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Research article

Glibenclamide fabricated transdermal wafers for therapeutic sustained delivery systems

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ABSTRACT

Transdermal wafers of the Glibenclamide (GBE) were developed employing Ethyl cellulose (EC) and Hydroxypropyl methylcellulose (HPMC), Ethyl cellulose and Polyvinyl pyrrolidone (PVP) as a film former. The effect of binary mixture of polymer and penetration enhancer on physicochemical parameters including thickness, weight variation, drug content, and *in vitro* permeation was evaluated. *In vitro* skin permeation study was conducted on the rat abdominal skin as a penetration barrier in Franz diffusion cell from the binary mixtures. EC/HPMC (8.5:1.5) and EC/PVP (3:2) combination showed the good permeability. The incorporation of penetration enhancer the binary mixture further enhances the permeability.

1. Introduction

Transdermal drug delivery System (TDDS) is self-contained discrete dosage forms, which when applied to the intact skin, deliver the drugs through the skin, at a controlled rate to the systemic circulation[1]. Transdermal delivery of the drugs has been subject of research interest since the introduction of the first transdermal product for delivery of scopolamine 1979. TDDS uses diffusion of the drug through the skin into the systemic circulation for distribution and therapeutic effect. Most TDD systems use passive delivery of drugs[2].

The appeal of using the skin as a portal of drug entry lies in ease of access, its huge surface area, and systemic access through underlying circulatory and lymphatic networks and the noninvasive nature of drug delivery. Scientists from various disciplines are bringing exciting developments in the field of enhanced skin permeability of drugs in the last decade. In spite of this excellent achievement, transdermal patches exist only for a few drugs such as scopolamine, nitroglycerin, nicotine, clonidine, fentanyl, estradiol, testosterone, and oxybutinin[3].

This reflects the inability to deliver sufficient quantities of therapeutic agents across the skin to maintain the desired plasma concentration. The stratum corneum is the commonly accepted barrier to transdermal permeation of drugs across the skin[4]. Overcoming this barrier safely and reverse is a fundamental problem that persists in the field of transdermal delivery.

Delivery of drugs through the skin for systemic effect, called transdermal delivery was first used in1981, when Ciba-Geigy marketed Transderm V (present day marketed as Transderm Scop) to prevent the nausea and vomiting associated with motion sickness[5,6]. Throughout the past 2 decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms[7]. It constitutes a new trend in controlled delivery system and has opened new scientific horizon in innovations[8]. A number of drug molecules such as fentanyl, nitroglycerin, estradiol, ethinyl estradiol, norethindrone acetate, testosterone, clonidine, nicotine, lidocaine, prilocaine, and scopolamine are now available in transdermal delivered form in the world market. The market for drugs delivered transdermally was valued at $5.6bn in 2009 with the majority of these sales being accrued by products utilizing first generation patch technologies.

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Hyperglycemia is the leading cause of death in the developed world. India is the world's second most popular country with an increasing incidence of sugar diseases. The survey indicates that about one million annual deaths occur from in India. WHO estimates that 60 % world's sugar patients will be Indian in 2010[9]. Renal disease and heart failure are the common diseases, which require constant medication and monitoring. A number of drugs have been employed for these conditions amongst which Glibenclamide is important and a popular drug. Successful treatment requires maintenance of blood sugar at a normal physiological level for which a constant and uniform input of drug is essential[10].

Glibenclamide is an oral hypoglycemic agent, used for the treatment of non-insulin dependent diabetes mellitus[11, 12]. The drug has a plasma half-life 4-6 hrs and needs frequent administration. Moreover, its oral use is associated with severe and sometime fatal hypoglycemic symptoms like nausea, vomiting, heartburn, anorexia and increase in appetite[13]. In 1997, Takahshi and coworkers[14] had investigated the sulfonylureas for transdermal administration and reported promising results. Glibenclamide is affected by first-pass metabolism, necessitating high and frequent doses, which results in undesirable side effects. A system of drug input directly into the blood at a constant rate may lower the high oral dose and minimize side effects[15, 16]. These twin objectives are expected to be fulfilled through Transdermal drug delivery of Glibenclamide.

2. Experimental

Materials

Glibenclamide was obtained as a gift sample from Sun Pharma. Polyvinyl pyrrolodone, Hydroxy propyl methylcellulose was purchased from CDH chemicals. All chemicals used were of analytical grade.

Preparation of Glibenclamide Transdermal wafers

Transdermal wafers containing drug were prepared by solvent casting technique employing glass and aluminium foil as substrate.

Table 1: Formulation composition of transdermal wafers

Formulation code	Polymer (%w/v)	Costing solvent	Plasticizer (%w/w)	Drug (mg)
F1	EC:PVP (4.5:0.5)	Ethanol	30	2.8
F2	EC:HPMC (8.5:1.5)	Chloroform	30	2.8
F3	EC:HPMC (1:0)	Chloroform	30	2.8
F4	EC:HPMC (9:1)	Chloroform	30	2.8
F5	EC:PVP (4:1)	Acetone	30	2.8
F6	EC:PVP(1:0)	Chloroform	30	2.8
F7	EC:PVP (3:2)	Chloroform	30	2.8

The whole mixture with the drug was rotated on a magnetic stirrer for 1 hour to remove the foam which was generated during the processes and these mixtures are also sonicated for 30 mins. For achieving complete mixing of drug and polymers. The whole mixture was transferred to petri plate and by the help of an inverted funnel the chloroform was evaporated at room temperature. Wafers obtained wrapped in aluminium foil, placed in a desiccator to remove the moisture in the presence of adsorbent and stored for further characterization and use.

Preparation of Rat Abdomen Skin

Male Wistar rats were purchased from CDRI, Lucknow, India. These animals were kept in light and dark cycles in the animal house of IFTM University, India. The animals were kept under standard laboratory conditions, at 25±10^{0}C and 50±5% relative humidity. The animals were housed in polypropylene cages, free access to a standard laboratory diet and water. All surgical and experimental procedures were reviewed and approved by the Animal and Ethics Review Committee, College of Pharmacy, IFTM, Moradabad, India. Male wistar rats weighing 180-220 gm (6-8 weeks old) wereanesthetized with urethane (20% w/w i.p). After shaving their abdomen carefully, a full thickness skin was excised from the shaved abdomen site. After removing the fat and subdermal tissues, it was used for skin permeation studies. At the time of use, the epidermis were spread on the cell and allowed to equilibrate with receptor fluid for 15 minutes before commencing the experiment.

Procedure for setting Franz Diffusion (F-D) cell with rat abdominal skin

The F-D cell was fabricated from a local purchaser. The receptor compartment was filled with 65 ml of phosphate buffer pH 7.4. Stirred by the use of the Teflon coated bead on a magnetic stirrer. The transdermal patch was placed over the skin The whole assembly was kept on the magnetic stirrer and the temperature was maintained at 37± 5°C with the water jacket. The withdrawal port was covered with the glass cork. The amount of drug permeated into the receptor compartment solution was determined by removing samples **(**1ml**)** at hourly intervals.

The withdrawn volume was replaced with an equal volume of fresh buffer solution. The drug permeated was determined by analyzing the samples at 228 nm.

Selection of the formulations for further studies

The screening of film formulations was based on the cumulative percent drug permeated and constants of percent drug diffuse per hour. The optimistic formulations from above all are F2 and F7. The amount of drug permeated was not satisfactory. Therefore, modifications in these two optimized batches were made by incorporating various permeation enhancers.

Optimization of Formulation F7

Enhancers Propylene glycol, Dimethyl sulphoxide (DMSO) and Isopropyl myristate were used. The transdermal patches were fabricated according to the methods given in the table[2]. They are designated as EC1, EC2, EC3, EC4 and EC5 respectively. Modification of formulation F2 containing EC:HPMC **(**8.5:1.5**)** was done by casting the films.

Table 2. Formulation composition of optimized formulations

Formulation code	Polymers	Casting solvent (% w/v)	Penetration Enhancer (% w/v)
EC1	EC:PVP	Chloroform	Propylene Glycol
EC2	EC:PVP	Ethanol	Propylene Glycol
EC3	EC:PVP	Chloroform	Isopropyl myristate
EC4	EC:PVP	Chloroform	Dimethyl sulphoxide
EC5	EC:PVP	Acetone	Isopropyl myristate

Optimization of Formulation F4

Modification of formulation F4 containing EC:PVP was effected by casting the films using permeation enhancers viz., Propylene glycol, DMSO, and Isopropyl myristate. The transdermal patches were fabricated according to the solvent costing methods.They are designated as ED1, ED2, ED3, ED4 and ED5 respectively. The detailed composition was given in the Table[3].

Table 3. Formulation composition of optimized formulations

Formulation code	Polymers	Casting solvent (% w/v)	Penetration Enhancer (% w/v)
ED1	EC:HPMC	Chloroform	Propylene Glycol
ED2	EC:HPMC	Ethanol	Propylene Glycol
ED3	EC:HPMC	Chloroform	Isopropyl myristate
ED4	EC:HPMC	Chloroform	Dimethyl sulphoxide
ED5	EC:HPMC	Acetone	Isopropyl myristate

3. Results and Discussion

In the present study GBE Transdermal wafers were prepared by solvent casting technique employing a glass and aluminium substrate as monolithic matrices using various polymers to achieve a controlled release and with reduction in dosing frequency of GBE. The film forming polymers used were EC, HPMC and PVP, Dibutyl phthalate, PG added as plasticizer in all the films on %w/w based on the polymer weight and were found to be optimum with respect to smoothness, flexibility and transparency. The prepared films were smooth, uniform and flexible.

Drug Excipients compatibility studies

The drug-Excipients studies were confirmed by an infrared spectrophotometer (Perkin Elmer) using the KBr disc method. The IR spectra obtained was elucidated for important groups. FTIR spectra of pure Glibenclamide exhibited bands appearing in 2934, 2855, and 3373 due to C-H stretching. The band at 1593 and 1346 due to N=O and O-H stretching.The bond due to C-N stretching was seen at 1529. The FTIR spectra at 1025 due to C-Cl stretching.

Due to the incorporation of polymer, O-H bond stretching at 3500-3400 due to vibration of intermolecular hydrogen bonding. Methyl and hydroxyl group show stretching at 2900. OH, OCH, C-CH, at 1500-1450, cyclic anhydride give stretching band at 1400-1350, whereas Epoxide show stretching at 1300-1250 and the band in 850-800 due to the CH_2 group. C=O stretching 1713.9, peak at 680.8 and 904.9 indicates aromatic compound, -CH stretching of CH_3 2856.5 and 2935.8 and –NH stretching 3327.8. The IR spectrum is depicted figure (1a, 1b, 1c).

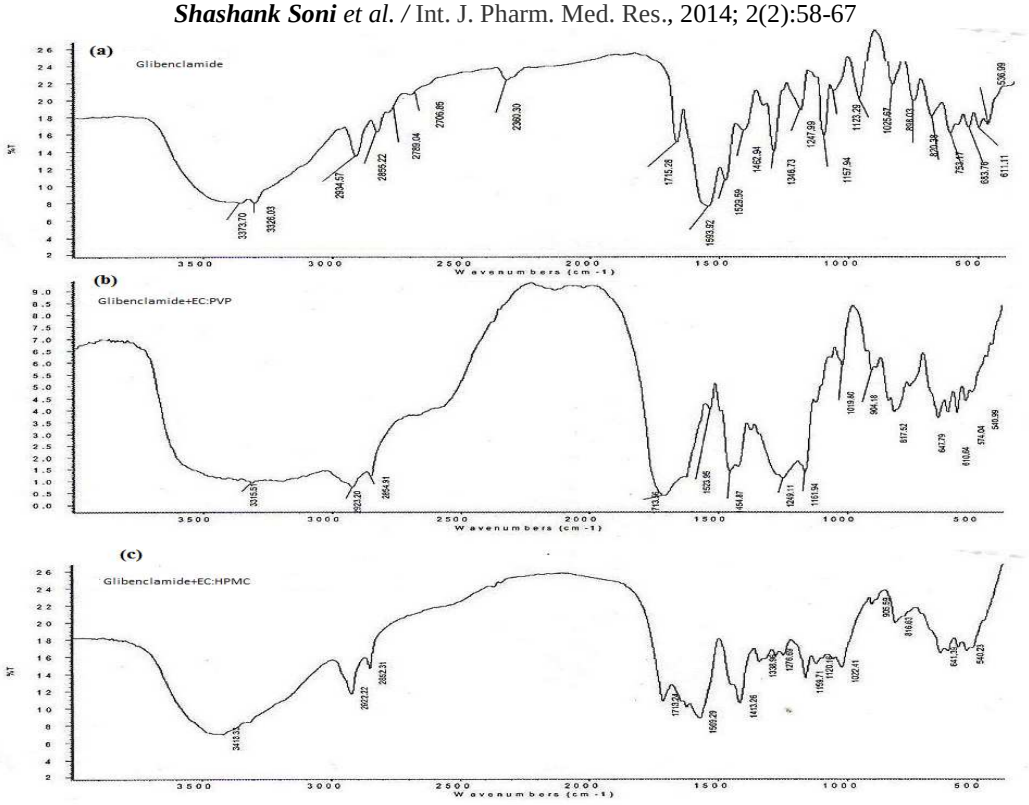

Figure 1: FTIR spectra of (a) Glibenclamide sample (b) Glibenclamide and EC:PVP K-30 sample (c) Glibenclamide and EC:HPMC sample

Thermal analysis

The DSC profile of GBE showed Exothermic peak at 175.16 °C and this corresponds to melting point. The DSC analysis of physical mixture of drug and polymer revealed a negligible change in melting point of Glibenclamide in the presence of any polymer mixture studies (174.06 and169.94 ^{0}c for a mixture of Glibenclamide, EC, PVP and HPMC respectively) in Figure (2). These studies suggest that there is no interaction between the drug and polymer used in the present study. It is already well known that the common polymers such as PVP, EC, and HPMC are popular in controlled/sustained release matrix type patch because of their compatibility with a number of drugs.

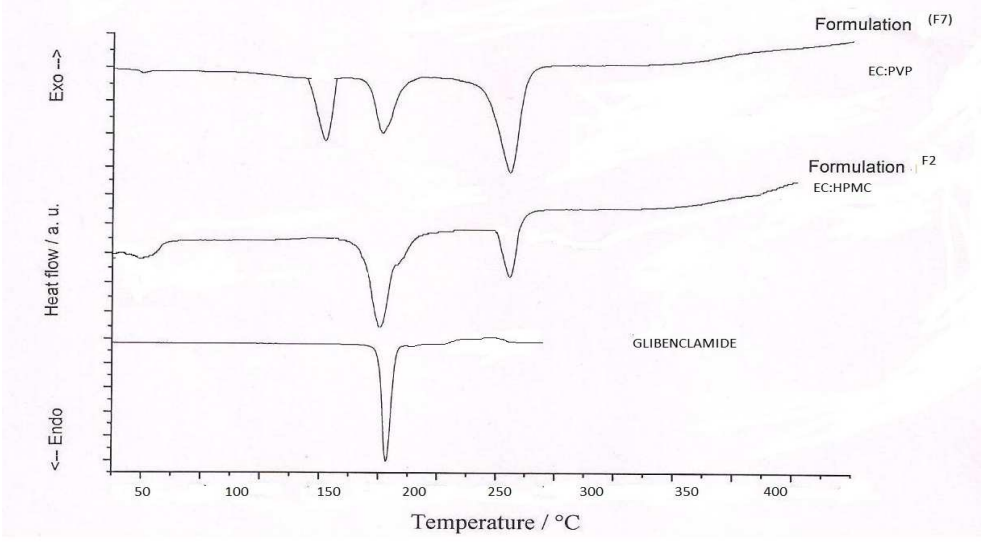

Figure 2: Thermograms of Formulations and Drug

Physicochemical properties of transdermal wafers

Weight variation was determined by weighing five films using digital balance Shimadzu and the average value was taken as the weight of the film. All the formulations exhibited uniform weight with standard deviation values indicating the uniformity of the films prepared by solvent casting method. The weight of the film varied between 27.59±2.52 mg to 113.57±2.36mg.

Thickness of transdermal films was measured by micrometer. The thickness of the films varies between 0.105±0.004mm to 0.215±0.003mm. A low standard deviation values in the film thickness measurements ensure uniformity of the films prepared by solvent casting technique. The area of the film was found to be 0.785cm^2.

The tensile strength of the films was found to vary with the nature of the polymer. It was found to vary between 0.357±0.009 kg/mm^2 to 2.129±0.005 kg/mm^2. Ethyl Cellulose has shown higher tensile strength. Incorporation of PVP into and HPMC, Ethyl Cellulose films decrease the tensile strength. Also the formulation F2 shows least percentage of elongation, where as F7 shows the highest percentage of elongation.

Folding endurance of the transdermal films was measured and it varied between 112.33 ± 2.04 to 323.33 ± 1.04. The drug content uniformity was determined for all the seven formulations by UV-Spectrophotometric method (Shimadzu UV-1800). The result of the drug content varies between 2.68±0.02 to 2.75±0.026. It was considered that the drug is dispersed uniformly throughout the film. The cumulative percent permeated, in *in-vitro* permeation studies were calculated on the basis of drug content in the respective film.

Table 4: Physicochemical characteristics of transdermal wafers of Glibenclamide

F. C.	**Weight Variation* (mg)**	**Thickness** (mm)**	**Tensile Strength** (kg/mm)**	**Percent of Elongation at Break****	**Folding Endurance****	**Drug *Content*** (mg)**
F1	54.46±1.94	0.121±0.002	0.766±0.024	17.35±0.25	202.6±1.50	2.61±0.040
F2	43.50±1.85	0.185±0.003	0.357±0.025	9.67±0.18	261±3.60	2.75±0.036
F3	93.84±2.40	0.147±0.004	0.838±0.025	18.7±0.21	112.3±2.04	2.69±0.056
F4	113.57±2.3	0.215±0.003	0.405±0.026	11.05±0.22	155.6±2.50	2.62±0.040
F5	48.47±1.98	0.124±0.003	0.470±0.024	11.29±0.26	169± 1.60	2.69±0.020
F6	27.59±2.52	0.105±0.004	1.135±0.025	21.34±0.23	306.3±2.14	2.63±0.025
F7	30.64±2.62	0.118±0.003	2.129±0.026	25.30±0.25	323.3±1.04	2.68±0.026

*** Indicates values are averages of five observations, ** indicates values are averages of three observations and figures ± are standard deviation (SD) values.**

In vivo permeation studies

The fabricated transdermal patches were subjected to *in-vitro* permeation study across excised Wistar abdominal Skin using modified FD cell permeation cell having a receptor volume of 65ml and an effective surface area of 0.785 cm^2. This study was carried out for 24 hours and cumulative permeated was calculated based on the amount of drug originally present in the formulation that was applied over the skin in the form of wafers. Cumulative drug permeated in milligrams was also calculated for different time intervals of sample withdrawn. The corresponding values of cumulative percent drug permeated for the said formulations were ranging from 18.22 % to 49.98 %.

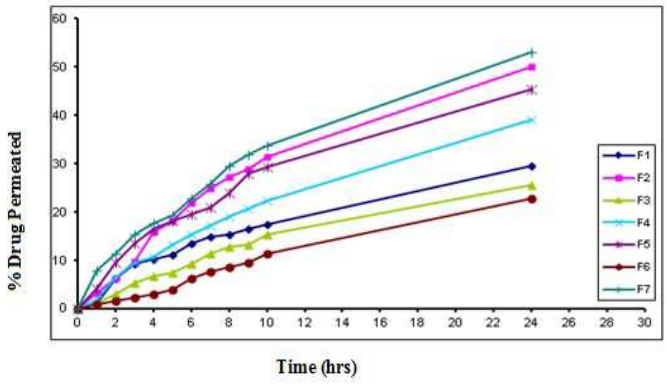

Figure 3: Plot of cumulative percent permeated versus time across Rat abdominal Skin for formulations F1-F7

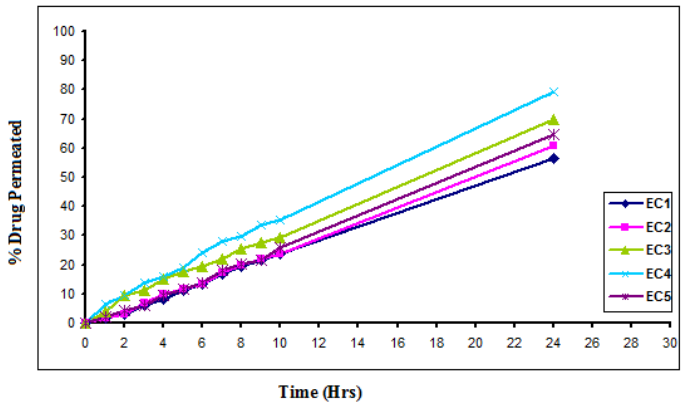

Figure 4: Plot of cumulative percent permeated versus time across Rat abdominal Skin for formulations EC1-EC5

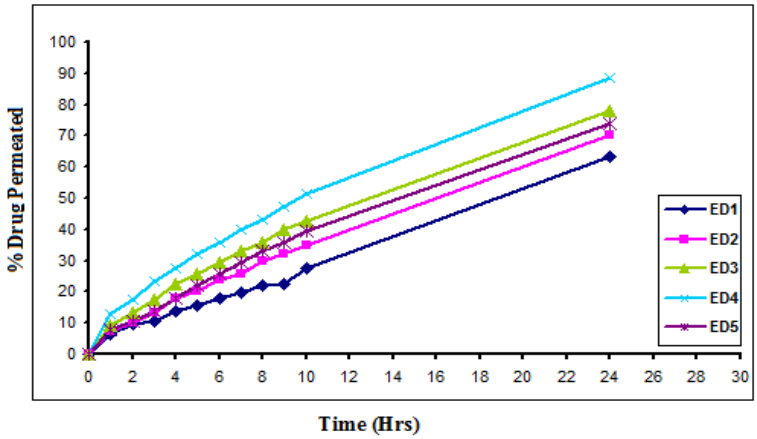

Figure 5: Plot of cumulative percent permeated versus time across Rat abdominal Skin for formulations ED1-ED5

Table 5. Rate of permeation and permeability coefficient of GBE through rat skin.

Formulation Code	Permeation Rate (mg/cm^2/hr)	Permeability Coefficient (/hr)
F1	0.266	0.130
F2	0.314	0.223
F3	0.242	0.124
F4	0.303	0.185
F5	0.253	0.148
F6	0.226	0.154
F7	0.326	0.227

Results indicated that, the order of permeation of drug from different monolithic polymeric membranes was Ethyl cellulose: Polyvinyl Pyrrolidone (3:2)> Ethyl cellulose: HPMC(8.5:1.5) > Ethyl cellulose : Polyvinyl Pyrrolidone(4:1) > Ethyl cellulose : HPMC (9:1) > Ethyl cellulose: PVP (4.5:0.5)> Ethyl cellulose : HPMC (9.5:0)> Ethyl cellulose : PVP(1:0)

The cumulative amount of drug permeated from the transdermal patch without PVP and HPMC was lower than that of the patch containing PVP and HPMC. Initially rapid permeation was observed gradually approaching to constant values for the rest of the time, thus confirming to the controlled release behavior of the formulations. The addition of Polyvinyl pyrrolidone in the formulation F_1, F5, F7, and HPMC in formulation F_2, F_4, F_3, significantly increase the amount of drug permeated. This is clearly apparent from the values of the cumulative percent drug permeated, flux and permeability coefficient values.

The Ethyl cellulose polymer being hydrophobic in nature yielded films which allowed very negligible quantities of drug to

diffuse during the course of diffusion study. Still the higher drug flux was observed with this polymer. Table 5 shows the skin permeation rate and permeability coefficient values of Glibenclamide through the rat abdominal skin. The flux of Glibenclamide for formulations F1-F7 were found 0.266, 0.314,

0.242, 0.303, 0.253 0.226 and 0.326 mg/cm^2/hr x 10^{-2} respectively. From the results it was observed that formulation F_7 and F_2 having highest drug flux.

The results indicated that formulations F7 and F2 are superior to other formulations in imparting better permeability to Glibenclamide. Permeation profiles of these films indicate that, the control of drug release was influenced by the characteristics of the polymer.

From the correlation coefficient values, it was found that the permeation followed zero order kinetics. Also, lower variation was obtained for zero order release rate constant as compared with first order release rate constants indicating a zero order release pattern from the formulations. Higuchi equation explains the matrix diffusion mechanism of drug permeation from the transdermal wafers.

Results obtained in the *in-vitro* experiments indicated that although the drug permeated across the Rate abdominal Skin, the amount of drug permeated was not satisfactory. From the results shown in Table (5)**,** the optimized batch selected was F2 and F7 containing Ethyl cellulose: PVP and Ethyl cellulose: HPMC as the drug diffusion was maximum as compared to other formulations and the % drug diffused per hour was almost constant. Moreover, these films are very flexible and easy to fabricate in patch form.

Optimization was therefore affected by casting the films using various permeation enhancers viz., propylene glycol, DMSO, and isopropyl myristate in both the batches at the concentration of 15% w/w based on polymer weight. Formulations containing EC:PVP also contains 30%w/w dibutyl phthalate which acted as a plasticizer. Polyvinyl pyrrolidone was added as a hydrophilic polymer which increases the flux. They are designated as EC1, EC2, EC3, EC4 and EC5.

Formulations containing EC:HPMC contains no plasticizer. Propylene glycol was added based on 15% w/w of the polymer in all the formulations as a hydrophilic polymer. They are designated as ED1, ED2, ED3, ED4 and ED5. Propylene glycol in case of ED1 acts as a permeation enhancer also.

The films were then evaluated for various physicochemical tests like weight variation, thickness uniformity, tensile strength and percent of elongation at break, folding endurance, drug content uniformity, *In-vitro* permeation study, interaction studies and stability studies.

The results of all the physicochemical characteristics are summarized in Table (6). The results showed that the physicochemical characteristics of the optimized batches were satisfactory with respect to weight variation, thickness uniformity, tensile strength and percent of elongation at break, folding endurance and drug content uniformity.

Table 6: Physicochemical characteristics of optimized transdermal wafers formulations of GBE

F. C.	**Weight Variation* (mg)**	**Thickness** (mm)**	**Tensile Strength** (kg/mm^2)**	**Percent of Elongation at Break****	**Folding Endurance****	**Drug *Content*** (mg)**
EC1	43.20±1.70	0.108±0.03	0.34±0.042	9.59±0.45	112.3±1.46	2.63±0.050
EC2	42.75±2.75	0.104±0.05	0.36±0.045	9.67±0.49	118.6±2.65	2.56±0.040
EC3	44.84±2.45	0.111±0.03	0.33±0.052	8.94±0.50	122.3±1.79	2.67±0.096
EC4	43.96±2.27	0.113±0.06	0.37±0.036	10.72±0.39	124.3±1.16	2.76±0.061
EC5	43.63±1.86	0.114±0.02	0.38±0.024	11.03±0.25	121.6±1.50	2.69±0.040
ED1	32.13±3.15	0.132±0.04	2.105±0.035	24.59±0.30	322±2.00	2.72±0.047
ED2	32.33±3.64	0.152±0.03	2.12±0.06	24.75±0.59	319.3±2.58	2.68±0.045
ED3	33.60±3.18	0.142±0.04	2.30±0.04	26.09±0.45	325±2.02	2.75±0.040
ED4	32.33±3.45	0.165±0.04	2.26±0.034	25.27±0.26	322.3±1.04	2.69±0.055
ED5	33.23±3.67	0.158±0.05	2.28±0.064	25.42±0.65	319.6±2.13	2.76±0.051

*** Indicates values are averages of five observations, ** indicates values are averages of three observations.**

The fabricated transdermal patches were subjected to *in-vitro* permeation study across excised Rat abdominal Skin using FD Cell permeation cell having a receptor volume of 65ml and an effective surface area of 0.785 cm^2. This study was carried out for 24 hours and cumulative permeated was calculated based on the amount of drug originally present in the formulation that was applied on the skin. Cumulative drug permeated in milligrams was also calculated for different time intervals of sample withdrawn.

Effect of permeation enhancers on drug permeation from the optimized batches through rate abdominal skin

The effect of enhancers such as DMSO, and IPM, propylene glycols on the transport of Glibenclamide through the skin was investigated at a concentration of 15% w/w based on polymer weight. Permeation enhancing efficacy was evaluated by the determination of enhancement factor as described in Table (7). It was calculated employing the following formula:

$$EF = \frac{\text{Drug flux from the matrix containing permeation enhancer}}{\text{Drug flux from the matrix without permeation enhancer}}$$

Table 7: Rate of permeation and permeability coefficient of GBE through rat skin

F.C	**Enhancer**	**Flux ($mg/cm^2/hrs\ 10^{-2}$)**	**Permeability Coefficient ($cm/hr \times 10^{-2}$)**
EC1	Propylene glycol	0.290	0.180
EC2	Propylene glycol	0.317	0.291
EC3	Isopropyl myristate	0.280	0.224
EC4	DMSO	0.382	0.282
EC5	Isopropyl myristate	0.289	0.158
ED1	Propylene glycol	0.358	0.173
ED2	Propylene glycol	0.306	0.228
ED3	Isopropyl myristate	0357	0.180
ED4	DMSO	0.355	0.193
ED5	Isopropyl myristate	0.307	0.285

Permeation data of Glibenclamide with and without enhancers. The permeation of drug from the EC: PVP and EC:HPMC matrix containing enhancers through Rate abdominal Skin showed better enhancing effect. Among enhancers used, Propylene glycol, showed the best enhancement. The permeation data shown in Table (7), depicts the films having highest permeability coefficient. These data support the principle that for the higher drug release the formulation should possess relatively higher permeability coefficient value. The rank order of permeation was found to be as follows: without enhancers<Propyleneglycol<Isopropyl myristate< DMSO.

The interaction studies were carried out to ascertain any kind of interaction of the drug with the excipients used in the preparation of transdermal films. For this the pure drug and medicated films were subjected to U.V analysis. The U.V absorption maxima **(λ_{max})** for the pure drug and the medicated formulations were found to be at 236nm. The results indicated that the drug remained intact in TDDS and there were no chemical interactions between drug and the polymers therein.

Drug permeability kinetics

In-vitro permeability pattern of various formulations was analyzed by R^2 and n values of various kinetic models table (8-9). In the case of formulation F1-F5, and EC1-EC5 and ED1-ED5. The in-vitro permeation profile of all formulations by plotting the cumulative amount of drug permeated against time show a similar pattern of drug permeation having initial faster (burst) Release followed by slower release. Hence the *in-vitro*

permeation data, neither fitted to Zero order, nor fitted to (R^2 = 0.9272 to 0.9831) nor first-order (R^2 = 0.9301 to 0.9755) kinetics completely. When the polymeric layer is placed in contact with the skin, the drug compound migrates through the polymer, partitions across the polymer/skin interface, and then migrates into skin. The initial faster release may be attributed to the rapid diffusion of the drugs immediately to the surface of the film. Thus the rapid depletion of the surface drug and consequent increase in mean diffusion path length might have caused slower release (except F3 and F6) and can also account for the increase in diffusion path length due to swelling of HPMC and PVP. The formulation F3 and F6 showed strong linearity with R^2 values. When the HPMC loaded formulation plotted with Eq. $Q = K_1 t^n$. The formulation show concentration high linearity (R^2=0.9720 to 0.9970) and n values 0.52 to 0.67. It indicated that drug release was leaning toward diffusion and swelling coupled mechanism. Presence of swellable polymer (HPMC and PVP) in matrix might be responsible for the drug release controlled by more than one process.

Table 8: Permeability kinetic models

Formulation Code	R^2 Value				
	Zero Order	Higuchi Equation	First Order	Korsmeyer-Peppa's model	n value
F1	0.9567	0.9545	0.9667	0.9910	0.56
F2	0.9485	0.9405	0.9522	0.9727	0.51
F3	0.9269	0.9453	0.9301	0.9926	0.44
F4	0.9581	0.9548	0.9682	0.9966	0.66
F5	0.9592	0.9294	0.9654	0.9728	0.54
F6	0.9272	0.9142	0.9305	0.9956	0.43
F7	0.9831	0.9711	0.9755	0.9861	0.65

Table 9: Permeability kinetic models

Formulation Code	R^2 Value				n value
	Zero Order	First Order	Higuchi Equation	Korsmeyer-Peppa's model	
EC1	0.9982	0.9864	0.9545	0.9829	0.64
EC2	0.9984	0.9754	0.9405	0.9906	0.53
EC3	0.9958	0.9712	0.9453	0.9976	0.48
EC4	0.9953	0.9662	0.9548	0.9914	0.55
EC5	0.9975	0.9663	0.9294	0.9802	0.55
ED1	0.9922	0.9673	0.9142	0.9227	0.76
ED2	0.9859	0.9905	0.9711	0.9269	0.60
ED3	0.9658	0.9930	0.9882	0.9897	0.77
ED4	0.9499	0.9811	0.9918	0.9777	0.59
ED5	0.9770	0.9941	0.9808	0.9974	0.57

4. Conclusion

GBE transdermal wafers were developed using Ethyl cellulose/Hydroxy propylmethylcellulose and Ethyl cellulose/Polyvinylpyrrolidone as a polymer in various combinations. Polymer was used alone and combination. It was concluded that the combination of polymer is more favorable for development of the transdermal patch of Glibenclamide. Among the penetration enhancer i.e. Propylene glycol, Dimethyl sulfoxide and Isopropyl myristate the highest penetration rate was noticed with Propylene glycol. The addition of the hydrophilic component such as Hydroxy propyl methyl cellulose and Polyvinylpyrrolidone to an insoluble film former such as Ethyl cellulose tends to enhance its release rate constants (swelling coupled diffusion control

drug release). This outcome can be attributed to the leaching of soluble component, which lead to the formation of pore and thus a decrease in the mean diffusion path length of drug molecules.

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References

[1]. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26 (11):1261-1268.

[2]. Margetts L, Sawyer R. Transdermal drug delivery: principles and opioid therapy. Contin Educ Anaesth Crit Care 2007;7(5):171-176.

[3]. Mbah CJ, Uzor PF, Omeje EO. Perspectives on Transdermal Drug Delivery. Journal of Chemical and Pharmaceutical Research 2011;3(3): 680-700.

[4]. Mutalik S, Udapa N. Pharmacological evaluation of membrane-moderated transdermal system of glibenclamide. Clin Exp Pharmacol Physiol 2011; 33:17-26.

[5]. Takahshi Y, Furuya K, Iwata M, Onishi H, Machida Y, Shirotake S. Trial for transdermal administration of sulfonylureas, Yakugaku Zassi. Journal of Pharm. Sc. 1997;12:1022- 1027.

[6]. Mutalik S, Udapa N. Effect of some permeation enhancers on the permeation of glibenclamide and glibenclamide through mouse skin. Pharmazie 2003;58:891-894.

[7]. Suwanpidokkul N, Thongnopnua P, Umprayn K. Transdermal delivery of zidovudine: The effects of vehicles, enhancers, and polymer membranes on permeation across cadaver pig skin. AAPS Pharm Sci Tech 2004;5(3):48-52.

[8]. Jamakandi VG, Ghosh B, Desai BG, Khanam J. Recent trends in transdermal cardiovascular therapy. Ind J Pharm Sci 2006; 68 (5): 556-561.

[9]. Anroop B, Ghosh B, Parcha V, Kumar A, Khanam J. Synthesis and comparative skin permeability of atenolol and propranolol esters. J Drug Del Sci Tech 2005; 15: 187-190.

[10]. Glikfield P, Cullander C, Hinz R, Guy R. A new system for *in vitro* studies of iontophoresis. Pharm Res 1988;5:443-446.

[11]. Ghosh B, Reddy LH Effect of physicochemical parameters on skin permeability of antihypertensives. Ind J Exp Biol 1998; 39:710.

[12]. Dhawan S, Singla AK. Performance liquid chromatographic analysis of glibenclamide: application to *in vitro* and *in vivo* studies. J Chrom Sci 2003;41: 295-300.

[13]. Goodman, M., and B.W. Barry. Lipid-protein-partitioning (LPP) theory of skin enhancer activity: finite dose technique. International Journal of Pharmaceutics 1989;57: 29–40.

[14]. Gurol, Z., S. Hekimoglu, R. Demirdamar, and M. Sumnu. Percutaneous absorption of Ketoprofen and *In vitro* release and percutaneous absorption of ketoprofen from different ointment bases. Pharmaceutical Acta Helvitae 1996;71: 205–212.

[15]. Kyuki, K., K. Tsurumi, and H. Fujimura. Anti-inflammatory activity of Ketoprofen cream in topical application. Oyo Yakuri 1985;29:969–976.

[16]. Morimoto, K., H. Tojima, T. Haruta, M. Suzuki, and M. Kakemi. Enhancing effects of unsaturated fatty acids with various structures on the permeation of indomethacin through rat skin. Journal of Pharmacy and Pharmacology 1996; 48:1133–1137.

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