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RESEARCH PAPER

MICROCAPSULES AND TRANSDERMAL PATCHES: A COMPARATIVE APPROACH FOR IMPROVED DELIVERY OF ANTIDIABETIC DRUG

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Glibenclamide (GL)-loaded microcapsules (MC) and transdermal patches (TDP) were formulated and *in vitro* and *in vivo* parameters were compared to find out the best route of drug administration. The formulation TDP1 having a drug-polymer ratio 1:1 showed comparatively higher drug release and better permeation across mice skin ($p < 0.05$). From the comparative study, it was concluded that the transdermal system of GL produced better improvement compared to oral microcapsule administration ($p < 0.05$). The transdermal system exhibited comparatively slow and continuous supply of GL at a desired rate to systemic circulation avoiding metabolism, which improved day-to-day glycemic control in diabetic subjects. Transdermal system of GL exhibited better control of hyperglycemia and prolonged plasma half-life by transdermal systems (9.6±1.2 h) in comparison with oral microcapsule (5.84±2.1 h), indicating that the drug, when administered by transdermal systems, will remain in the body for a longer period. From the glucose tolerance test, transdermal route effectively maintained the normoglycemic levels in contrast to the oral group (MC1), which produced remarkable hypoglycemia ranging from -12.6±2.1% to -18±2.3%. The significantly high ($p < 0.05$) area under the curve values observed with transdermal system (1,346.2±92.3 ng ml^{-1} h^{-1}) also indicated increased bioavailability of the drug from these systems compared to the oral route (829.8±76.4 ng ml^{-1} h^{-1}).

Key words: Bioavailability, Glibenclamide, Oral microcapsules, Pharmacokinetics, Transdermal delivery.

INTRODUCTION

In the modern era, diabetes mellitus is one of the major crippling diseases in the world, leading to huge economic loss. Studies conducted in India highlighted that not only the prevalence of diabetes is high but also, it is increasingly rapid in urban population [1]. Groundbreaking drug delivery systems may allow formulation scientists to utilize chemicals that are otherwise difficult to use because of stability, toxicity, or bioavailability problems. Drug administration with specific delivery systems can potentially facilitate the delivery of drugs to the particular site of action while reducing the undesired side effects, thus drastically increasing patient compliance. Nowadays, transdermal patch-type drug delivery systems are used as a new frontier for the administration of various drugs [2-6]. Drugs are delivered directly to the systemic circulation through intact skin, bypassing hepatic "first-pass" metabolism, and provide controlled release of drugs for an extended and safe use [7-19].

Glibenclamide (GL), a sulfonylurea used in the treatment of non-insulin-dependent diabetes

mellitus (**Figure 1**), has been associated with severe and sometimes fatal hypoglycemic reactions after oral therapy because of higher inter-individual variations [20, 21]. Transdermal drug delivery system provides a means to sustain drug release as well as reduce the intensity of action and thus, reduce the side effects associated with its oral therapy. Glibenclamide (molecular weight, 494; pKa, 5.3) showed favorable partition coefficients (log octanol/buffer, 0.32±0.007; log of isopropylmyristate/buffer, 0.5±0.05) and very negligible skin degradation [22, 23]. The present study aims at developing transdermal patches (TDP), microcapsules (MC) loaded with an identical dose of GL and comparing the hypoglycemic activity of GL from the two formulations.

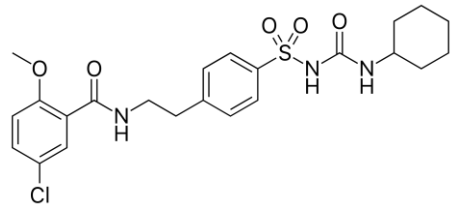

Fig. 1. Structure of sulfonyl urea – Glibenclamide

MATERIALS

Glibenclamide was received as a gift sample from Zydus Cadila Pharmaceuticals Ltd., Gujarat, India. Hydroxypropyl methylcellulose (HPMC), isopropyl myristate (IPM), and sodium alginate (SA) were obtained from SD Fine Chemicals, Mumbai, India. Calcium chloride ($CaCl_2$) and alloxan was procured from the Merck Limited, Mumbai, India. Other reagents used were of analytical grade.

METHODS

Preparation of microcapsules

GL-loaded MC formulations were prepared by ionic gelation method [24]. SA (5%, *w/v*) dispersion was prepared in distilled water. SA dispersion (80 ml) was dropped through a 1.2 mm inner diameter needle from a hypodermic syringe into 0.45 M calcium chloride solution (200 ml). The composite gel MC was cured in this solution for 12 h, then filtered, and rinsed several times with distilled water. The beads were dried at room temperature for 48 h and followed at 45°C for 12-16 h. To prepare GL-loaded MC, the required amount of GL was added into the dispersion and completely dispersed with a sonicator for 5 min before cross-linking process, and then, the preparation proceeded as described above.

Preparation of transdermal patches

GL-loaded TDP formulations were prepared by solvent casting method [25] with slight modification. Hydroxypropyl methylcellulose was dissolved in a mixture of acetone/isopropyl alcohol/ethanol (50:30:20) with continuous stirring in a closed system at 25°C.

Dibutyl phthalate was added followed by the addition of IPM with continuous stirring. Calculated amount of GL was added to the solution of the polymer matrix and poured into the backing membrane. The solvent was allowed to evaporate overnight at RT (**Table 1**).

Table 1. Formulations and drug contents of microcapsule and transdermal patch (mean±SD; *n*=6)

Microcapsule				Transdermal patch				
Formulation	**GL:SA**	**$CaCl_2$ (M)**	**%Drug content**	**Formulation**	**GL:HPMC**	**DBT (%, *w/w*)**	**IPM (%, *v/v*)**	**% Drug content**
MC1	1:1	0.45	89.2 ± 2.3	TDP1	1:1	30	1.5	99.6 ± 1.8
MC2	1:2	0.45	81.6 ± 2.8	TDP2	1:2	30	1.5	98.9 ± 1.7
MC3	1:3	0.45	80.2 ± 1.9	TDP3	1:3	30	1.5	98.1 ± 2.0

GL - glibenclamide, SA - sodium alginate, HPMC – hydroxypropyl methylcellulose, DBP - dibutyl phthalate, IPM - isopropyl myristate

FTIR studies

Drug–polymer interaction studies were conducted by Fourier transform infrared (FTIR) spectroscopy. The spectra were recorded for GL, Hydroxypropyl methylcellulose (HPMC), GL-loaded MC, and TDP in FTIR spectrophotometer (SHIMADZU, Japan) using KBr pellets at 400-4000 cm^{-1}.

X-Ray powder diffraction studies

The X-ray powder diffraction (PXRD) studies were carried out in a powder X-ray diffractometer (Philips, PW 1050/37) with a vertical goniometer using CuKα radiation with Ni filter at a voltage of 40 kV and a current of 20 mA. Powder XRD patterns for GL, SA, and GL-

loaded MC formulations were obtained by scanning from 0° to 50° 2θ.

Particle size determination

Particle size analysis study of the prepared microcapsules were determined by sieving the beads on a mechanical shaker using a nest of standard sieves (BP test sieves) with a shaking time of 15 min [26]. In the current study, microcapsules with a mean diameter of 240 µm were used for further investigations.

Drug content studies

For drug content determination, 200 mg of GL-loaded MC and 1 cm^2 GL-loaded TDP were taken into a 100 ml volumetric flask and dissolved in ethanol, and the solution was filtered through a 0.45 µm membrane filter and adjusted with phosphate buffer to pH 7.4, prior to drug content analysis using UV-Vis spectrophotometer (SHIMADZU, 1601, Japan) at 292 nm taking phosphate buffer (pH 7.4), with ethanol as blank.

In vitro dissolution studies

Dissolution studies of GL-loaded MC formulations were carried out in USP XXI dissolution apparatus type II. GL-loaded MC were suspended in 900 ml of phosphate buffer of pH 7.4 as dissolution medium stirring at 100 rpm and maintained at constant temperature (37±1°C). At predetermined time intervals, 5 ml aliquots were withdrawn and replaced by an equal volume of fresh pre-warmed dissolution medium. After suitable dilution, the samples were analyzed at 292 nm using UV-Vis spectrophotometer. The concentration of the GL released at different time intervals was determined. *In vitro* release (flux) study of the TDP was evaluated for drug release using Keshary-Chien-type glass cells. Cellophane sheets treated with 5% (*v/v*) of glycerol [27, 28] were mounted between the donor and receptor compartments. The patch was placed on the cellophane sheet and the compartment clamped together. The cell was placed in a water bath maintained at 37±1°C. The receptor compartment (75 ml capacity) was filled with phosphate buffer (pH 7.4), and the hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 100 rpm. At predetermined time intervals, samples were withdrawn and an equal volume of pre-warmed buffer was replaced. The samples were analyzed after appropriate dilution for GL content at 292 nm using UV-Vis spectro photometer taking phosphate buffer pH 7.4 as blank. The *in vitro* skin permeation studies of TDP were carried out in a similar manner as that of *in vitro* release studies except that the membrane barrier used in this study was the dorsal section of full-thickness skin from Swiss albino mice (weighing between 25 and 30 g) whose hair has been removed on the previous day using an electric clipper.

In vivo studies

The animals used for *in vivo* experiments were adult Swiss albino mice (6-8 weeks old) of either sex, weighing 25–30 g, from the Department of Pharmacology, School of Pharmaceutical Sciences, Bhubaneswar, Odisha. The animals were housed in polypropylene cages, four per cage, with free access to standard laboratory diet (Lipton Feed, Mumbai, India) and water. They were kept under standard environmental conditions (23±2°C; 55±5% relative humidity; 12 h light/dark cycle). The *in vivo* experimental protocol was approved by the Institutional Animal Ethical Committee (CPCSEA registration no. 1171/08/c). Diabetes was induced by intraperitoneal injection of 140 mg/kg of alloxan monohydrate in sterile saline [26]. After 72 h of injection, the diabetic mice (blood glucose level >250 mg/dl) were separated and used for the study.

Hypoglycemic activity

For evaluating the hypoglycemic activity of GL-loaded MC1 and GL-loaded TDP1, healthy mice were divided into four groups (n=6).

All the mice were kept fasting before 24 h of the experiment. During the start of the experiment, the mice were fed with the microcapsules orally according to the group mentioned. Group I (control)—0.2 ml of 2% (*w/v*) acacia suspension orally [29]. Group II—GL (5 mg/kg) orally [29] in suspension form using oral gavages followed by sufficient volume of drinking water, and the dose of 5 mg/kg was selected by conducting a series of experiments with graded doses ranging between 1 and 10 mg/kg. Group III—MC1 containing 2 mg GL were administered orally in suspension form.

For evaluating the hypoglycemic activity of GL-loaded TDP1 in mice, the hair on the backside of the mice was removed with an electric hair clipper on the previous day of the experiment. Following an overnight fast, mice were divided into three groups (n=6) as mentioned above, but group III mice were treated with 4 cm^2 GL-

loaded TDP1 containing 2 mg GL instead of GL-loaded MC1. Blood samples were collected from orbital sinuses using heparinized capillaries, and the blood glucose levels were determined by placing one drop of the fresh blood on Glucoscan test strip (Lifescan Inc., CA, USA) and reading by a Glucoscan 3000 meter (Lifescan Inc.).

Blood glucose concentrations were measured at 0, 2, 4, 6, 8, 10, and 12 h after dosing, respectively. Results were shown as percentage reduction of blood glucose level (±SD) of six animals. The mean blood glucose levels determined in samples collected before GL administration were taken as the baseline levels. Using these data, the percentage of glucose reduction at each time after dosing was calculated and plotted against time.

Glucose tolerance test

The animals were fasted overnight and divided into four groups (n=6). Group 1 served as control administered with 0.2 ml of acacia suspension, group 2 was treated with oral GL pure drug (5 mg/kg), and groups 3 and 4 were administered oral GL-loaded MC1 and topical TDP1, respectively. Two hours later, glucose was administered orally (3.5 g/kg) to all the four groups.

Blood samples were collected just prior to and at 0.5, 1, 2, and 3 h after the glucose feeding and glucose level was determined. The percentage change in blood glucose was estimated in comparison with the control group.

Pharmacokinetic studies

For conducting pharmacokinetic studies, the animals were fasted overnight and divided into three groups (n=6). Group I was treated with oral GL pure drug (5 mg/kg), group II administered with MC1 orally containing 2 mg GL, and group III treated with 4 cm^2 TDP1 containing 2 mg GL on the fasted mice skin whose hair was previously removed. At different time intervals after treatment, blood was collected from the orbital sinuses using heparinized capillaries.

Plasma was separated by centrifugation (Eltek instruments, India) and analyzed by reverse phase high-performance liquid chromatography method [30].

Statistical analysis

Statistical analysis of the results was performed using Student's t-test; $p < 0.05$ was considered as significant. Values are reported as mean±SEM.

RESULTS AND DISCUSSION

FTIR Studies

The IR spectral analysis of GL alone showed that the principal peaks should be at wave numbers of 1527.50, 1157.2, 1618.2, 1714.6, and 819.7 cm^{-1} as per established standards [31], and in the MC formulation, the major peaks (**Figure 2**) of GL was found to be at wavenumbers of 1531.53, 1159.26, 1620.26, 1712.85, and 819.77 cm^{-1}, indicating no drug-polymer interaction and confirming the purity of the drug.

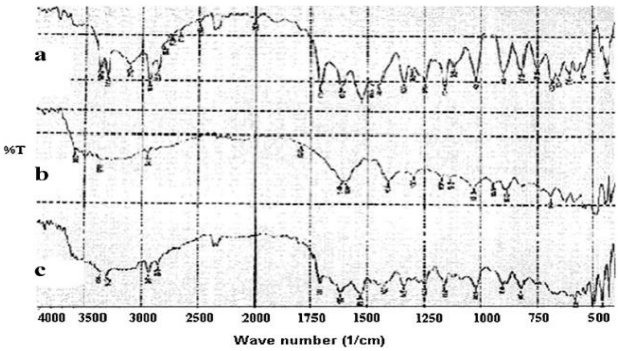

Fig. 2. IR spectra of GL and MC formulation

PXRD studies

The PXRD spectra of the pure GL, SA, and GL-loaded MC were portrayed in **Figure 3**. PXRD spectral study revealed the presence of sharp peaks, indicating the crystalline nature of pure GL. After being formulated into MC, the X-ray diffractogram showed comparatively less sharp peaks, indicating that GL embedded within the polymer matrix. The presence of the drug within the polymeric matrix could be responsible for the controlled drug release from formulations.

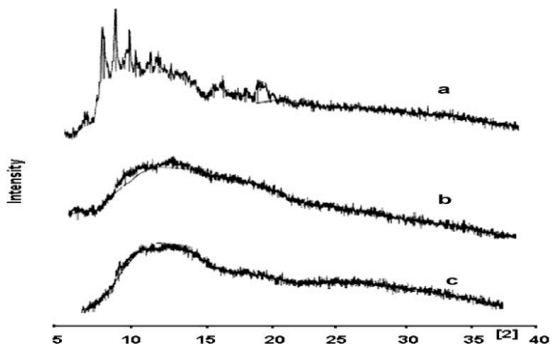

Fig. 3. Powder X-ray diffraction patterns of glibenclamide, sodium alginate, glibenclamide-loaded microcapsule formulation

Drug content studies

Drug content study of the GL-loaded formulations is shown in **Table 1**. Comparatively higher GL content was found in TDP than MC.

Among the various formulations, MC1 (89.2±2.3%) and TDP1 (99.6±1.8%) with 1:1 drug–polymer ratio exhibited significantly higher GL content ($p < 0.05$) compared to other formulations.

In vitro dissolution studies

In vitro dissolution studies of different batches of GL-loaded MC and TDP are depicted in **Figure 4**. From this comparative study, MC exhibited greater cumulative percentage of drug release than TDP in pH 7.4 phosphate buffer as dissolution medium. Among the different batches of microcapsules and transdermal systems, formulation MC1 and TDP1 exhibited comparatively higher drug release which were significantly different ($p < 0.05$) from MC2, MC3, and TDP2, TDP3, respectively. In the case of MC1, a biphasic release was observed, *i.e.* initial burst effect and subsequent controlled effect. The initial burst effect was due to the rapid dissolution of the surface drug. The rapid leaching out of SA results in the formation of pores and thus leads to the decrease of mean diffusional path length of the drug molecules to release into dissolution medium and, hence, higher release rates [26]. In the different batches of MC, maximum portion of drug released within 8 to 9 h, whereas in the case of TDP, the release extended up to 12 h, exhibiting better control on the release of drug.

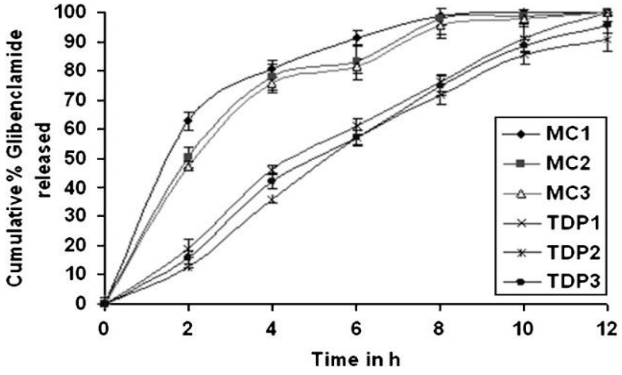

Fig. 4. *In vitro* dissolution studies

The formulation TDP1 having a GL/HPMC ratio 1:1 showed comparatively higher permeation across mice skin, which was significantly higher ($p < 0.05$) compared to formulations TDP2 and TDP3.

In vivo hypoglycemic activity

To study *in vivo* hypoglycemic activity of the GL-loaded different formulations, diabetes was induced in normal mice by the application of alloxan. Alloxan, a cytotoxin, was demonstrated to produce a massive destruction of β cells of the islets of Langerhans, resulting in reduced synthesis and release of insulin [32]. It has been reported that sulfonylureas produce hypoglycemia by increasing the secretion of insulin from pancreas, and these compounds are active in mild alloxan whereas they are inactive in intense alloxan diabetes (nearly all β cells have been destroyed) [33]. The *in vivo* study (**Figure 5**) indicated that the transdermal system of GL produced better improvement compared to oral administration. This statement can be supported by an earlier report of a multicenter, randomized clinical trial designed to compare intensive therapy with conventional diabetic therapy [34]. The intensive therapy regimen was designed to achieve blood glucose levels as close to the normal range as possible with three or more daily insulin injections or with an external insulin pump. Conventional therapy consisted of one or two daily injections of insulin. The results were definitive. The intensive therapy reduced the mean risk of retinopathy by 76%, nephropathy by 34%, hypercholesterolemia by 34%, and macrovascular disease by 41% compared to conventional therapy. Thus, it might be assumed that improving day-to-day glycemic control in diabetic mice by transdermal patches can dramatically reduce and slow the development complications of diabetes. Further, the slow and continuous release of the drug from transdermal systems might reduce manifestations like sulfonylurea receptor down-regulation and the risk of chronic hyperinsulinemia, a major risk factor for atherosclerosis frequently observed with oral therapy of GL [35-37]. Transdermal system of GL produced significantly higher ($p < 0.05$) hypoglycemic response (64.08±5.81%) compared to oral microcapsule (47.61±3.66%) after 12 h. The present study showed that the transdermal system of GL exhibited better control of hyperglycemia besides more effectively reversing the complications associated with diabetes mellitus than oral administration in mice.

Glucose tolerance test

From the glucose tolerance test, the control group showed highly elevated blood glucose levels ($p < 0.05$) after glucose administration (**Figure 6**). The control group showed highly elevated blood glucose levels ($p < 0.05$) after glucose administration (+80.1±5.32%, +72.06±

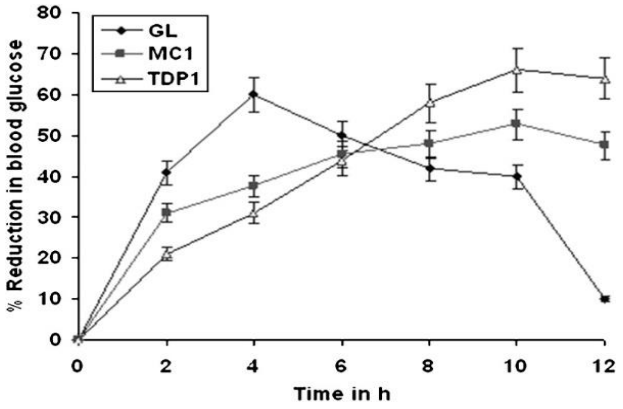

Fig. 5. Percentage reduction in blood glucose levels after oral and transdermal administration of glibenclamide-loaded formulations

4.61%, +46.09±2.46%, +23±1.21% at 0.5, 1.0, 2.0, and 3.0 h, respectively). The hypoglycemia produced after transdermal delivery was significantly lower ($p < 0.05$) than the control group. On the contrary, the orally GL-administered group (MC1) showed severe hypoglycemia ranging from −12.6±2.1% to −18±2.3% at all intervals of the study period. The results of glucose tolerance test show that glucose tolerance curve (control) was completely inhibited in the treated groups. Transdermal route effectively maintained the normoglycemic levels in contrast to the oral group, which produced remarkable hypoglycemia, an indication that a similar incident might be prevented in diabetic patients.

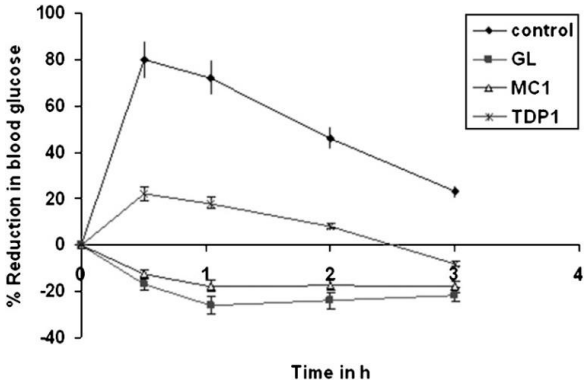

Fig. 6. Glucose tolerance test

Pharmacokinetic studies

The plasma concentrations of GL after transdermal and oral administration against time are shown in **Figure 6**. The pharmacokinetic parameters were calculated from the plasma concentration of the drug and recorded in **Table 2**. The pharmacokinetic parameters obtained with GL transdermal system were significantly different ($p < 0.05$) from those obtained with respective oral GL administration, which could be due to the rapid absorption of drugs *via* oral route, whereas drug in transdermal route were slowly but continuously absorbed. In this study, though the rise in drug concentration was slower than oral administration, the drug concentration in plasma remained high for longer periods with transdermal systems. GL binds to plasma proteins to the extent of 99% [38]. The prolongation of plasma half-life by transdermal systems (9.6±1.2 h) in comparison with oral microcapsule (5.84±2.1 h) indicates that the drug, when administered by transdermal systems, will remain in the body for a longer period. The significantly high ($p < 0.05$) mean residential time (MRT) values of GL obtained with transdermal systems further support the slow release of drug from the system. Although the C_{max} was significantly less with transdermal systems, the area under the curve (AUC) values were significantly high (1346.2±92.3 ng ml^{-1} h^{-1}) compared to oral route (829.8±76.4 ng ml^{-1} h^{-1}), which could be due to maintenance of concentration of drug within the pharmacologically effective range for longer periods of time. The significantly high AUC values observed with transdermal devices also indicate increased bioavailability of drug from these systems compared to oral route.

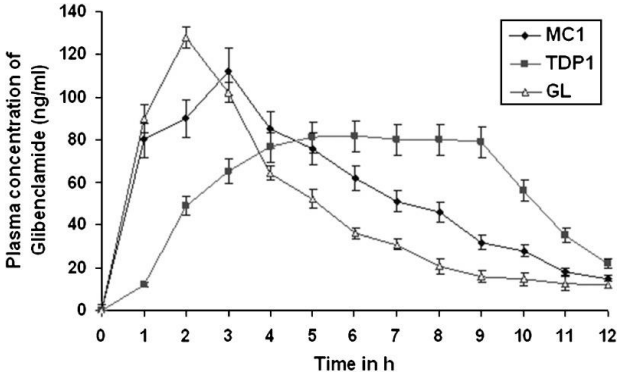

Fig. 7. Pharmacokinetics studies

CONCLUSIONS

From the comparative study, it was concluded that the transdermal system of GL produced better improvement compared to the oral microcapsule administration. The transdermal system showed a comparative slow and continuous supply of GL at a desired rate to systemic circulation avoiding the fast pass metabolism, which improves day-to-day glycemic control in diabetic subjects and might

Table 2. Pharmacokinetic parameters obtained after oral and transdermal administration of glibenclamide-loaded formulations in mice (mean±SE; n=6)

Parameter	Microcapsule (MC1)	Transdermal patch (TDP1)
C_{max} (ng/ml)	112.8±18.6	80.2±2.6
t_{max} (h)	3.0±0.8	6.5±2.7
MRT (h)	7.6±3.2	10.3±4.1
equation M1	829.8±76.4	1346.2±92.3

reduce manifestations like sulfonylurea receptor downregulation and the risk of chronic hyperinsulinemia. The present study showed that the transdermal system of GL exhibited better control of hyperglycemia besides more effectively reversing the complications associated with diabetes mellitus (DM) than oral administration in mice. The significantly higher AUC values observed with transdermal systems also indicated increased bioavailability of drug from these systems as compared to oral route.

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