RESEARCH ARTICLE

# Design and evaluation of transdermal drug delivery system of gliclazide

Anilkumar J Shinde, Amit L Shinde, Harinath N More

Department of Pharmaceutics, Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India

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, a second-generation hypoglycemic agent, faces problems like its poor solubility, poor oral bioavailability with large individual variation and extensive metabolism. In the present work, transdermal matrix-type patches were prepared by film casting techniques on mercury using polymers like HPMC, Eudragit RL-100, and chitosan. Also an attempt was made to increase the permeation rate of drug by preparing an 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 an 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 the synergistic effect indicates that the HP β- CD in conjunction with other CPE showed a higher permeation flux.

***Key words:*** *Gliclazide, inclusion complex, permeation enhancer, transdermal patch*

## INTRODUCTION

Delivering medicine to the systemic circulation via skin is seen to be a desirable alternative for administrating it by mouth. The penetration across skin layer 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) and its low hydration of 15 to 20%. The barrier function is further facilitated by the continuous replacement of the stratum corneum.

It offers many important advantages over oral drug delivery, e.g., avoids gastrointestinal tract and hepatic first-pass metabolism, reduces variations in delivery rates, avoids interference due to the presence of food, controls absorption rate, increases patient compliance, suitable for unconscious patients, and enables fast termination of drug delivery, if needed.[1] The technique is generally non-invasive so it is well accepted by patients and can be used to provide local as well as systemic delivery over several days.[2] Limitations include slow penetration rates, drug formulation may cause skin irritation, patient may develop contact dermatitis, and be restricted to relatively low dosage drugs.

There are a number of routes by which a molecule can cross the stratum corneum, these are intercellular, transcellular, and transappendageal. Both polar and non-polar substances diffuse via transcellular and intercellular routes by different mechanisms.[3] The transappendageal route transports substances via sweat glands and the hair follicles with their associated sebaceous glands. This route is considered to be of minor importance because of its relatively small area. There has been much debate over the past decades on the route of penetration but experimental evidence suggests that, under normal circumstances, the predominant route is through the intercellular spaces.[4-6]

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 sulfonyl urea 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

**Address for correspondence:**
*Prof. Anilkumar J Shinde, Department of Pharmaceutics, Bharati Vidhyapeeth College of Pharmacy, Near Chitranagari Kolhapur – 416 013, Maharashtra, India.*
*E-mail: ajshinde07@rediffmail.com*

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insoluble in water. This limits its oral bioavailability with large individual variation. After absorption it gets extensively metabolized by hydroxylation, N-oxidation, and oxidized to several inactive metabolites. It is slightly soluble in water having half life 6-8 h. The drug is neutral in nature, molecular weight 323.4, melting point about 181°C, and partition coefficient 2.1. As the drug contains ideal properties required for transdermal preparation, it can be used for present work. 200 mg of drug have been incorporated in a patch having a 9 cm diameter. The drug content can be determined by total surface area of the patch. After deciding the dose, the patch may cut off into various sizes depending on the dose.

HPMC, Eudragit RL 100, and chitosan are used for preparing the matrix type patch because of their nature; HPMC is hydrophilic whereas Eudragit RL 100 is hydrophobic; also the effect of natural polymer chitosan on the release pattern is studied. 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 given parentally shows toxicity, hence, derivative of β-cyclodextrin with increased water solubility [e.g. hydroxypropyl β- cyclodextrin (HP- β-CD)] is 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 the 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]

The skin, being a semi-permeable membrane, allows only a small quantity of any drug molecule to passively infiltrate it.[8] The stratum corneum is thought to be the site of activity of the chemical penetration enhancers (CPE). 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, by denaturation (e.g. azone and oleic acid),[12] while others act by both mechanisms (e.g. DMSO and propylene glycol).[13] Another possible mechanism by altering the skin hydration.

In this investigation, an attempt was made to determine the synergistic effect of three CPE in which HP- β-CD increases transdermal drug transport by increasing drug solubility and drug partitioning into the stratum corneum, propylene glycol acts by solvating alpha keratin and occupying hydrogen bonding site, thus reducing drug/tissue binding, and oleic acid acts by increasing the fluidity of lipid bilayers.

## 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). Chitosan was obtained from Marine Chemicals (Cochin, India). 3M™ Scotchpack™ 9733 backing membrane and 3M™ Scotchpack™ 1022 release liner were obtained from 3M (USA). Cellulose acetate membrane (0.45 $\mu$m) was obtained from Pall Corporation (USA). HP- β-CD was obtained from Finer Chemicals Ltd (Ahemadabad, India), oleic acid and propylene glycol was obtained from Research Lab (Mumbai, India). All other chemicals used were of pharmaceutical grade.

### Methods

*Compatibility studies of drug and polymers*

The pure drug, the mixture of polymers (HPMC, Chitosan and Eudragit RL 100), 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 (XRD) were obtained using an 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 $3^3$ full factorial design was applied. The batch 1 containing minimum quantity of all polymers showed minimum thickness, while the batch 27 containing higher quantity of all polymers showed maximum thickness. As we know thickness of the patch will affect each and every physical parameter (folding endurance, moisture content, moisture uptake, etc.), also it will affect 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, and chitosan polymer along with 200 mg of drug and 5% wt/wt of plasticizer, triethyl citrate. A $3^3$ full factorial design were applied to formulate the matrix type transdermal film of gliclazide and to determine the effect of each polymer on the release pattern of drug from the transdermal drug delivery system. The layout of factorial design is shown in Table 1 whereas amount of variables

are shown in Table 2. Hydrophilic materials i.e. HPMC and chitosan were dissolved in 10 ml water and hydrophobic materials i.e. Eudragit RL 100 and gliclazide 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 accomplish a homogeneous mixture. The resulting whole solution was poured in a Petri dish containing mercury. Mercury is used to avoid the adherence of film to dish. The solvent were allowed to evaporate for 24 h 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 a desiccator until further use.

*Collection and preparation of the rat skin*

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

*Evaluation of transdermal formulation*

The 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.[17] Longitudinal strips (1.5×0.75 cm) were cut out from the prepared medicated matrix films. The initial length of films was measured, and then it was 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 constriction of strips and a zero percent of constriction was considered to be equal to 100% flatness.[17]

**Table 1: Full factorial experimental design layout**

| Batch | X1 | X2 | X3 | Batch | X1 | X2 | X3 |
|---|---|---|---|---|---|---|---|
| 1 | -1 | -1 | -1 | 15 | 1 | 0 | 0 |
| 2 | 0 | -1 | -1 | 16 | -1 | 1 | 0 |
| 3 | 1 | -1 | -1 | 17 | 0 | 1 | 0 |
| 4 | -1 | 0 | -1 | 18 | 1 | 1 | 0 |
| 5 | 0 | 0 | -1 | 19 | -1 | -1 | 1 |
| 6 | 1 | 0 | -1 | 20 | 0 | -1 | 1 |
| 7 | -1 | 1 | -1 | 21 | 1 | -1 | 1 |
| 8 | 0 | 1 | -1 | 22 | -1 | 0 | 1 |
| 9 | 1 | 1 | -1 | 23 | 0 | 0 | 1 |
| 10 | -1 | -1 | 0 | 24 | 1 | 0 | 1 |
| 11 | 0 | -1 | 0 | 25 | -1 | 1 | 1 |
| 12 | 1 | -1 | 0 | 26 | 0 | 1 | 1 |
| 13 | -1 | 0 | 0 | 27 | 1 | 1 | 1 |
| 14 | 0 | 0 | 0 | | | | |

**Table 2: Amount of variables in a $3^3$ factorial design**

| Coded level | -1 | 0 | 1 |
|---|---|---|---|
| HPMC (X1) mg | 400 | 450 | 500 |
| Eudragit RL 100 (X2) mg | 300 | 350 | 400 |
| Chitosan (X3) mg | 50 | 75 | 100 |

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 (2 cm × 2 cm) 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 set 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 $kg/cm^2$.

To determine the percentage of moisture content, the films were weighed individually and kept in a desiccator containing activated silica at room temperature for 24 h. Individual films were weighed repeatedly, until they showed a constant weight.[19] To determine the percentage of moisture uptake, a weighed film was kept in a desiccator at room temperature for 24 h, taken out and exposed to 84% relative humidity in a 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 weights with respect to the initial weight.[20]

*Determination of drug content*

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

*Skin irritation study*

Irritation may be defined as a local, reversible inflammatory response of the skin to the application of an agent without the involvement of an immunological mechanism.

Skin irritation studies were performed on healthy rabbits (CPCSEA approval Number BVCPK/CPCESA/IAEC/17/2009, Institutional Animal Ethics Committee: Reg. No. 988/C/06/CPCSEA). The dorsal surface of the rabbits was cleaned, and

the hairs were removed by shaving. The skin was cleansed with rectified spirit. Treated skin areas were then evaluated according to a modified Draize scoring method and the irritation index was evaluated. The first or "Primary Irritation Index" (P.I.I.) was studied which is an average value reflecting irritation both immediately after dressing removal and 72 h later.

The rabbits were divided into two groups (n = 6). Group I received prepared transdermal patch and Group II received 0.8% v/v aqueous solution of formalin as a standard irritant.[21] At 24 and 72 h after test article application, the test sites were examined for dermal reactions in accordance with the Draize scoring criteria[22] [Table 3].

The scores for erythema and edema are totaled for all rabbits at 24 and 72 h. The primary irritation index (P.I.I.) is calculated, based on the sum of the scored reactions divided by 24 [two coring intervals multiplied by two test parameters multiplied by six rabbits (Thomas)] and evaluated for the any skin reaction.

*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. The modified cell having higher capacity (27 ml) is used to maintain sink condition. This skin was mounted between the donor and receptor compartment of a diffusion cell. 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 of pH 7.4 containing 0.5% of sodium lauryl sulfate. The hydrodynamics in the receptor compartment were 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.[23] The diffusion was carried out for 12 h and 1 ml sample was withdrawn at an interval of 1 h. 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 HP β- CD (GCD)*

As the drug is very slightly soluble in water, its complex was formed with HP β-CD in the molar ratio of 1:2 by the 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 h at 75°C. After that it was dried at 50°C, for one day, crushed, sieved, stored at temperature of 25±2.0°C, and relative humidity between 40 and 50%.

*Preparation of patch containing chemical enhancers*

The batch B 25 showed extended (minimum) release hence, composition of this batch was selected for preparation of a patch containing a chemical enhancer. The various trials for permeation study are shown in Table 4. The patches were prepared by the same procedure mentioned for preparation of the plain transdermal patch except that in this preparation plain 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 of 3%, 6%, 10% solution of oleic acid in propylene glycol were added for the preparation of patches.

**Table 3: Draize evaluation of dermal reaction**

| Score | Reaction | |
|---|---|---|
| | Erythematic | Edema |
| 1 | No erythema | No edema |
| 2 | Very slight erythema | Very slight edema |
| 3 | Well-defined erythema | Slight edema |
| 4 | Moderate to severe erythema | Moderate edema |
| 5 | Severe erythema | Severe edema |

**Table 4: Trials for permeation study**

| Trial | Formulation |
|---|---|
| T1 | Gliclazide |
| T2 | GCD |
| T3 | GCD + Propylene Glycol |
| T4 | GCD + Propylene Glycol + Oleic acid (3) |
| T5 | GCD + Propylene Glycol + Oleic acid (6) |
| T6 | GCD + Propylene Glycol + Oleic acid (10) |

Figures in parenthesis are in percentage

## RESULTS AND DISCUSSIONS

**Compatibility studies of drug and polymers**

The 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 are shown in Figures 1 and 2, respectively. The characteristic peaks are shown in Table 5. From the IR spectra, 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.

The XRD patterns of pure drug and patch are represented in Figure 3. The diffractograms of pure gliclazide and patch exhibited a series of intense peaks, which are indicative of their crystallinity. In the case of a patch, the total number of peaks is 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 the patch.

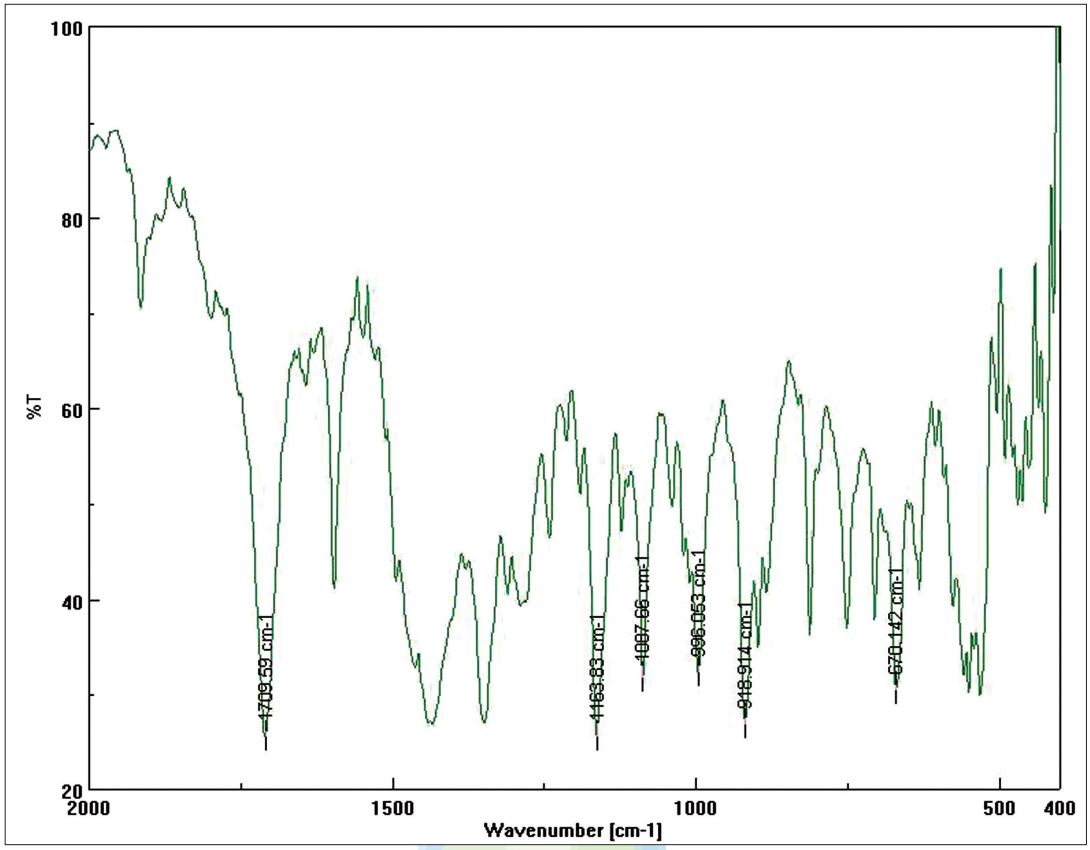


**Figure 1:** FTIR spectra of gliclazide

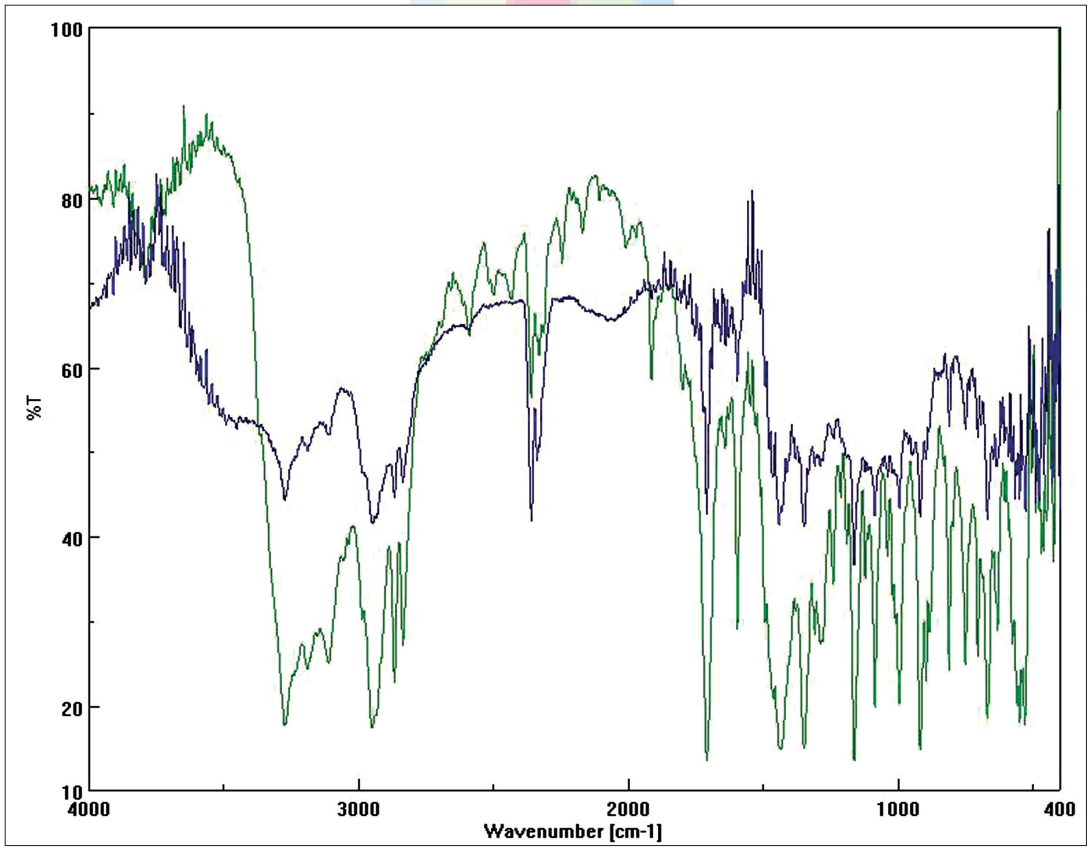


**Figure 2:** FTIR spectra of gliclazide (Green) and physical mixture of drug with HPMC, Eudragit RL 100, and chitosan (Blue)

**Table 5: Characteristic peaks of group**

| Wave number range | Group |
|---|---|
| 1710 | C = O Stretching |
| 1162 | S = O Vibration |
| 1089 | C = $(CH)^2$ Bending |
| 997 | C = C Bending |
| 920 | Aromatic P-substitution phenyl |
| 667 | Aromatic ring |

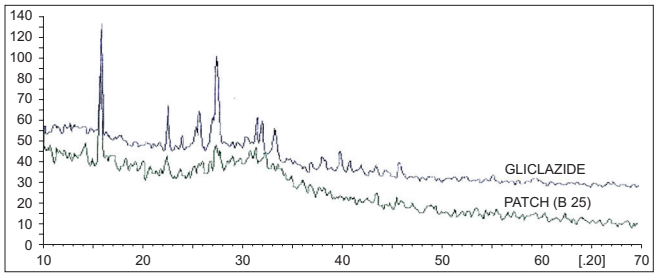


**Figure 3:** XRD pattern of pure drug and patch

**Table 6: Evaluation of transdermal patch of gliclazide (*n*=3)**

| Code | Thickness (mm) | Folding endurance | Tensile strength ($Kg/cm^2$) | % Moisture content | % Moisture uptake | % Drug content | % Drug release in 12 h |
|---|---|---|---|---|---|---|---|
| B1 | 0.19±0.01 | 142.33±2.52 | 0.536±0.002 | 5.26±0.12 | 10.61±0.43 | 103.81±2.12 | 74.07±2.14 |
| B2 | 0.186667±0.005 | 138±2.00 | 0.527±0.025 | 5.30±0.09 | 11.05±0.23 | 98.40±1.25 | 76.04±1.46 |
| B3 | 0.186667±0.015 | 136.33±1.53 | 0.517±0.032 | 5.41±0.18 | 10.86±0.65 | 102.64±0.98 | 79.17±.958 |
| B4 | 0.186667±0.025 | 148.33±0.58 | 0.557±0.023 | 5.04±0.14 | 10.43±0.14 | 97.28±2.14 | 71.56±1.02 |
| B5 | 0.186667±0.020 | 144.33±1.53 | 0.543±0.032 | 4.86±0.13 | 10.12±0.36 | 104.23±1.04 | 73.57±1.58 |
| B6 | 0.183333±0.015 | 141.33±0.58 | 0.530±0.010 | 5.04±0.19 | 10.43±0.21 | 99.33±1.06 | 75.54±2.58 |
| B7 | 0.18±0.01 | 154.66±1.15 | 0.567±0.021 | 4.14±0.08 | 9.58±0.58 | 101.16±1.82 | 68.81±3.45 |
| B8 | 0.183333±0.015 | 150.33±1.53 | 0.555±0.030 | 4.86±0.14 | 9.52±0.43 | 101.53±2.14 | 71.1±1.35 |
| B9 | 0.183333±0.005 | 146.33±2.52 | 0.544±0.035 | 4.96±0.13 | 9.76±0.59 | 99.41±3.41 | 73.15±2.14 |
| B10 | 0.196667±0.005 | 138.33±3.51 | 0.536±0.036 | 5.88±0.2 | 11.76±0.42 | 99.37±2.19 | 73.21±3.47 |
| B11 | 0.2±0.017 | 135±1.00 | 0.523±0.022 | 5.95±0.11 | 11.88±0.27 | 104.34±2.92 | 75.42±4.26 |
| B12 | 0.196667±0.005 | 131.33±1.15 | 0.514±0.013 | 5.36±0.12 | 11.50±0.37 | 97.05±1.24 | 77.39±1.07 |
| B13 | 0.196667±0.015 | 145.33±0.58 | 0.550±0.049 | 5.56±0.14 | 11.40±0.61 | 98.82±2.12 | 70.61±2.73 |
| B14 | 0.2±0.01 | 141.66±1.15 | 0.538±0.025 | 5.63±0.19 | 11.52±0.22 | 99.65±1.25 | 72.84±0.83 |
| B15 | 0.196667±0.005 | 137±1.00 | 0.527±0.037 | 5.66±0.14 | 11.58±0.44 | 96.50±1.02 | 74.84±3.26 |
| B16 | 0.196667±0.005 | 150.33±1.53 | 0.565±0.059 | 5.73±0.11 | 10.75±0.54 | 99.37±2.14 | 68.28±2.48 |
| B17 | 0.193333±0.015 | 146±1.73 | 0.550±0.026 | 5.77±0.13 | 10.81±0.24 | 102.29±3.25 | 70.52±1.57 |
| B18 | 0.19±0.01 | 143.33±1.15 | 0.542±0.022 | 5.66±0.18 | 11.11±0.64 | 96.91±2.58 | 72.58±2.46 |
| B19 | 0.21±0.02 | 134±1.73 | 0.530±0.010 | 6.59±0.14 | 13.39±0.43 | 96.90±1.25 | 72.5±1.27 |
| B20 | 0.203333±0.020 | 131.33±1.15 | 0.521±0.008 | 6.63±0.13 | 13.06±0.73 | 105.32±3.67 | 76.59±3.67 |
| B21 | 0.203333±0.030 | 112.33±1.15 | 0.517±0.012 | 6.59±0.17 | 11.88±0.13 | 103.40±3.14 | 76.57±2.92 |
| B22 | 0.206667±0.032 | 142±3.00 | 0.547±0.035 | 6.18±0.13 | 12.50±0.44 | 96.71±2.82 | 70.05±1.42 |
| B23 | 0.203333±0.040 | 137±1.73 | 0.536±0.017 | 6.21±0.11 | 12.56±0.26 | 100.40±3.57 | 72.21±1.94 |
| B24 | 0.2±0.02 | 134.33±0.58 | 0.525±0.021 | 6.25±0.12 | 12.21±0.63 | 99.02±3.48 | 74.17±1.52 |
| B25 | 0.203333±0.005 | 146.33±1.53 | 0.561±0.025 | 6.29±0.1 | 11.85±0.54 | 100.81±1.78 | 67.71±2.58 |
| B26 | 0.2±0.01 | 143.66±0.58 | 0.550±0.040 | 5.78±0.11 | 12.02±0.75 | 100.53±0.98 | 69.92±1.48 |
| B27 | 0.196667±0.020 | 140±1.00 | 0.541±0.030 | 5.81±0.18 | 12.08±0.23 | 103.15±1.25 | 72.27±3.54 |

### Formulation of transdermal patches having uniform thickness

Non-uniform thickness in the patches shows a difference in their physical parameters as well as in 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 patches have been prepared were taken of uniform diameter (8.7 cm). The maximum differences between the thicknesses of patches were 0.02 mm, which indicates that all the prepared patches were of uniform thickness.

### Evaluation of transdermal formulation

The results of the characterization of the patches are shown in Table 6. The thicknesses of all the batches were nearly similar because the quantity of polymers was 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, chitosan, and Eudragit RL 100) 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 100% flatness, which indicates negligible amount of constriction

of the prepared transdermal patches. Thus, a patch does not constrict, when it is applied on the skin.

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 112 and 154. It was found to be high in patches containing higher amount of the Eudragit RL 100. Strength of the film and the risk of film cracking were indicated by its tensile strength. The prepared transdermal films showed 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 lies in between 0.514 and 0.567 kg/cm$^2$; the difference depends on the composition of polymer used. There was an increase in tensile strength with an increase in Eudragit RL 100 in the polymer blend. Also there was a decrease in the tensile strength with increasing concentration of chitosan and HPMC.

Moisture content and moisture uptake studies indicate that the increase in the concentration of hydrophilic polymer i.e. HPMC and chitosan was directly proportional to the increase in moisture content and moisture uptake of the patches. Eudragit RL 100 is a hydrophobic polymer; hence, there is a decrease in the moisture content with an increase in Eudragit RL 100 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 protects 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 have been reported for matrix film containing hydrophilic polymers.

**Determination of drug content**

Drug content of all batches were well within the range between 96.50 and 105.32±3.67%. 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.

**Skin irritation study**

The dermal observation of skin irritation study is shown in Table 7. In Group I, there is no sign of either erythema or edema after 24 h of application, but there is very slight erythema or edema observed in some rabbit after the application of 72 h. According to Draize *et al*, formulations producing scores of 2 or less are considered negative (no skin irritation). The PII for the test was found to be 0.084 and it indicates barely perceptible irritation. The skin irritation test

**Table 7: Dermal observation of skin irritation test**

| Rabbit no. | Reaction | Test (I) | | Standard (II) | |
|---|---|---|---|---|---|
| | | 24 h | 72 h | 24 h | 72 h |
| 1 | Erythema | 0 | 0 | 2 | 2 |
| | Edema | 0 | 1 | 1 | 2 |
| 2 | Erythema | 0 | 0 | 1 | 3 |
| | Edema | 0 | 0 | 2 | 2 |
| 3 | Erythema | 0 | 0 | 1 | 2 |
| | Edema | 0 | 0 | 1 | 2 |
| 4 | Erythema | 0 | 0 | 1 | 3 |
| | Edema | 0 | 0 | 1 | 3 |
| 5 | Erythema | 0 | 1 | 1 | 2 |
| | Edema | 0 | 0 | 1 | 2 |
| 6 | Erythema | 0 | 0 | 2 | 2 |
| | Edema | 0 | 0 | 1 | 2 |

of the transdermal formulation showed a skin irritation score (erythema and edema) of less than 1. Hence, the developed transdermal formulations are free from the skin irritation. In Group II, which contain formalin as a standard irritant, showed the slight to sever skin irritation reaction.

***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. Drug release profiles from different formulations are shown in Figures 4-6.

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 B3 containing highest amount of HPMC showed maximum release 79.17%, while batch B21 containing both HPMC and chitosan at maximum concentration showed 76.59% release due to the sustaining property of chitosan. The batch B25 containing the higher proportion of the Eudragit RL 100 shows only 67.71% drug release within 12 h, which was the lowest amount of the drug release among the all 27 batches.

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

In the present study, complexation of drugs with HP β–CD has

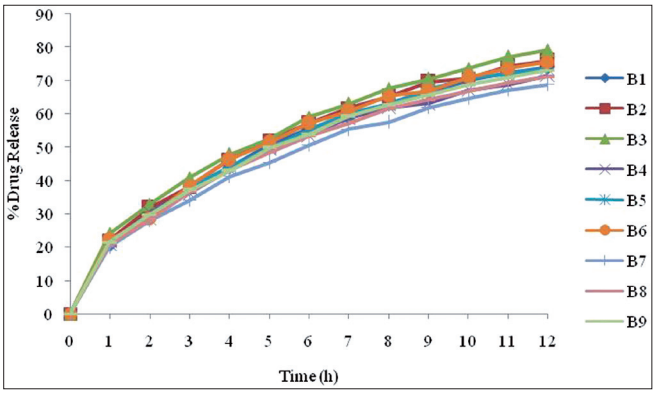


**Figure 4:** Drug release profile of B1- B9

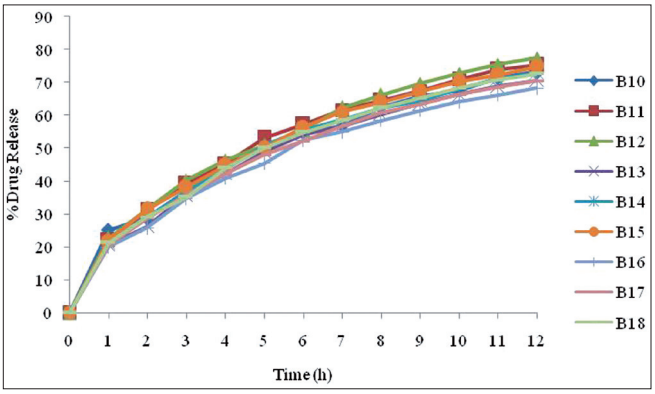


**Figure 5:** Drug release profile of B10- B18

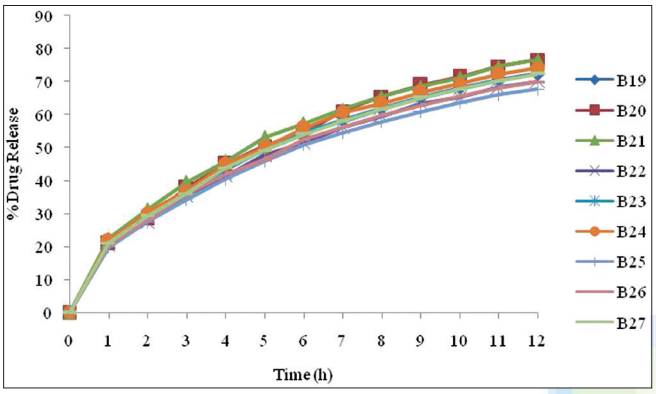


**Figure 6:** Drug release profile of B19- B27

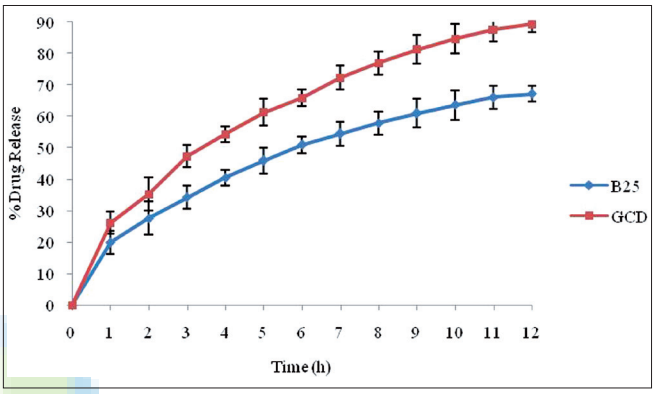


**Figure 7:** Comparison of drug release from B25 and GCD

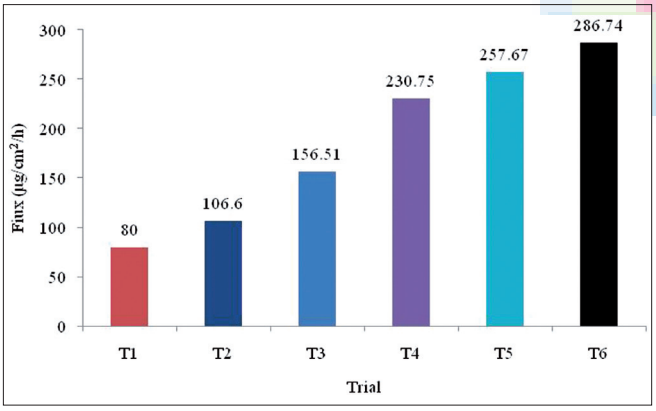


**Figure 8:** Permeation flux of gliclazide from different trial

been used to enhance aqueous solubility, skin permeability, and drug stability. The result of complexation of drug with HP β–CD showed both an increase in the permeation rate through the membrane and an increase in the solubility of drug [Figure 7]. The percentage of drug release from the complex after 12 h was found to 89.25% compared with B25 which showed only 67.71% release. The permeation flux [(Average Drug release/hour) × 1000 ÷ Surface area] of plain gliclazide patch (B25) was found to be 80.00 $\mu g/cm^2/h$, whereas the flux of complex was 106.60 $\mu g/cm^2/h$. Hence, we can conclude that there is an increase in the permeation of drug from the complex.

*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, oleic acid, and propylene glycol has been studied. The patch T6 containing propylene glycol 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 Figure 8. 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.[24] In contrast, 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.[25]

## CONCLUSION

The transdermal matrix patches of gliclazide were prepared by film casting techniques on mercury, and effects 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.

## REFERENCES


1. Singh P, Maibach HI. Iontophoresis in drug delivery: Basic principles and applications. Crit Rev Ther Drug Carrier Syst 1994;11:161-213.
2. Joseph R, Robinson, Vincent HL. Controlled drug delivery fundamentals and applications. Revised and Expanded. Lee: Marcel Dekker, Inc;2005. p. 524.
3. Moser K, Kriwet K, Naik A, Kalia YN, Guy RH. Passive skin penetration enhancement and its quantification *in vitro* . Eur J Pharm Biopharm 2001;52:103-12.
4. Albery WJ, Hadgraft J. Percutaneous absorption: In vivo experiments. J Pharm Pharmacol 1979;31:140-7.
5. Bodde HE, Van den Brink I, Koerten HK, Dehaan FHN. Visualization of *in vitro* percutaneous penetration of mercuric chloride transport through intercellular space versus cellular uptake through desmosomes. J Cont Rel 1991;15:227-36.
6. Heisig M, Lieckfeldt R, Wittum G, Mazurkevich G, Lee G. Non steady-state descriptions of drug permeation through stratum corneum. The biphasic brick-and-mortar model. Pharm Res 1996;13:421-6.
7. Vollmer U, Muller BW, Mesens J, Wilffert B, Peters T. In vivo skin pharmacokinetics of liarozole: Percutaneous absorption studies with different formulations of cyclodextrin derivatives in rats. Int J Pharm 1993;99:5l-8.
8. Kassan DG, Lynch AM, Stiller MJ. Physical enhancement of dermatologic drug delivery: Iontophoresis and phonophoresis. J Am Acad Dermatol 1996;34:657-66.
9. Williams AC, Barry BW. Terpenes lipid-protein-partition theory of skin penetration enhancement. Pharm Res 1991;8:17-24.
10. Ogiso T, lwaki M, Paku T. Effect of various enhancers on transdermal penetration of indomethacin and urea, and relationship between penetration parameters and enhancement factors. J Pharm Sci 1995;84:482-8.
11. Smith SW, Anderson BD. Human skin permeability enhancement by lauric acid under equilibrium aqueous conditions. J Pharm Sci 1995;84:551-6.
12. Green PG, Hinz RS, Kim A, Cullander C, Yamane G, Szoka FC, *et al*. Transdermal lontophoresis of amino acids and peptides *in vitro* . J Cont Rel 1992;21:187-90.
13. Yamane MA, Williams AC, Barry BW. Terpene penetration enhancers in propylene glycol/water co-solvent systems: Effectiveness and mechanism of action. J Pharm Pharmacol 1995;47:978-89.
14. Aqil M, Ali A. Monilithic matrix type transdermal drug delivery systems of pinacidil monohydrate: *In vitro* characterization. Eur J Pharm Biopharm 2002;54:161-4.
15. Aqil M, Ali A, Sultana Y, Dubey K, Najmi AK, Pillai KK. In vivo characterization of monolithic matrix type transdermal drug delivery systems of pinacidil monohydrate: A technical note. AAPS PharmSciTech 2006;7:E6.
16. Amnuaikit C, Ikeuchi I, Ogawara K, Higaki K, Kimura T. Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. Int J Pharm 2005;289:167-78.
17. Bhatt DC, Dhake AS, Khar RK, Mishra DN. Development and in-vitro evaluation of transdermal matrix films of metoprolol tartrate. Yakugaku Zasshi 2008;1325-31.
18. Tanwar YS, Chauhan CS, Sharma A. Development and evaluation of carvedilol transdermal patches. Acta Pharm 2007;57:151-9.
19. Mukherjee B, Kanupriya, Mahapatra S, Das S, Patra B. Sorbitan monolaurate 20 as a potential skin permeation enhancer in transdermal patches. The J App Res 2005;1:96-108.
20. Ubaidulla U, Reddy MV, Ruckmani K, Ahmad FJ, Khar RK. Transdermal therapeutic system of carvedilol: Effect of hydrophilic and hydrophobic matrix on *in vitro* and in vivo characteristics. AAPS PharmSciTech 2007;8:2.
21. Mutalik S, Udupa N, Glibenclamide transdermal patches: Physicochemical, pharmacodynamic, and pharmacokinetic evaluations. J Pharm Sci 2004;93:1577-94.
22. Thomas J. Skin irritation test in the rabbit of water jel burn dressing, Available from: www.waterjel.com/public/SkinIrritationTest.pdf [accessed on 2009 Oct 3].
23. Taepaiboon P, Rungsardthong U, Supaphol P. Vitamin-loaded electrospun cellulose acetate nanofiber mats as transdermal and dermal therapeutic agents of vitamin A acid and vitamin E. Eur J Pharm Biopharm 2007;67:387-97.
24. Barry BW, Bennett SL. Effect of penetration enhancers on the permeation of mannitol, hydrocortisone and progesterone through human skin. J Pharm Pharmacol 1987;39:535-46.
25. Aungst BJ, Rogers NJ, Shefter E. Enhancement of naloxone penetration through human skin *in vitro* using fatty acids, fatty alcohol, surfactant, sulfoxides and amides. Int J Pharm 1986;33: 225-34.


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