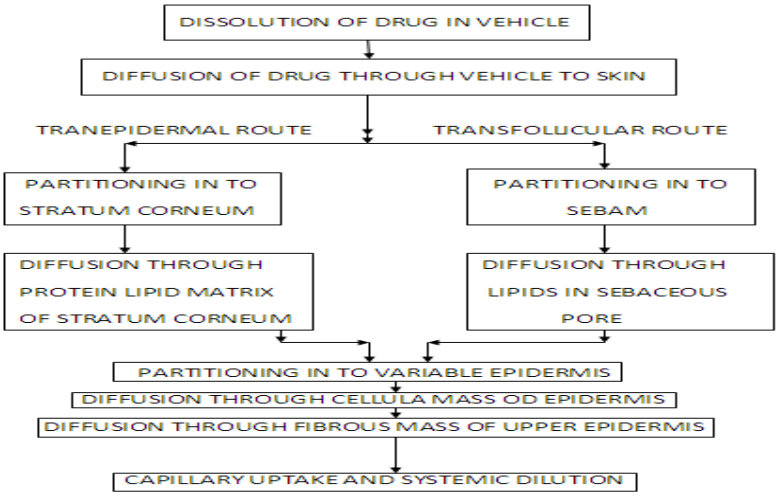

Figure 1. Events Governing Percutaneous Absorption.

Approaches to development of transdermal therapeuticsystems[6]

Several technologies have been successfully developed to provide a rate control over the release and the transdermal permeation of drugs. These technologies can be classified into four approaches as follows:

1. Membrane permeation – controlled systems.
2. Adhesive dispersion – type systems.
3. Matrix diffusion – controlled systems.
4. Micro reservoir type or micro sealed dissolution controlled systems.

1. Membrane Permeation – Controlled Systems

In this type of system drug reservoir is encapsulated in a shallow compartment moulded from a drug-impermeable metallic plastic laminate and a rate controlling polymeric membrane which may be micro porous or non-porous. The drug molecules are permitted to release only through the rate – controlling polymeric membrane. Examples of this system are *Transderm – Nitro:* Nitroglycerine – releasing transdermal system for once a day medication in angina pectoris.

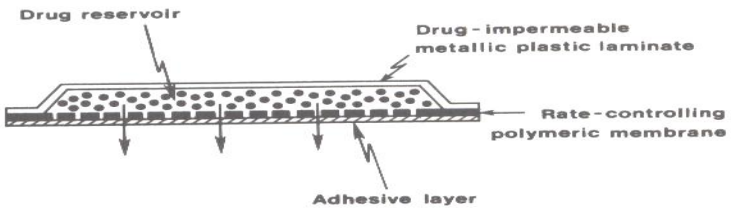

Figure 2: Membrane-Moderated Transdermal Drug Delivery System.

1. Adhesive Dispersion – Type Systems

This is a simplified form of the membrane-permeation controlled system. The drug reservoir is formulated by directly dispersing the drug in an adhesive polymer e.g. Poly (isobutylene) or poly (acrylate) adhesive and then spreading the medicated adhesive, by solvent casting or hot melt, on to a flat sheet of drug impermeable metallic plastic backing to form a thin drug reservoir layer. On the top of the drug reservoir layer, thin layers of non-medicated, rate-controlling adhesive polymer of a specific permeability and constant thickness are applied to produce an adhesive diffusion – controlled delivery system. Examples are ***Frandol tape***: Releases Isosorbide dinitrate for once-a-day medication of angina pectoris.[7]

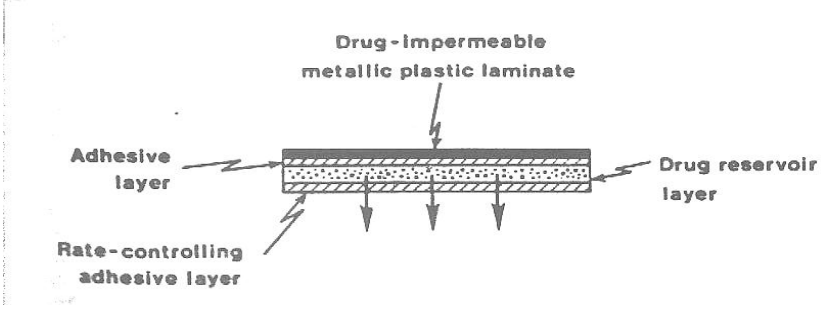

Figure 3: Adhesive diffusion-controlled transdermal drug delivery system.

2. Matrix Diffusion- Controlled Systems

In this approach, the drug reservoir is formed by homogenously dispersing the drug solids in a hydrophilic or lipophillic polymer matrix. The resultant medicated polymer is then moulded into a medicated disc with a defined surface area and controlled thickness.[8] The drug reservoir can also be formed by dissolving the drug and the polymer in a common solvent followed by solvent evaporation in a mould at an elevated temperature and/or vaccum. This drug reservoir containing polymer disc is then pasted onto an occlusive base plate in a compartment fabricated from a drug-impermeable plastic backing membrane.

E.g.*, *Nitro-Dur: Delivers nitroglycerine for the treatment of angina pectoris.[9]

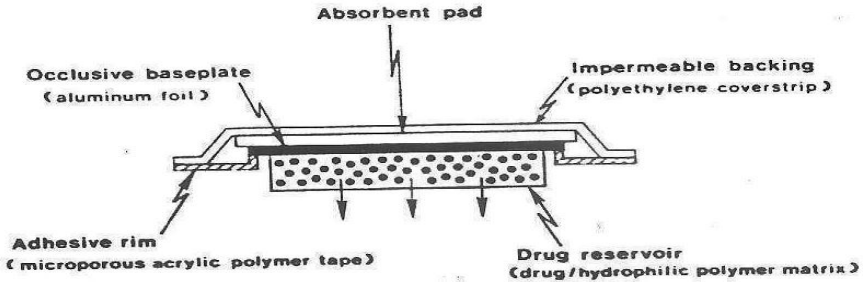

Figure 4: Matrix dispersion-type transdermal drug delivery system

3. Micro reservoir type or Micro sealed Dissolution

The micro reservoir type drug delivery system can be considered a combination of the reservoir and matrix diffusion type drug delivery systems.[10]In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of water soluble liquid polymer (e.g. Polyethylene glycol) and then dispersing the drug suspension homogenously in lipophillic polymer viz. silicone elastomers by high energy dispersion technique to form several discrete, unleachable micro spheres of drug reservoirs. A transdermal therapeutic system is then produced by positioning the medicated disc at the centre and surrounding it with an adhesive rim. *E.g.*, *Nitroglycerine:* Releasing transdermal therapeutic system for once – a day treatment of angina pectoris.

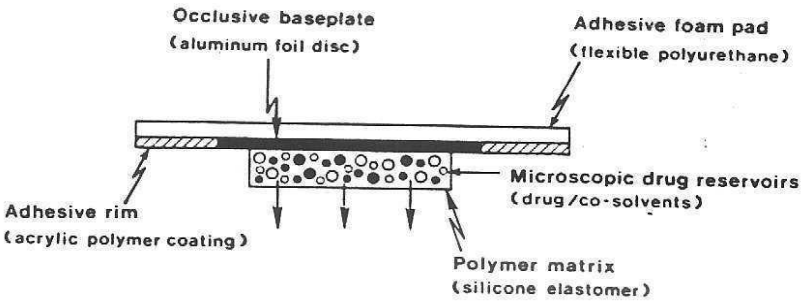

Figure 5: Micro reservoir-type transdermal drug delivery system[11]

2. Materials and methods

Table1: Materials used in the formulation

S.NO	Materials	Source
1	Glimepiride	Natco Pharma; Hyderabad
2	Sodium alginate	Natco Pharma; Hyderabad
3	Xantham Gum	Natco Pharma; Hyderabad
4	Ethyl cellulose	Natco Pharma; Hyderabad
5	Acetone	Merck Finar Ltd, India
6	Alcohol	Merck Finar Ltd, India
7	Propylene glycol	Ozone International, Mumbai
8	Dibutyl phthalate	Natco Pharma; Hyderabad

Table2: Equipments used.

S.NO	Materials	Source
1	Electronic Balance AX200	Dolphin,India
2	Digital Balance ELB 300	K-ray
3	Digital pH meter L1120	Dolphin,India
6	Single beam UV-Visible Spectrophotometer	Elico,Hyderabad SL159

METHODOLOGY

Pre formulation studies

Pre formulation testing is an investigation of physical and chemical properties of drug substances alone and when combined with pharmaceutical excipients. It is the first step in the rational development of dosage form.

Compatibility studies (Fourier Transform Infrared Spectroscopic studies)

To study the compatibility of various formulation excipients with Glimepiride, solid mixtures were prepared by mixing the drug with each formulation excipient separately in the ration of 1:1 and it was filled enclosed vial sand placed instability chamber at 30±2 °C/65±5%RH.

The solid admixtures were characterized using Fourier transform infrared spectroscopy (FT-IR).

Development of Analytical Method of Drug

Calibration curve of Glimepiride in phosphate buffer pH 7.4

Preparation of phosphate buffer pH 7.4

50 ml of the potassium dihydrogen phosphate (0.2M) solution was mixed with 39.5 ml of the sodium hydroxide (0.2M) solution in a 200 ml volumetric flask and then the volume was made up with water.[12]

0.2 Potassium dihydrogen phosphate solution

27.218 g of potassium dihydrogen phosphate was dissolved in water and diluted with water to make the volume1000ml.

0.2 N NaOH

8 g of NaOH was dissolved in 1000 ml of water.

A) Detection of absorption maxima (λ max): The prepared Glimepiride solution was scanned between 200-400nm regions on UV-Visible spectrophotometer. The absorption maximum was found to be 228.4nm shown in Figure 6.

B) Construction of standard calibration curve

Standard solution: Accurately weighed 10mg of Glimepiride was dissolved in 10ml of methanol to get a solution containing 1000 µg/ml.

Stock solution: From standard solution, a stock was prepared to give a concentration of 100mcg/ml in 7.4 pH buffer. Aliquots of 0.2, 0.4, 0.6, 0.8 and 1ml of stock solution were pipetted out into 10ml volumetric flasks. These dilutions were gives 2, 4, 6, 8, 10 µg/ml concentration of Glimepiride respectively. The absorbance of above solutions was measured at 228.4nm in UV-Visible spectrophotometer against a blank (7.4 pH buffer).The concentration and absorbance data was given in Table 4 and shown in Figure 7.

Preparation of TDDS patches of Glimepiride

Transdermal patches of Glimepiride were prepared by solvent evaporation method. The polymer was weighed and dissolved/dispersed in 8ml of water and allowed to swell by keeping it aside for 5 min. Glycerin was incorporated as a plasticizer at concentration of 30%W/W of dry weight of polymer(0.01-0.02cm^3 approximately 2-3 drops). Propylene glycol (0.11-0.02cm^3 2-3 drops) was added to solution as permeation enhancer. Glimepiride was dispersed in 2ml of acetone solution and added to the above solution. The mixer was mixed thoroughly with the help of magnetic stirrer. The total solution was poured into the petridish covered with backing membrane of aluminum foil and kept for 24 hours. Inverted funnel was placed over to avoid sudden evaporation. After 24 hours the dried films were taken out and stored in desiccators.[13]

Rate controlling membrane preparation

Ethyl cellulose 300mg was dissolved in 1oml ethanol. Dibutylphthalate was used as a plasticizer and the solution was poured within a petriplate and left for drying. After 24hr, a membrane of 3.14cm^2 area was cut, and placed on the patch. Xanthan gum was applied to the sides of the patch as an adhesive.[14]

Table 3: Composition of TDDS formulations F1-F6.

Ingredients	F1	F2	F3	F4	F5	F6
Glimepiride	70.45	70.45	70.45	70.45	70.45	70.45
Sodium alginate	300	400	400	400	-	-
Xanthan gum	-	-	100	200	300	400
Propylene glycol (%)	30	30	30	30	30	30
Glycerin (%)	30	30	30	30	30	30
Water: acetone	8:2	8:2	8:2	8:2	8:2	8:2

Table 4: Composition of TDDS formulations EF2-EF6.

Formulations	EF2	EF4	EF6
Backing membrane	Aluminum foil	Aluminum foil	Aluminum foil
Layer 1	Patch 2(F2)	Patch5(F4)	Patch 6(F6)
Layer 2	Rate controlling Membrane	Rate controlling membrane	Rate controlling Membrane

CALCULATION OF SURFACE AREA OF PETRI PLATE AND TEST TUBE

Calculation of Surface area of Petriplate

Radius of the Petriplate = 4.2cm

Surface area ($\prod r^2$) = 3.14 × 4.2 ×4.2 =55.3cm^2

The net quantity of water taken=10ml

Recommended dose of the drug = 4mg

Calculation of Surface area of Franz Diffusion cell

Radius of the tube used in diffusion cell=1cm

Surface area of Franz diffusion cell ($\prod r^2$) = 3.14 × 1 ×1 =3.14cm^2

i.e., 4mg of drug require for each 3.14cm^2 patch

Franz diffusion cell surface area (3.14 cm^2)requires ⟶ 4mg of drug

Petriplate surface area (55.3cm^2) requires. ⟶ ?

$\frac{55.3 \times 4}{3.14}$ = 70.45 mg

The net amount of drug used to formulate Transdermal patch was 72mg; include the wastage of drug during mixing process.

In vitro characterization of Glimipiride transdermal patch

Thickness uniformity: The thickness of the films was measured by a 'dial caliper'. The mean of the five observations were calculated.

Weight uniformity: The uniformity of weight was determined by weighing 5 films (3.14cm^2) individually of each formulation on digital balance. The average weight of the film was taken as weight of film.

Folding Endurance: A strip of specific area was cut evenly (2x2cm^2) 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.

Drug content: A 3.14 cm^2 film was cut into small pieces and then dissolved in 100ml buffer solution. The drug content was estimated spectrophotometrically at 228.4nm.

Percentage of moisture uptake: The weighed films were kept in desiccators at room temperature for 24hrs containing saturated solution of potassium chloride in order to maintain 84% RH. After 24hrs the films are to be reweighed and determine the percentage moisture uptake from the below mentioned formula.[13]

$$\%Moisture\ uptake = \frac{Final\ weight - Intialweight}{Intial\ weight} \times 100$$

Drug Diffusion Study: Drug diffusion study was conducted using Franz diffusion cell. The receptor compartment was filled with 100 ml of phosphate buffer having pH 7.4 as diffusion media. Polymeric film was mounted on the donor compartment with the help of an adhesive. Magnetic stirrer was set at 50 rpm and whole assembly was maintained at 37 ± 2 ^{0}C. The amount of drug released was determined by withdrawing 1 ml of sample at regular time intervals for 2 hours. The volume withdrawn was replaced with equal volume of fresh buffer solution. Samples were analyzed for drug content using a UV spectrophotometer at 228.4 nm.

Drug release kinetics models

Zero-order equation: Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$Q_t=Q_0+K_0t$

Where Q_0 is the initial amount of drug in solution (it is usually zero), Q_t is the amount of drug released or dissolved at time t, and K0 is the zero-order release constant.

First order equation: This model is used to describe absorption and/or elimination of some drugs.

$Qt=Q_0e^{-k1t}$ or $\ln Q_t=\ln Q_0+K_1t$

Where Q_0 is the initial amount of drug in solution (it is usually zero), Qt is the amount of drug released or dissolved at time t, and Kt is the first-order release constant.

Higuchi model: Higuchi describes the drug release as a diffusion process base in the Fick's law, square root of time dependent. This relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems and matrix tablets with water soluble drugs.

$Q_t=K_Ht^{½}$

Where Q_t is the amount of drug released at time t, K_H is the Higuchi dissolution constant.

Korsmeyer-peppas model: Koresmeyer et al. developed a simple, semi-empirical model, relating exponentially the drug release to elapsed time (t):

$M_t/M_\infty= k\ t^n$ or $\log M_t= \log k +n \log t$

Where M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, k is a constant incorporating structural and geometric characteristics of the drug dosage form is the release exponent, indicative of the drug release mechanisms and the function of t is Mt/M_∞ (fractional release of drug), n=0.5 for Fickian diffusion and higher values of n between 0.5 to 1.0 for mass transfer following a non-Fickian model, n=1 for case II transport(independent of time), n>1 for super case II transport.

RESULTS AND DISCUSSION

PRE-FORMULATION STUDIES: To formulate a dosage form preformulation studies of the drug and polymers were required. In this study the physical characteristics of the drug and polymers like color,

appearance, solubility, melting point and compatibility were observed. The obtained results were complying with the specification given in literature.

Table 5: Standard Calibration data of Glimepiride in pH 7.4 buffer.

Conc (µg/ml)	Absorbance at 228.4nm				
	Trail-I	Trail-II	Trail-III	AVG	S.D
0	0	0	0	0	0
2	0.12	0.14	0.12	0.13	0.009
4	0.26	0.28	0.26	0.27	0.01
6	0.38	0.39	0.38	0.38	0.006
8	0.5	0.51	0.50	0.50	0.007
10	0.63	0.65	0.63	0.64	0.009

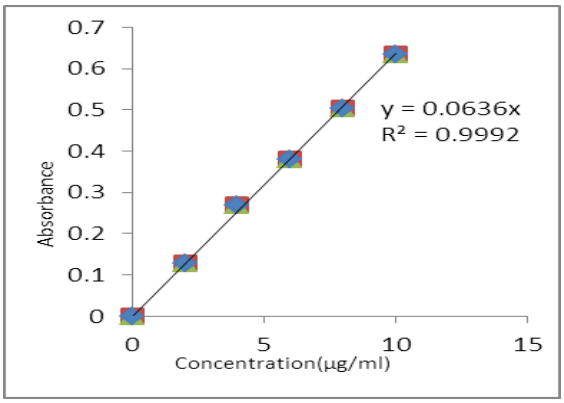

Figure 6 :Calibration curve of Glimepiride.

DRUG- EXCIPIENTS COMPATIBILITY STUDY: The IR spectral analysis of Glimepiride alone showed that the principle peaks were observed at wave length of 3373 (3300-3500) (N-H), 2934.57 and 2855.22 (2850 – 3000) (C-H), 2789.04 and 2706.85(3300 - 2500 (O-H), 1529.59, 1462.94 and 1346.73 (1350 –1550) (N=O), 1025.67 (1220 -1020) (C-N), 1157.94 and 1123.29 (1000 –1300) (C-O).When compared to blend of drug with polymer which shows there were no physical interactions between drug and polymers.

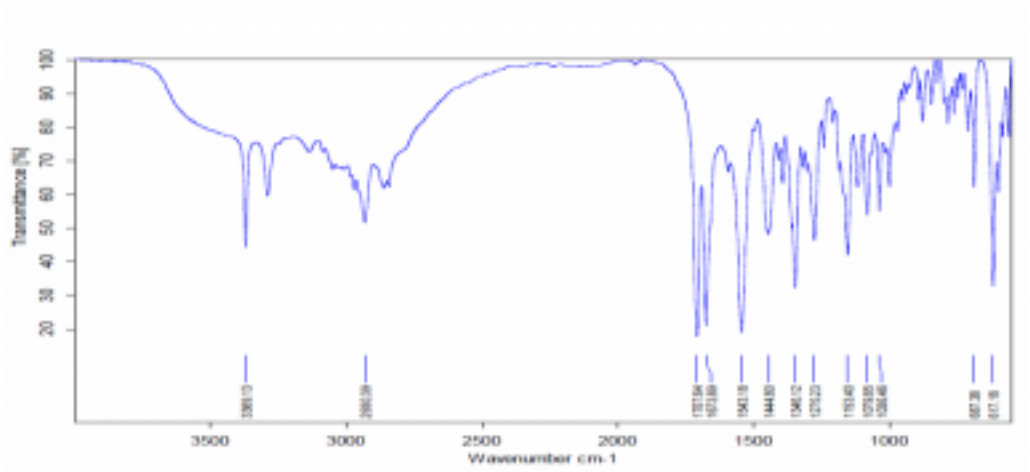

Figure 7: FTIR of Glimepiride.

Physicochemical Properties Of Glimepiride Transdermal Patches

Drug content: These results were in range of 97.8% to 102.8 %(n=3) (Table 6) which indicated that the process employed to prepare films in this study was capable of producing films with uniform drug content and minimal batch variability.

Uniformity of thickness: The thickness of films varied from 0.135 to 0.235 µm with the standard deviation values of 0.0045-0.0076(Table 6). The low standard deviation in thickness of the films ensured the uniformity of the thickness in each film.

Folding endurance: The results suggested that the patches would not break and would maintain their integrity with general skin folding when applied (Table 6).

Percentage moisture uptake: The results suggested the moisture uptake of the formulation was low, which would protect the formulation from microbial contamination and reduce bulkiness.

Table 6: Physicochemical properties of Glimepiride Transdermal patches. F1-EF6.

Formulation code	Drug Content (%)	Thickness(mm)	Folding endurance	%Moisture uptake
F1	101.2	0.135±0.0074	176	5.63
F2	99.7	0.138±0.0062	256	6.58
F3	97.84	0.165±0.0058	245	8.86
F4	98.33	0.179±0.0075	274	9.23
F5	102.8	0.156±0.0048	184	7.25
F6	100.5	0.163±0.0075	195	8.85
EF2	99.7	0.218±0.0052	125	2.97
EF4	98.33	0.225±0.0045	156	3.85
EF6	100.6	0.236±0.0061	146	3.13

IN VITRO DIFFUSION STUDIES

In vitro drug release studies were carried out for the different formulations using French diffusion cell. The diffusion results reveal that as the concentration of polymers sodium alginate and xanthan gum were increases, the drug release rate controlled as shown in table7. During study, sodium alginate and xanthan gum in the film absorbed a significant amount of water to hydrate and swell. The characteristic swellability of polymer decreases the rate of drug release from matrix patches.

Table 7: *In vitro* drug release of Glimepiride Transdermal patches of F1-F6.

Time (Hr)	Cumulative percentage of drug release ±S.D					
	F1	F2	F3	F4	F5	F6
1	32.99±0.09	30.38±0.24	27.60±0.18	13.33±0.74	26.042±1.2	19.96±0.52
2	59.72±0.25	39.24±0.34	33.85±0.52	18.30±1.02	35.41±0.85	29.37±0.85
3	75.35±0.12	54.86±0.51	43.40±0.62	26.18±0.42	43.40±0.74	35.06±0.54
4	99.96±0.14	64.93±0.64	52.78±0.71	30.59±0.47	60.76±0.98	42.36±0.85
5		87.15±0.25	67.71±0.14	38.19±0.36	71.18±1.25	50.34±0.96
6		97.96±0.34	81.60±0.23	44.44±0.45	85.06±0.47	60.76±0.56
7			88.54±0.52	54.86±0.26	95.48±0.23	71.18±0.84
8			98.99±0.23	61.46±0.78		85.06±0.45
9				70.14±0.91		98.95±0.75
10				81.60±0.95		
11				89.58±0.48		
12				98.96±0.75		

Effect of rate controlling membrane on drug release

Ethyl cellulose is a hydrophobic polymer. When ethyl cellulose membrane was placed on the device, the initial burst release of drug was suppressed. The drug release follows the square root of time release kinetics as shown in table below.

Table 8: In vitro drug release of Glimepiride Transdermal patches of EF2-EF6.

Time(Hr)	Cumulative percentage of drug release ±S.D		
	EF2	EF4	EF6
2	4.93±0.25	1.45±0.75	2.15±0.07
4	7.56±0.52	5.19±0.85	6.23±0.12
6	11.45±0.42	7.62±0.68	9.84±0.52
8	17.77±0.12	11.43±0.59	15.59±0.76
10	27.15±0.95	16.14±0.75	25.09±0.85
16	42.36±0.85	25.25±0.53	35.41±0.97
18	52.77±0.74	36.80±0.84	42.01±0.54
20	67.01±0.56	44.44±0.96	50.34±0.73
22	77.77±0.45	48.95±0.48	64.23±0.56
24	88.88±0.15	59.37±0.99	70.13±0.43
26	98.95±0.57	70.13±0.52	81.59±0.59

CURVE FITTING ANALYSIS OF FORMULATIONS

The *in vitro* drug release data of all transdermal patches were subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equations, Higuchi's and korsmeyer -peppas models to ascertain the mechanism of drug release. The results of linear regression analysis including correlation coefficients were summarized in Tables 9-10 and shown in Figures 8- 15.

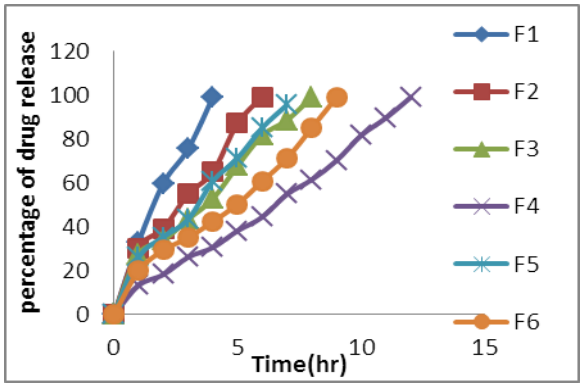

Figure8: % Drug release *vs* Time plot (Zero order) of formulations F1-F6 (Zero order) of formulations EF2-EF6

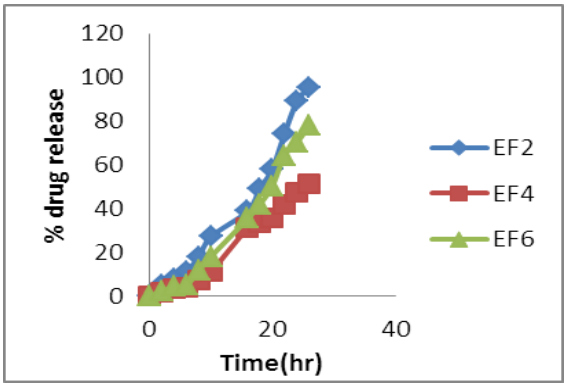

Figure 9: % Drug release vs Time plot (Zero order) of formulations EF2-EF6.

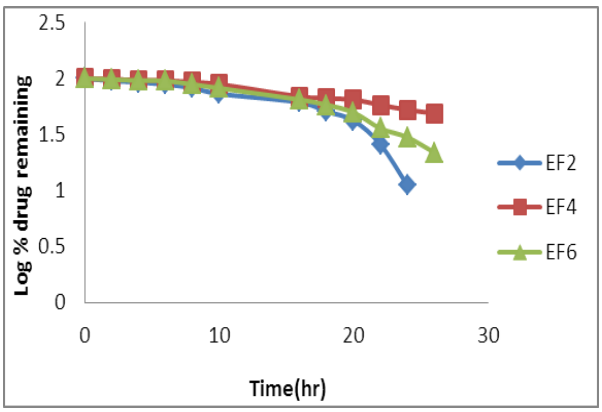

Figure 10: Log percentage drug remaining *vs* Time plot (First order) of formulations F1-F6

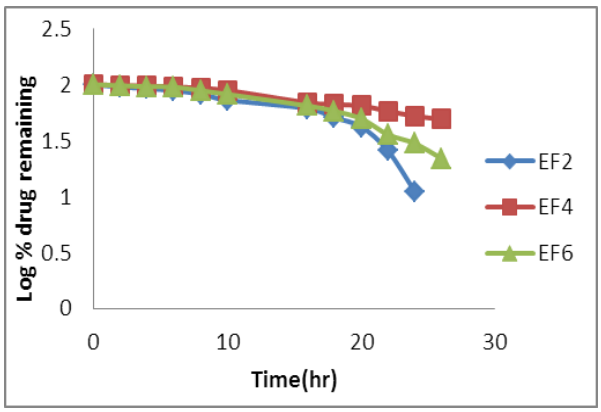

Figure 11: Log percentage drug remaining *vs* Time plot (First order) of formulations EF2-

The zero order plots of all the films were found to be fairly linear as indicated by their high regression values. The drug permeation from formulations follows zero order kinetics.

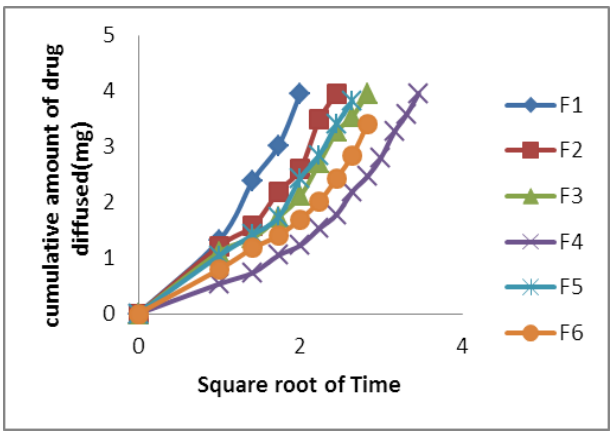

Figure 12: Cumulative amount of drug diffused *vs* square root of time plot (Higuchi's) of formulations F1-F6

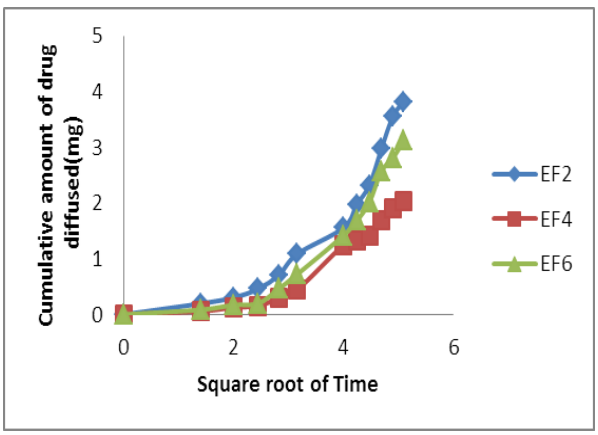

Figure 13: Cumulative amount of drug diffused *vs* square root of time plot (Higuchi's) of formulations EF2-EF6

In Higuchi plot, the correlation coefficient(r) values in the range 0.956 to 0.996, it confirmed that the drug release by diffusion mechanism.

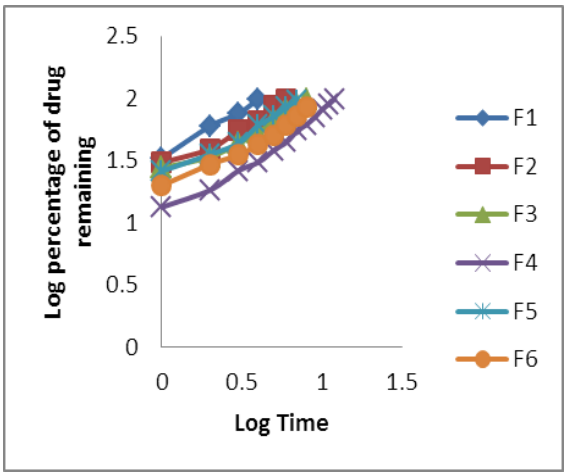

Figure14: Log % drug remaining *vs* Log Time plot (peppas plot) of formulations F1-F6

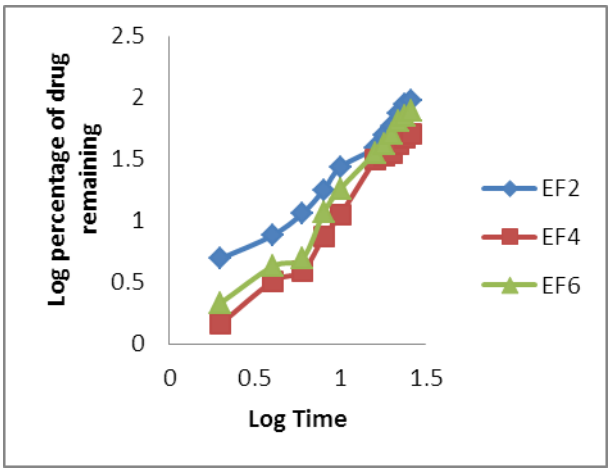

Figure 15: Log % drug remaining *vs* Log Time plot (peppas plot) of formulations EF2-EF6

In Peppas plot, the slope values (n) for F1- F6 are 0.5 to 1; it indicates the drug permeation from patches follows non-fickian diffusion mechanism. The slope values (n) for EF2-EF6 is greater than 1, it indicates the drug permeation from patches follows super case II transport mechanism

TABLE 9 : DRUG RELEASE KINETIC DATA

Formulation code	Zero order		First order		Higuchi Model		Korsmeyer peppas	
	K_0	r	K_1	r	kH	r	K	R
F1	25.81	0.99	0.204	0.88	1.783	0.98	1.524	0.997
F2	17.17	0.989	0.156	0.86	1.424	0.973	1.439	0.981
F3	13.11	0.99	0.125	0.87	1.246	0.976	1.377	0.977
F4	8.006	0.996	0.076	0.826	0.906	0.95	1.039	0.987
F5	14.32	0.992	0.069	0.931	1.276	0.975	1.37	0.984
F6	10.66	0.991	0.167	0.87	0.997	0.956	1.262	0.981
EF2	3.376	0.984	0.033	0.802	0.56	0.996	0.189	0.988
EF4	0.23	0.975	0.018	0.936	0.377	0.992	0.424	0.992
EF6	0.261	0.981	0.024	0.927	0.44	0.975	0.22	0.994

Table 10: Dissolution Parameters Of F1-EF6 Patches.

Formulation code	T50	T70	T90	n
F1	1.7	2.6	3.7	0.775
F2	2.7	4.2	7.5	0.673
F3	3.6	5.0	7.1	0.651
F4	6.6	9.0	11.0	0.839
F5	3.6	5.0	6.6	0.689
F6	5.0	6.8	8.5	0.674
EF2	17.5	20.6	24.8	1.241
EF4	22.0	24.0	28.0	1.564
EF6	20.0	24.0	27.6	1.421

The dissolution parameter T50% increases as the concentration of polymers increases in the formulations of F1 to F6. The rate controlling membrane increases the T50% value of F4 formulation from 6.6 to 22hrs.

CONCLUSION

In this study transdermal patches of Glimepiride were prepared by solvent casting method by using natural polymer like sodium alginate and xanthan gum. The polymers were more suitable to formulate patches and exhibit uniform thickness. The results indicated that, as the concentration of polymer increases the diffusion of drug from patches decreases due to increase swellability nature of polymer. From the results of F3 and F4, it can be concluded that drug diffusion from the films was controlled due to increased amounts of XG showed higher swellability of the film and leached plasticizer from the film could reduce tortuosity of aqueous pore channels of the films, respectively. Based on the drug release and physicochemical values, formulation EF4 was considered as an optimized formulation which shows higher percentage of drug release (70.13±0.26% at 24 hour) with diffusion mediated mechanism. Korsmeyer-Peppas exponential plots shows fairly linear

and it is well supported by their regression coefficient values & slope values (n) which suggest that drug was released by Super Case-II transport. The results suggest that the developed transdermal patches of glimepiride could perform better than conventional dosage forms, leading to improve efficacy and better patient compliance.

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