

## Original Research Article

# Enhancement of *In Vitro* Skin Transport and *In Vivo* Hypoglycemic Efficacy of Glimepiride Transdermal Patches

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## Abstract

**Purpose:** To utilize hydroxybutyl- $\beta$ -cyclodextrin (HB- $\beta$ -CD) and polyvinyl pyrrolidone (PVP) for the enhancement of the transdermal delivery of glimepiride (GMD).

**Methods:** Matrix-type transdermal patches containing GMD, drug coprecipitate or its inclusion complex were prepared using different gelling agents, viz, hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carbopol and chitosan. *In vitro* skin permeation evaluation of the formulations was conducted using automated diffusion system. Selected patch formulations were assessed for hypoglycemic activity as well as for GMD plasma concentration in rats.

**Results:** GMD- hydroxybutyl- $\beta$ -cyclodextrin (HB- $\beta$ -CD) binary systems (1:2 molar ratio) enhanced GMD aqueous solubility by > 10-fold. Diffusion test showed improved release of GMD-HB- $\beta$ -CD inclusion complex compared with GMD alone. Maximum cumulative amounts of GMD- HB- $\beta$ -CD that permeated through rat skin was 26.97 and 14.28  $\mu\text{g}/\text{cm}^2$  for patches prepared with chitosan and HPMC, respectively. Thus, GMD-chitosan patches showed significantly higher ( $p < 0.05$ ) drug permeation than GMD-HPMC after 6 h. Both chitosan and HPMC patches of GMD-HB- $\beta$ -CD demonstrated substantial reduction ( $p < 0.05$ ) in blood glucose level ( $192.67 \pm 21.18$  and  $201 \pm 15.11$  mg/ dl, respectively), compared with the baseline value of 240 mg/ dl.

**Conclusion:** Application of chitosan and HPMC transdermal patches of GMD-HB- $\beta$ -CD can serve as a potential alternative to peroral GMD with improved bioavailability and patient compliance.

**Keywords:** Glimepiride, Transdermal patch, Coprecipitate, Inclusion complex, Hydroxypropyl methylcellulose, Polyvinyl pyrrolidone, Chitosan, Skin permeation

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## INTRODUCTION

The market value of transdermal drug delivery systems (TDD) is growing slowly, but steadily. Implementations of recent innovative technologies to deliver drugs have revolutionized

success in the field of transdermal drug delivery [1,2]. Transdermal patches, if successful, are considered alternative convenient strategy of drug administration when the oral route is not feasible. The transdermal route offers several distinct advantages as it is devoid of the

variability in gastrointestinal absorption including influence of pH and motility; avoid hepatic first-pass effect; and reduce the typical dosing schedule, hence improve patient compliance [3]. Efforts have been devoted to overcome the permeability barrier of the skin through development of various approaches [4]. Chemical and physical enhancement techniques have been developed to increase the series of drugs available for transdermal delivery [5].

GMD is a third generation sulfonylurea derivative and one of the top three prescribed oral antidiabetic drugs. However, GMD as well as with other oral hypoglycemic drugs has shown several adverse and potential side effects related to hypoglycemia with inaccurate dosing. Recently, there is a growing interest to enhance and control the transdermal delivery of GMD using matrix of natural and synthetic materials [6-9]. The aim of the current study was to develop GMD transdermal patches to control insulin non-dependent diabetes (type II).

## EXPERIMENTAL

### Chemicals

GMD was a gift from Medical Union Pharmaceuticals (MUP), Abu Sultan, Ismailia, Egypt. Linoleic acid, Carveol, Isopropyl myristate, Polyvinylpyrrolidone (PVP) K30, PVP K90, Carbopol 940® (C-940®), Terpene-4-ol and hydroxypropyl methylcellulose (HPMC) viscosity 4000-cp (2 % solution) were procured from Acros Organics, New Jersey, USA. Dimethyl sulfoxide (DMSO) was purchased from Techno Pharmchem, Bahadurgarh, India. Hydroxypropyl cellulose (HPC/Klucel) average MW of 1,000,000, Chitosan high molecular weight, acetonitrile and propylene glycol (PG) from Sigma-Aldrich, St. Louis, USA. Potassium dihydrogen orthophosphate, was from BDH Chemicals Ltd., Dorset, UK. Alpha,  $\beta$ ,  $\gamma$ , hydroxy propyl (HP) and hydroxy butyl- $\beta$ -cyclodextrin (HB-  $\beta$ -CD) were generous gifts from Nihon Shokuhin Kako Co, Ltd, Japan.

### Preparation of drug-solid dispersions and inclusion complexes

Drug-CD inclusion complexes were prepared using  $\alpha$ ,  $\beta$ ,  $\gamma$ -CD, HP and HB- $\beta$ -CD in molar ratios of 1:1 and 1:2 (drug-to-CD) by kneading technique [10]. Drug coprecipitates with PVP K30 and K90 were prepared at 1:1, 1:2 and 1:4 (w/w) drug-to-polymer ratio employing the same technique.

### Solubility study of GMD inclusion complexes and coprecipitates

The equilibrium solubility of GMD was determined for the inclusion complexes, coprecipitates and the drug alone. Excess amount of each sample was added to 3 mL of distilled water and agitated at 37 °C for 48 h in shaking water bath. The resulting suspensions were centrifuged and filtered. The filtrates were diluted and analyzed using modified method for their GMD contents using Agilent 1200 series HPLC system (Agilent, USA) [11]. Mobile phase was acetonitrile and 0.02 M phosphate buffer of pH 5 (60: 40, V/V) with flow rate of 1.5 mL/min and detected at 238 nm.

### Fabrication of transdermal patches

Transdermal patches containing GMD, drug-coprecipitate or its inclusion complex were prepared by evaporation technique using different viscosity increasing agents (HPC, HPMC, C-940®, and Chitosan), plasticizer (PG) and skin permeation enhancer (DMSO). HPMC, HPC and C-940® aqueous solutions were prepared using 3, 2 and 0.3 % of HPMC, HPC and C-940®, respectively. PG (1 % w/ w) and DMSO (1 % w/ w) were added. A known weight of GMD or its equivalent GMD- HB  $\beta$ CD/ GMD-PVP K90 of solid-dispersion/coprecipitate was added to the gel mixture. The pH of the formulation was adjusted to pH 8 in case of C-940®. For chitosan solution, chitosan was dispersed in 1.5 % acetic acid solution. GMD transdermal patches were prepared by pouring polymeric solutions in petri dishes covered with silicone-coated liner (Scotchpak™, 3M, St Paul, USA), kept at room temperature for 20 min and then at 40 °C in an oven until complete evaporation of the solvent. The patches were then covered with backing membrane (CoTran™, 3M, St Paul, USA), packed in aluminum foil and stored in a desiccator.

### Compatibility studies

Drug/polymers compatibility was studied using Fourier transforms infrared (FTIR) spectrophotometer (Perkin Elmer Spectrum One, Model 16 PC, Germany), and differential scanning calorimetry (DSC, Shimadzu DSC TA-50 ESI DSC apparatus, Tokyo, Japan).

### In vitro GMD release study

The diffusion of GMD from the prepared patches and corresponding gels containing either plain GMD or its coprecipitate/ inclusion complex was carried out using automated franz diffusion cell

apparatus (MicroettePlus™, Hanson Research, Chatsworth, CA, USA) with 1.76 cm<sup>2</sup> of diffusion area. The patch was placed in position and covered with a synthetic nylon membrane of 0.45 μm pore size and mounted on the donor chamber. Phosphate buffer saline of pH 5.8 was used as a receiver medium in the receptor chamber in which the temperature was kept at 32 ± 0.5 °C and the stirring rate was 400 rpm. Samples were analyzed by HPLC. The release patterns of GMD were determined by plotting the cumulative amount of the drug permeated (Q) per unit area as a function of time. The steady-state flux (JSS) was calculated from the slope. The permeability coefficient (Pc) was calculated by dividing the flux by the initial drug load (C0) [12]. The enhancement factor (EF) was calculated by dividing Q of GMD transdermal patch by that of its corresponding prepared gel (control). The diffusion coefficient (D) was obtained by plotting Q versus square root of time min as in Eq 1.

$$D = [\text{slope}/2C_0]^2 \times \pi \dots \dots \dots (1)$$

### Ex vivo skin permeation of GMD

Full thickness skin of 3 × 3 cm area from the abdominal region of shaved male Wistar rats were excised, freed from any subcutaneous fats, and examined using magnifier to assure skin integrity. The prepared skin was mounted between the donor and receptor compartments of the diffusion cells with the dermal side in direct contact with the receptor medium. Permeation from GMD patches prepared with chitosan and HPMC containing GMD as an inclusion complex with HB-β-CD were evaluated. The amounts of GMD permeated were determined using HPLC.

### Assessment of GMD transdermal patch hypoglycemic activity

Male Wistar rats weighing 200 - 250 g were maintained on standard diet under controlled conditions. The animals were provided by King Fahd Medical Research Center, Jeddah, Saudi Arabia. Animal use was approved by the local Institutional Review Board for Preclinical & Clinical Research (approval date: June 27, 2013) and conformed to the guidelines in the care and use of laboratory animals [13]. Diabetes was induced by intraperitoneal injection of fasted rats with 50 mg/kg streptozotocin 10 - 14 days prior to the study. Rats with fasting blood glucose levels in the range of 200-300 mg/ dl were selected. Animals were divided into 7 groups of 12 rats/each. The first and second groups (negative controls) were subjected to transdermal application of plain HPMC and chitosan patches,

respectively. Third group (positive control A) was given commercial GMD tablets orally in a dose of 10 mg/ kg body weight [14]. The Fourth and Fifth groups (Positive controls B and C) were subjected to transdermal application of GMD in HPMC and chitosan patches, respectively. The sixth and seventh groups were subjected to transdermal application GMD, 10 mg/ kg, as an inclusion complex with HB-β-CD using HPMC and chitosan patches, respectively. Blood glucose levels were assessed using Accu-Chek® Go (Roche, Mannheim, Germany).

### Pharmacokinetic evaluation of GMD patches

Plasma GMD concentrations in the tested groups were analyzed by LC-MS/MS method applying Kim et al reported procedure [15] using HPLC Agilent 1200 system (Agilent Technologies, Germany) with a detector, Agilent 6420, triple quad mass spectrometer (TQ-MS) controlled by MassHunter software. Kinetica™ (Version 4, Thermo Electron Corporation, MA, USA) was used to compute the following pharmacokinetic parameters namely; maximum plasma concentration (C<sub>max</sub>), time point of maximum plasma concentration (t<sub>max</sub>), elimination rate constant (k<sub>e</sub>), area under the plasma concentration–time curve (AUC), and mean residence time (MRT).

### Statistical analysis

Data, expressed as mean ±SD, were analyzed using GraphPad Prism 6 (GraphPad Software, California, USA). Two-way ANOVA followed by Tukey's multiple comparison test were used to assess the significance of differences between quantitative variables. *P* < 0.05 was considered statistically significant.

## RESULTS

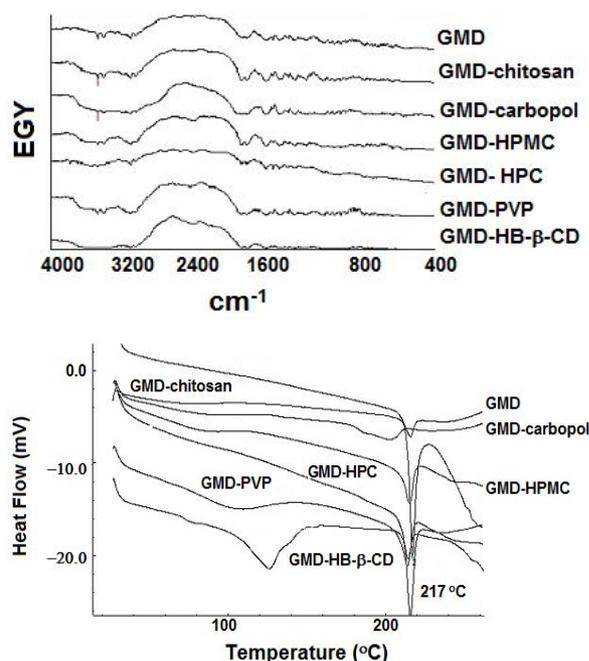
### GMD solubility

GMD-CD binary systems results indicated that, GMD aqueous solubility enhanced by more than 10 times with HB-β-CD (1:2 molar ratio) compared with GMD alone (Data not shown). In addition, PVP K90 (1:2 weight ratio) showed improved solubility results.

### Physicochemical compatibility

FTIR of pure GMD showed characteristic sharp peaks at 3369 cm<sup>-1</sup> and 3288 cm<sup>-1</sup> due to N-H stretching, 1707 cm<sup>-1</sup> and 1674 cm<sup>-1</sup> due to carbonyl group, 1345 cm<sup>-1</sup> indicating C-N stretching vibration, 1153 cm<sup>-1</sup> confirmed S=O stretching vibration [9] as depicted in figure (1A).

Mixing the drug with the studied polymers; chitosan, carbopol, HPMC, HPC, PVP and CD does not greatly affect the characteristic peaks of the drug except for CD which could be attributed to drug-cyclodextrin inclusion complexation. DSC thermograms of pure drug exhibited endothermic peaks at about 217 °C corresponding to its melting point, indicating GMD crystalline nature [9], Figure (1B). Thermograms of the drug-polymer physical mixtures showed the same characteristic peak of GMD, indicating the absence of possible interaction.



**Fig 1:** FTIR spectra (A) and DSC thermograms (B) of GMD and GMD-polymer physical mixtures

### Drug diffusion

Permeation parameters of the prepared patches showed that the highest cumulative amount of

GMD permeated during 12 h was achieved from chitosan and HPMC in the form of GMD- HB-β-CD (Table 1). Figure 2A illustrates the release pattern for GMD-complex and GMD alone chitosan and HPMC patches. The results indicated that, release of GMD from its inclusion complex with HB-β-CD was improved compared with its corresponding drug alone.

### Ex vivo skin permeation

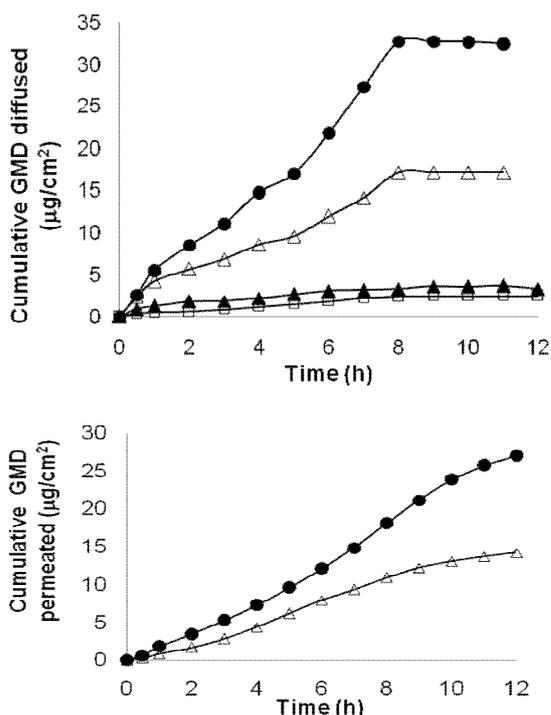
Chitosan and HPMC containing GMD as an inclusion complex with HB-β-CD were used in this study. The selected patches exhibited permeation of GMD through rat skin at the end of 12 h (Figure 2B) by 26.973 and 14.28  $\mu\text{g}/\text{cm}^2$  for chitosan and HPMC patches, respectively. GMD-chitosan patches showed significant ( $p < 0.05$ ) improvement in permeation data compared with GMD-HPMC data after 6 h according to ANOVA.

### Hypoglycemic activity

Results revealed that the commercial product lowered significantly ( $p < 0.05$ ) the blood glucose level at 2, 4, and 6 h from the start of the treatment, compared with the corresponding control at time zero (Table 2). Positive control groups 4 and 5 showed no significant reduction ( $p < 0.05$ ) in glucose levels. On the other hand, group 6 lowered significantly ( $p < 0.05$ ) the blood glucose level compared to control at time zero after 6 h from the start of the treatment. Group 7 lowered significantly ( $p < 0.05$ ) the blood glucose level, after 4, 6 and 12 h from the start of the treatment (Table 2). These results revealed that administration of GMD-chitosan patches, group 7, provoked sustained lowering of plasma glucose concentration compared with commercial tablets.

**Table 1:** Permeation data for GMD transdermal patches

Patch code	Polymer used	Polymer content (% w/w)	Drug form	$D_{\max}$ ( $\mu\text{g}$ )	$J_{ss}$ ( $\mu\text{g}/\text{cm}^2.\text{h}$ )	$P$ (cm/h)	$D$ ( $\text{cm}^2/\text{h}$ )	EF
F1	HPMC	3	Pure drug	3.703	0.264	$0.176 \times 10^{-2}$	$4.557 \times 10^{-5}$	0.557
F2	HPMC	3	D-HB-β-CD	15.192	1.329	$0.886 \times 10^{-2}$	$4.835 \times 10^{-4}$	3.339
F3	HPMC	3	D-PVP K90	3.871	0.301	$0.2 \times 10^{-2}$	$4.765 \times 10^{-5}$	0.582
F4	HPC	2	Pure drug	0.7517	0.066	$0.004 \times 10^{-2}$	$1.274 \times 10^{-6}$	0.265
F5	HPC	2	D-HB-β-CD	2.176	0.241	$0.160 \times 10^{-2}$	$1.290 \times 10^{-5}$	0.549
F6	HPC	2	D-PVP K90	1.195	0.132	$0.088 \times 10^{-2}$	$9.18 \times 10^{-6}$	0.302
F7	C-940 <sup>®</sup>	0.3	Pure drug	1.078	0.110	$0.073 \times 10^{-2}$	$8.23 \times 10^{-6}$	0.614
F8	C-940 <sup>®</sup>	0.3	D-HB-β-CD	7.000	0.663	$0.442 \times 10^{-2}$	$2.111 \times 10^{-4}$	1.887
F9	C-940 <sup>®</sup>	0.3	D-PVP K90	1.401	0.150	$0.1 \times 10^{-2}$	$2.896 \times 10^{-5}$	0.919
F10	Chitosan	1.5	Pure drug	0.779	0.085	$0.056 \times 10^{-2}$	$2.265 \times 10^{-6}$	0.281
F11	Chitosan	1.5	D-HB-β-CD	32.669	3.038	$2.025 \times 10^{-2}$	$2.504 \times 10^{-3}$	1.964
F12	Chitosan	1.5	D-PVP K90	1.252	0.136	$0.091 \times 10^{-2}$	$2.076 \times 10^{-5}$	0.415



**Fig 2:** Cumulative amount of GMD diffused (free and complexed) (A) and permeated across male rat skin (B) from chitosan & HPMC transdermal patches. Each point represents mean  $\pm$  SD,  $n = 3$ . **Note:** (●) Chitosan-complex patch, (Δ) HPMC-complex film, (◻) chitosan drug patch, (▲) HPMC drug patch

### Pharmacokinetics of GMD patches

Plasma concentrations of GMD from GMD-HB- $\beta$ -CD chitosan and HPMC patches after transdermal administration declined more slowly than the corresponding oral GMD tablets. Pharmacokinetic results are summarized in

**Table 2:** Hypoglycemic activity of GMD in rats

Group	0 h	2 h	4 h	6 h	12 h	24 h
Gp1	253.67 $\pm$ 28.68	243.33 $\pm$ 18.48	251.00 $\pm$ 25.90	248.00 $\pm$ 24.34	245.33 $\pm$ 18.81	252.00 $\pm$ 17.00
Gp2	266.33 $\pm$ 21.50	251.33 $\pm$ 10.50	262.33 $\pm$ 19.60	261.67 $\pm$ 19.24	271.33 $\pm$ 28.01	257.00 $\pm$ 13.11
Gp3	258.00 $\pm$ 21.38	159.00* $\pm$ 13.86	173.67* $\pm$ 19.76	193.67* $\pm$ 16.19	220.00 $\pm$ 23.66	229.33 $\pm$ 25.48
Gp4	255.67 $\pm$ 26.11	236.67 $\pm$ 21.72	240.67 $\pm$ 20.50	229.33 $\pm$ 20.60	233.67 $\pm$ 29.67	234.00 $\pm$ 21.53
Gp5	265.67 $\pm$ 25.38	245.00 $\pm$ 14.42	238.33 $\pm$ 12.06	223.00 $\pm$ 24.73	230.67 $\pm$ 22.66	234.00 $\pm$ 32.51
Gp6	261.67 $\pm$ 18.15	247.67 $\pm$ 24.58	213.67* $\pm$ 10.01	201.67* $\pm$ 15.11	213.00 $\pm$ 19.92	238.33 $\pm$ 30.01
Gp7	268.67 $\pm$ 19.07	241.00 $\pm$ 32.23	205.67* $\pm$ 21.89	192.67* $\pm$ 21.18	198.00* $\pm$ 26.66	231.33 $\pm$ 16.51

\*Significantly different from corresponding control at  $p < 0.05$

**Table 3:** Pharmacokinetics of GMD after its oral and transdermal administration to rats

Group	$C_{max}$ (ng/ml)	$T_{max}$ (h)	$K_{el}$ ( $h^{-1}$ )	AUC (0-inf) (ng/ml*h)	MRT (0- $\infty$ ) (h)
Group 3	2964.4	2	0.093532	30983.37	11.52579
Group 4	696.65	6	0.046035	18686.63	23.52757
Group 5	597.13	6	0.043865	17736.4	24.15842
Group 6	1662.92	6	0.03864	45392.49	29.78818
Group 7	1951.5	6	0.03178	63610.74	35.35873

Table 3. Results revealed that oral tablets (gp 3) produced mean value of  $C_{max}$  2964.4 ng/ml after 2 h. Our findings are similar to the reported mean value of  $C_{max}$ , 1705.02 ng/ml with  $t_{max}$  2 - 3 h administered after 6 mg/kg glimepiride oral dose [15]. GMD in HPMC (gp 6) and chitosan (gp 7) patches showed delayed  $t_{max}$  and MRT compared with oral tablets.

### DISCUSSION

GMD delivery as transdermal patches has numerous advantages over the oral route include, avoidance of hepatic metabolism, improved patient compliance, as well as minimization/elimination of the risks of hypoglycemia via simple, instant removal of the patch when necessary. Transdermal route is a challenge for drug delivery through the impermeable epithelium of the skin. One of the approaches to improve GMD skin permeation is to utilize GMD complexation with cyclodextrins [8]. PVP was also investigated for its ability to improve GMD solubility through complexation technique. Ahmed *et al* [16] illustrated increase in the aqueous solubility of mefenamic acid after complexation with PVP.

The improved GMD-binary systems solubility results indicated that HB-  $\beta$ -CD is the most efficient fast dissolving carrier for GMD, a drug known for its limited solubility, among the investigated carriers. These results were in go agreement with the findings of Ishiguro *et al* [17] who reported faster dissolution rate for inclusion

complex with HB-  $\beta$ -CD compared with HP- $\beta$ -CD. The improved GMD-HB-  $\beta$ -CD solubility could be attributed to improved inclusion ability of HP- $\beta$ -CD compared to the other investigated carriers. Previous studies showed the effect of inclusion complexes of GMD in different cyclodextrins as;  $\beta$ -CD, HP-  $\beta$ -CD and sulfobutylether-  $\beta$ -CD [8,18]. Our work investigated GMD complexation with different type of cyclodextrin, HB-  $\beta$ -CD and also with PVP, in which our results were superior compared with the previously published work [8].

GMD inclusion complexes were formulated as transdermal patches utilizing 1.5 % chitosan, 3 % HPMC, 2 % HPC and 0.3 % C-940® polymeric solutions. Previous reports utilized similar concentrations of polymeric solutions to prepare transdermal patches [8,19,20]. The improved permeation parameters achieved from chitosan (1.5 %) and HPMC (3 %) in the form of GMD-HB- $\beta$ -CD, Table 1, were in good agreement with the results obtained by Yener *et al* [19].

Pharmacodynamic effects and pharmacokinetic parameters were used as the basis for comparison of *in vivo* performance of GMD (2.5 mg) and its inclusion complex in the selected transdermal patches. Ladrière *et al* [14] reported a significant reduction of glucose levels by 32 % compared to control after 4 h for oral administration of similar 2.5 mg GMD dose. GMD-chitosan patches lowered the glucose level for a longer duration compared to GMD-HPMC patches. These results correlated well with the ex-vivo permeation results as chitosan patches showed a significant ( $p < 0.05$ ) drug/skin permeation difference compared with HPMC patches after 6 h. Plasma concentrations of GMD in chitosan and HPMC films after transdermal administration declined more slowly than the corresponding commercial orally administered GMD product. This could be attributed to the controlled release of GMD for longer duration from transdermal patches compared with the immediate release action of the commercially available tablets. These findings propose the usefulness of the studied GMD transdermal system in controlling the blood glucose level and sustaining the drug release.

## CONCLUSION

The present study indicates that there is improvement in the delivery of GMD through skin when GMD used as inclusion complex with HB- $\beta$ -CD and formulated as a patch. Transdermal delivery of GMD- HB- $\beta$ -CD in the form of either chitosan or HPMC patches results in significantly lower blood glucose level in diabetic rats and

hence can serve as a potential alternative to peroral GMD for improved bioavailability and also, greater patient convenience and compliance.

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