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DESIGN AND EVALUATION OF GLICLAZIDE TRANSDERMAL PATCH CONTAINING FILM FORMER

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ABSTRACT

Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence, an anti-diabetic agent of both therapeutic and prophylactic usage has been subjected to transdermal investigation. Gliclazide is a second generation hypoglycemic agent faces problems like its poor solubility, which limits its oral bioavailability with large individual variation and its extensive metabolism. In the present work, transdermal matrix type patches were prepared by film casting techniques on mercury using polymers like HPMC and Eudragit RL-100. Also an attempt was made to increase the permeation rate of drug by preparing inclusion complex with hydroxypropyl β-cyclodextrin (HP β- CD). The possibility of a synergistic effect of chemical penetration enhancers (CPE) (propylene glycol and oleic acid) on the transdermal transport of the drug was also studied. Folding endurance was found to be high in patches containing higher amount of the Eudragit. There was increase in tensile strength with increase in Eudragit in the polymer blend. In vitro drug release profile indicates that the drug release is sustained with increasing the amount of Eudragit in patches. The patches containing inclusion complex of drug showed higher permeation flux compared with patches containing plain drug. The result of synergistic effect indicates that the HP β-CD in conjunction with other chemical penetration enhancer showed higher permeation flux. In conclusion, the present data confirm the feasibility of developing Gliclazide transdermal patches.

***Keywords*:** Gliclazide, hydroxypropyl β-cyclodextrin Inclusion complex, Permeation enhancer, Transdermal patch,

INTRODUCTION

Transdermal drug delivery offers many important advantages. For instance, it is easy and painless, it protects the active compound from gastric enzymes, and it avoids the hepatic first-pass effect, controls absorption rate, variations in delivery rates, interference due to the presence of food, increases patient compliance, suitable for unconscious patients and enables fast termination of drug delivery, if needed. But skin is a natural barrier, which are mainly composed of lipids & proteins and only a few drugs can penetrate the skin easily and in sufficient quantities to be effective. [1] Recently it is evident that the benefits of intravenous drug infusion can be duplicated, without its hazards, by using the skin as the port of drug administration to provide continuous transdermal drug infusion in to the systemic circulation. The penetration across epithelial borders is a slow process due to the effect of the barrier properties. The skin, in particular the stratum corneum, possesses a barrier to drug penetration due to its high density (1.4 g/cm^2 in dry state), its low hydration of 15 to 20%. The barrier function is further facilitated by the continuous replacement of stratum corneum, thereby limiting the topical & transdermal bioavailability. Therefore, in recent years, numerous studies have been conducted in the area of penetration enhancement. [2] Limitations include slow penetration rates, lack of dosage flexibility and a restricted to relatively low dosage drugs. [3]

Transdermal systems are ideally suited for diseases that demand chronic treatment. Hence, anti-diabetic agents of both therapeutic and prophylactic usage have been subjected to transdermal investigation. Gliclazide is a second generation sulphonylurea oral hypoglycemic agent used in the treatment of non-insulin dependent diabetes mellitus. But the problem with this potentially useful hypoglycemic agent is that it is practically insoluble in water. This limits its oral bioavailability with large individual variation. After oral administration it get extensively metabolised by hydroxylation, N-oxidation and oxidation to several inactive metabolites. It is slightly soluble in water having half life 6-8 hrs. The drug is neutral in nature, molecule

weight 323.4, melting point about 181°C and partition coefficient 2.1. Hence a potential candidate for the present works on transdermal studies. [4, 5, 6].

As the drug is slightly soluble in water complexation of Gliclazide with cyclodextrin has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance contain 6, 7 or 8 dextrose molecules (α-, β-, γ-cyclodextrin) bound in a 1, 4- configuration to form rings of various diameters. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability. As β-cyclodextrin shows toxicity, when given parentrally. Hence, derivatives of β -cyclodextrin with increased water solubility [e.g. hydroxypropyl- β- cyclodextrin (HP- β-CD] are used in transdermal formulation. Cyclodextrin complexes have been shown to increase the stability, wettability, penetrability and dissolution of the lipophilic drugs. Skin penetration enhancement has been attributed to extraction of stratum corneum lipids by cyclodextrins. However, cyclodextrins alone were determined to be less effective as penetration enhancers than when combined with fatty acids and propylene glycol [7, 8]

CPE are molecules which reversibly decrease the barrier nature of the Stratum corneum [9, 10] CPE act by interaction with intercellular lipids leading to disruption of their organization and increasing their fluidity [11]. Some of them also interact with intercellular protein, keratin denaturation (e.g. Azone and oleic acid) [12], while others act by both mechanisms (e.g. DMSO and propylene glycol) [13]. Another possible mechanism is by altering the skin hydration.

In this investigation an attempt was made to determine the synergistic effect of three chemical penetration enhancer (CPE) in which β- cyclodextrin, which increase transdermal drug transport by increasing drug solubility and drug partitioning into the stratum corneum, propylene glycol acts by increasing their fluidity of lipid bilayers and Oleic acid which acts by disrupting the intracellular proteins.

MATERIALS AND METHODS

Materials

Gliclazide was received as a gift sample from Cipla Pharmaceutical Ltd. (Pune, India) Eudragit RL-100 was obtained from Degussa India Pvt. Ltd. (Mumbai, India). HPMC obtained from Colorcon Asia Pvt. Ltd. (Goa, India). 3M™ Scotchpack™ 9733 backing membrane and 3M™ Scotchpack™ 1022 release liner were obtained from 3M (USA). Cellulose Acetate membrane (0.45μ) was obtained from Pall Corporation (USA). Hydroxyl propyl β-cyclodextrin was obtained from Finer Chemicals Ltd (Ahmadabad, India), Oleic acid and Propylene glycol were obtained from Research Lab (Mumbai, India). All other chemicals were used of pharmaceutical grade.

Methods

Compatibility studies of drug and polymers

The pure drug, the mixture of polymers (HPMC and Eudragit) and a mixture of drug with the polymers were mixed separately with IR grade KBr in the ratio of 100:1. The base line correction was done using dried KBr. Infrared spectra of the mixture were taken over a wave number range of 4000-400/cm (Shimadzu, Japan). Also the infrared spectra of the drug and polymers were run individually. Then it was investigated for any possible interaction between polymer and drug. The X-ray diffractograms were obtained using on X-Ray diffraction instrument. (Philips X-ray diffractometer, PW-3710, Holland) and interpreted for any polymorphic change in the gliclazide.

Formulation of transdermal patches having uniform thickness

In this work a 3^2 full factorial design was applied. The batch 1 containing minimum quantity of all polymers showed minimum thickness, while the batch 9 containing higher quantity of all polymers showed maximum thickness. As we know thickness of the patch will affects each and every physical parameter also it will affects the release profile of drug. Hence to overcome this problem, we have determined the percentage contribution of each factor at each level and the patches were prepared according to their contribution.

Preparation of transdermal patches

The transdermal patches were prepared by film casting techniques on mercury [14, 15]. The transdermal film contains HPMC, Eudragit RL-100 polymer along with 200 mg of drug and 5% wt/wt of plasticizer, triethyl citrate shown in table no.1 & table no.2. A 3^2 full factorial design were applied to formulate the matrix type transdermal film of gliclazide and to determine the effect of each polymer on release pattern of drug from transdermal drug delivery system. Hydrophilic materials i.e. HPMC was dissolved in 10 ml water and hydrophobic materials i.e. Eudragit RL-100 were dissolved in 10 ml blend of dichloromethane (DCM) and ethanol (50:50). Then both the solution were mixed and stirred on magnetic stirrer to accomplished homogeneous mixture. The resulting solution was poured in a petri dish containing mercury. The solvent were allowed to evaporate for 24 hrs. at 35° C. A 9772L PVC foam tape (adhesive) and a release liner (3M™ Scotchpack™ 1022) on either side of the film were applied and an occlusive base plate (3M™ Scotchpack™ 9733) was placed between the adhesive and film to avoid the possible interaction of drug with adhesive and to complete the transdermal therapeutic system of gliclazide. The prepared transdermal gliclazide patches were store in dessicator until further use.

Table1: Full factorial experimental design layout

Batch	X1	X2
GLP1	-1	-1
GLP 2	0	-1
GLP 3	1	-1
GLP 4	-1	0
GLP 5	0	0
GLP 6	1	0
GLP 7	-1	1
GLP 8	0	1
GLP 9	1	1

Table 2: Amount of Variables in a 3^2 Factorial Design

Coded Level	-1	0	1
HPMC (X1) mg	350	400	450
Eudragit (X2) mg	250	300	350

Collection and Preparation of the rat skin

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

Evaluation of transdermal formulation

Thickness of Film:

Thickness of the films was measured using Digital Screw Gauge (Mitutoyo, Japan) at three different places and the mean value was calculated [16]. The construction of a film strip cut out from a drug loaded matrix film is an indicator of its flatness. Longitudinal strips (1.5×0.75cm) were cut out from the prepared medicated matrix films. The initial length of each film is measured, and then they were kept at room temperature for 30 min. The variations in the length due to non uniformity in flatness were measured. Flatness was calculated by measuring construction of strips and a zero percent of construction was considered to be equal to hundred percent flatness [17].

Folding endurances:

Folding endurances were measured to determine the ability of patch withstand to rupture. Folding endurance of films was determined by continually folding a small strip of film (2cm × 2cm) at the same place till it broke. The number of time the film could be folded at the same place without breaking was the folding endurance value of that prepared transdermal film [18]. The tensile strength was determined by using a modified pulley system. It contains two clamps, one was fixed and other was movable. The strip of the patch (2×1 cm^2) was cut and hold between these two clamps. Weight was gradually increased on the pan, so as to increase the pulling force till the patch broke. The force required to break the film was consider as a tensile strength and it was calculated as kg/cm^2.

Percentage of moisture content:

To determine the percentage of moisture content, the films were weighed individually and kept in a desiccators containing activated silica at room temperature for 24 hours. Individual films were weighed

repeatedly, until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to final weight [19]. To determine the percentage of moisture uptake a weighed film was kept in a desiccators at room temperature for 24 hours was taken out and exposed to 84% relative humidity in programmable environmental test chamber until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as the difference between final and initial weight with respect to initial weight [20].

Determination of Drug Content:

To determine drug content a 2 cm^2 film was cut into small pieces, putted into a 100 ml of isotonic phosphate buffer pH 7.4 and ultrasonicated for 30 minutes, then the solution were shaken continuously for 24 hours. After filtration, the drug concentration was analyzed by using UV spectrophotometer at a wavelength of 226 nm and the drug content was determined.

Ex-vivo Drug Permeation study:

The *Ex-vivo* study of drug permeation through the rat skin was performed using a modified Keshary-Chien type glass diffusion cell. This skin was mounted between the donor and receptor compartment of the diffusion cell having capacity of 27ml. The transdermal patch was placed on the skin and covered with aluminum foil. The receptor compartment of the diffusion cell was filled with isotonic phosphate buffer pH 7.4 containing 0.5% of sodium lauryl sulphate. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at constant rpm and the temperature was maintained at 32 ± 0.5°C because the normal skin temperature of human is 32°C. The diffusion was carried out for 12 hours and 1 ml sample was withdrawn at an interval of 1 hour. The samples were analyzed for drug content spectrophotometrically at 226 nm. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal.

Solubility Enhancement of Gliclazide by Complex Formation with Hydroxy Propyl β-Cyclodextrin (HP β - CD) (GCD):

As the drug is very slightly soluble in water, its complex were formed with HP β-CD in the molar ratio of 1:2 by kneading method. In this method HP β-CD was added in mortar, and a small quantity of 50% v/v ethanol was added, while triturating to get slurry like consistency. Then slowly the drug was incorporated into the slurry and trituration was continued further for 1 hr at 75°C. After that it was dried at 50°C, for one day, crushed, sieved and stored at temperature of 25 ± 2.0°C and relative humidity between 40-50%.

Preparation of Patch Containing Chemical Enhancers:

The patches were prepared by the same procedure maintained for preparation of plain transdermal patch except that in this preparation plane drug is replaced with GCD and chemical enhancers were added. For T3 along with other ingredients 0.5 ml of propylene glycol was added, in T4, T5 and T6 0.5 ml 2.5%, 5%, 10% solution of oleic acid in propylene glycol were added for the preparation of patches.

RESULT AND DISCUSSION

Compatibility studies of drug and polymers:

FTIR study was 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. FTIR of plain drug and physical mixture were shown in Fig.1 and Fig.2 respectively. From the IR spectrums it was clear that there was no change in peak positions of gliclazide, when mixed with the polymers. Thus there was no interaction between Gliclazide and polymers.

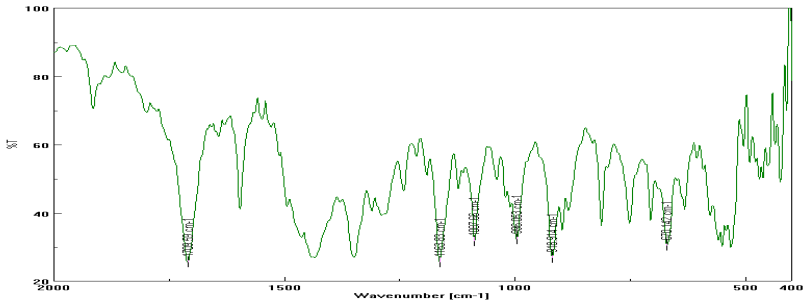

Figure1: FTIR spectra of Gliclazide.

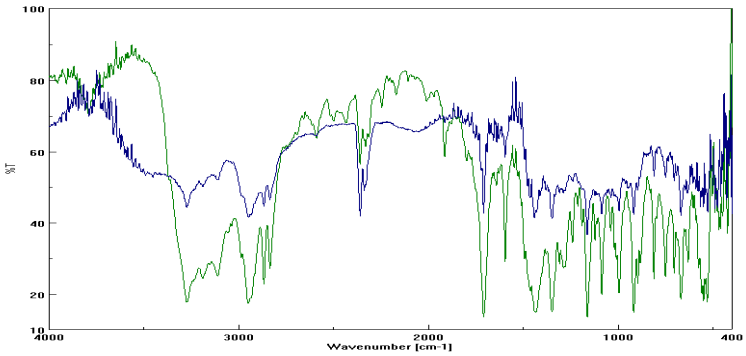

Figure 2: FTIR spectra of Gliclazide (Green) and Physical mixture of drug with HPMC, ERL (Blue)

The X-ray diffraction (XRD) pattern of pure drug and patch are represented in Fig.3. The diffractograms of pure gliclazide and patch exhibited a series of intense peaks, which are indicative of their crystallinity. In case of patch, the total number of peaks has been reduced due to use of HPMC as constituents of film. In this case, the dilution of drug due to excipients has reduced the intensity of peaks. This concludes that, no any polymorphic change has taken place in gliclazide during the preparation of patch.

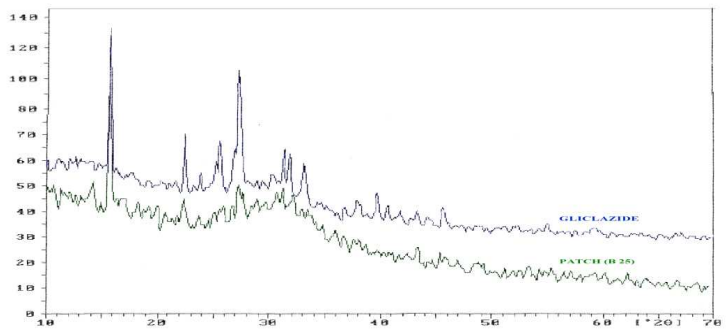

Figure 3: XRD pattern of pure drug and patch

Formulation of transdermal patches having uniform thickness:

Non uniform thickness in the patches shows difference in their physical parameters as well as on the release profile of the drug. To overcome this problem, we have determined the percentage contribution of each factor at each level and the patches were prepared according to their contribution. Also the dishes on

which patch have been prepared were taken of uniform diameter (8.7cm). The maximum differences between the thicknesses of patches were 0.02 mm, which indicates that all the prepared patches of uniform thickness.

Evaluation of transdermal formulation:

The results of the characterization of the patches are shown in Table no.3. The thicknesses of all the batches was nearly similar because to quantity of polymers were taken as per their percent of contribution also, it indicates physical uniformity indicative of their crystallinity. The thickness of the patches (with varying ratios of HPMC, and ERL) varied slightly from 0.18 to 0.226 mm. The low values for standard deviation indicate physical uniformity of the patches. All the patches were showed near to hundred percent flatness, which indicates negligible amount of constriction of the prepared transdermal patches. Thus, patches does not constrict, when it is applied on the skin.

Table 3. Results of Thickness, Tensile Strength and Folding Endurance

Code	Thickness in mm	Folding Endurance	Tensile Strength(Kg/cm^2)
GLP1	0.19 ± 0.03	141.33 ± 2.52	0.538 ± 0.002
GLP2	0.186667 ± 0.006	136 ± 2.00	0.525 ± 0.025
GLP3	0.186667 ± 0.025	135.33 ± 1.53	0.514 ± 0.032
GLP4	0.186667 ± 0.027	147.33 ± 0.58	0.554 ± 0.023
GLP5	0.186667 ± 0.020	143.33 ± 1.53	0.542 ± 0.032
GLP6	0.183333 ± 0.015	140.33 ± 0.58	0.532 ± 0.010
GLP7	0.18 ± 0.01	153.66 ± 1.15	0.564 ± 0.021
GLP8	0.183333 ± 0.015	150.32 ± 1.53	0.554 ± 0.030
GLP9	0.183333 ± 0.005	146.34 ± 2.52	0.534 ± 0.035

*Indicates average ± standard deviation (n=3)

Folding endurance test results indicates that all the patches will withstand to rupture and would maintain their integrity with general skin folding, when used. The folding endurance was measured manually and it lies in between 138 to 154. It was found to be high in patches containing higher amount of the Eudragit. Strength of the film and the risk of film cracking were indicated by its tensile strength. The prepared transdermal films were shown good tensile strength and there was no sign of cracking in prepared transdermal film. This might be attributed to the addition of the plasticizer, triethyl citrate. Plasticizers are generally used to improve the mechanical properties of a polymer matrix. Tensile strength was lies in between 0.517 to 0.567 Kg/cm^2, the difference depend on the composition of polymer used. There was increase in tensile strength with increase in Eudragit in the polymer blend. Also there was decrease in the tensile strength with increasing the concentration of HPMC.

Moisture content and moisture uptake studies indicates that, the increase in the concentration of hydrophilic polymer i.e. HPMC was directly proportional to the increase in moisture content and moisture uptake of the patches. Eudragit is a hydrophobic polymer hence; there is decrease in the moisture content with increase in Eudragit concentration in the blend of polymer. The moisture content of the prepared transdermal film was low, which maintains suppleness, thus preventing drying and brittleness. The moisture uptake of the transdermal formulations was also low, which protect the film from microbial contamination as well as bulkiness of transdermal patch. Due to moisture uptake from the atmosphere, significant changes in properties like increased porosity, increased pore diameter and reduced crushing strength has been reported for matrix film containing hydrophilic polymers results shown in table no. 4

Table 4. Results of Moisture content, Moisture uptake, Drug content and Drug release

Formulation Code	% Moisture content	% Moisture uptake	% Drug content	% Drug release
GLP1	5.23 ± 0.12	10.31 ± 0.43	103.41 ± 2.12	74.07 ± 2.14
GLP2	5.33 ± 0.09	11.05 ± 0.23	98.44 ±1.25	76.05 ± 1.46
GLP3	5.45 ± 0.18	10.85 ± 0.65	02.64 ± 0.98	79.17 ± .958
GLP4	5.06 ± 0.14	10.48 ± 0.14	97.25 ± 2.14	73.56 ± 1.02
GLP5	4.85 ± 0.13	10.17 ± 0.36	04.24 ± 1.04	73.57 ± 1.58
GLP6	5.08 ± 0.19	10.43 ± 0.21	99.33 ± 1.06	74.54 ± 2.58
GLP7	4.15 ± 0.08	9.53 ± 0.58	101.17 ± 1.82	68.81 ± 3.45
GLP8	4.86 ± 0.14	9.52 ± 0.43	101.52 ± 2.14	72.1 ± 1.35
GLP9	4.94 ± 0.13	9.73 ± 0.59	99.31 ± 3.41	78.15 ± 2.14

*Indicates average ± standard deviation (n=3)

Determination of Drug Content:

Drug content of all batches were well within the range between 98.40 ± 1.25 to 103.81 ± 2.12 %. As per shown result, it was much closed to 100%, means there is no any loss of drug during the preparation of the transdermal patches and also there was homogeneous mixture of drug in polymer matrix.

Ex-vivo Drug Permeation study:

Release of the drug from transdermal patches was controlled by the chemical properties of the drug and delivery form, as well as physiological and physicochemical properties of the biological membrane. The study was designed to formulate transdermal film of Gliclazide using a polymeric matrix film shown in table no. Drug release profiles from different formulations are shown in Fig. 4.

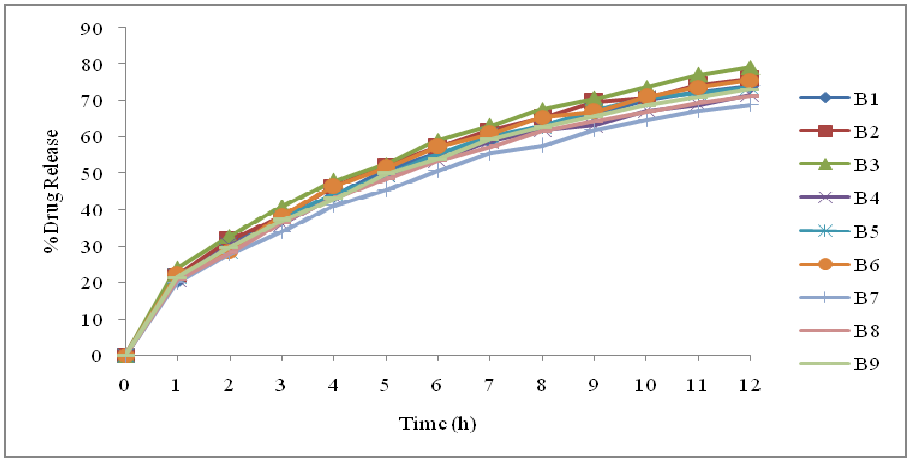

Figure 4: Drug Release Profile of GLP1- GLP9

The matrix allows one to control the overall release of the drug via an appropriate choice of polymers and their blends. The blends of polymers create several diffusion pathways to generate overall desired steady and sustained drug release from the patches. The manner by which drug release in most of the controlled / sustained release devices including transdermal patches is governed by diffusion. The addition of hydrophilic component to an insoluble film former leads to enhance its release rate constant. This may be due to dissolution of the aqueous soluble fraction of the film, which leads to creation of pores and decrease of mean diffusion path length of the drug molecule to be released. The batch GLP3 containing highest amount of HPMC showed maximum release 79.17 %, The batch GLP7 containing the higher proportion of the Eudragit shows only 68.81 ± 3.45% drug release within 12 hours, which was the lowest amount of the drug release among the all nine batches.

Effect of complex formation with HP β – CD on drug solubility and permeability:

In the present study complexation of drugs with cyclodextrins has been used to enhance aqueous solubility, skin permeability and drug stability shown in table 5. The result of complexation of drug with HP β – CD showed both increase in the permeation rate through membrane as well as increase in the solubility of drug (Fig.5). The percentage of drug release from the complex after 12 h was found to 89.25% compared with GLP7 which showed only 67.71% release. The permeation flux of plain gliclazide patch (GLP7) was found

to be 80.00 µg/cm^2/h were as the flux of complex was 106.60 µg/cm^2/h. Hence, we can conclude that there is increase in the permeation of drug from the complex.

Table 5: Trials for Permeation Study

Trial	Formulation
T1	Gliclazide
T2	GCD
T3	GCD + Propylene Glycol
T4	GCD + Propylene Glycol + Oleic acid (2.5%)
T5	GCD + Propylene Glycol + Oleic acid (5%)
T6	GCD + Propylene Glycol + Oleic acid (10%)

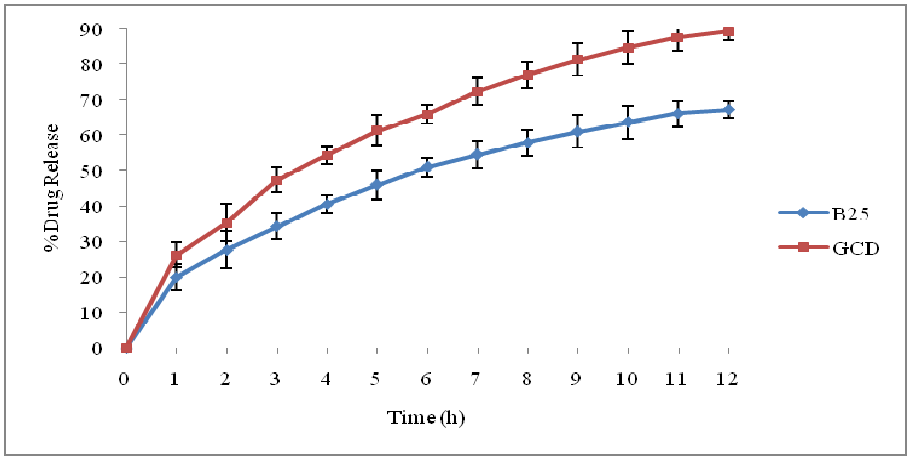

Figure 5: Comparison of drug release from GLP7 and GCD

Effect of various penetration enhancers on ex vivo penetration of Gliclazide:

It is reported that cyclodextrins alone were determined be to less effective as penetration enhancers than when combined with fatty acids and propylene glycol [5]. Hence, the synergistic effect of cyclodextrin and other chemical enhancer have been done. The patch T6 containing propylene glycol (PG) and oleic acid (10%) have shown highest flux rate compared with other mixture. The permeation flux of Gliclazide in Propylene glycol was very low. With the addition of fatty acids, the permeation rates increased markedly as depicted in Fig.6. The highest maximum flux was obtained with the patch containing 10% oleic acid in propylene glycol. Propylene glycol is known to have relatively low skin cell toxicity and has been widely used for formulation of transdermal delivery systems. It was suggested that the probable mechanism of propylene glycol is solvating alpha keratin and occupying hydrogen-bonding sites, thus reducing drug / tissue binding. On the contrary, fatty acids are known to be enhancers with lipophilic properties, and many studies have shown that the skin permeability enhancing effects of fatty acids are greatest with propylene glycol vehicles.

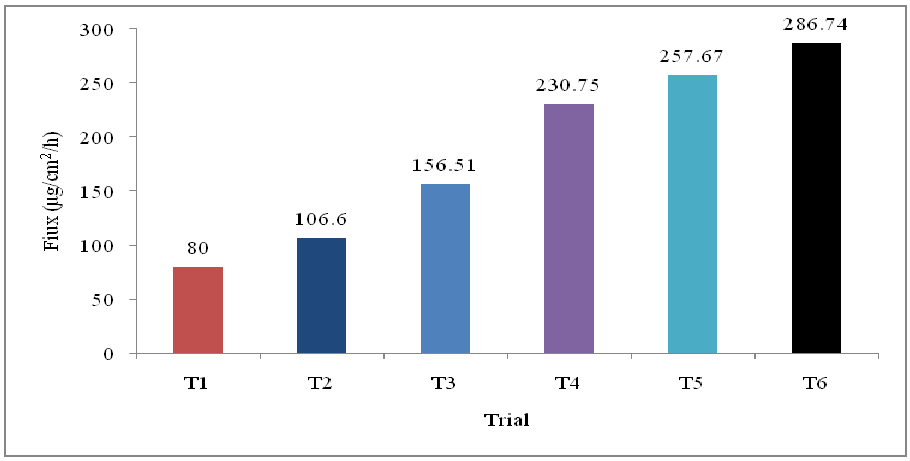

Figure 6: Permeation Flux of Gliclazide from Different Trial

CONCLUSION

The transdermal matrix patches of Gliclazide were prepared by film casting techniques on mercury and effect of various penetration enhancers on the permeation of Gliclazide were studied. For this the batch containing

10% solution of oleic acid in propylene glycol is the permeation enhancer of choice for the percutaneous absorption of Gliclazide. The prepared patches showed good uniformity with regards to their thickness and flatness. The patches were showed significant folding endurance and tensile strength. The moisture content and moisture uptake were found to be in limit. The prepared patches were showed good homogeneity with regards to their drug content and drug release. In conclusion, the present data confirm the feasibility of developing Gliclazide transdermal patches.

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