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Research paper

Development and evaluation of osmotically controlled oral drug delivery system of glipizide

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Abstract

Extended release formulation of glipizide based on osmotic technology was developed and evaluated. The effect of different formulation variables, namely, level of solubility modifier in the core, membrane weight gain, and level of pore former in the membrane, were studied. Drug release was found to be affected by the level of solubility modifier in the core formulation. Glipizide release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP) in the membrane. Burst strength of the exhausted shells increased with the weight gain of the membrane. On the other hand, burst strength decreased with an increase in the level of pore former in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the release media. Results of SEM studies showed the formation of pores in the membrane from where the drug release occurred. The numbers of pores were directly proportional to the initial level of pore former in the membrane. The manufacturing procedure was found to be reproducible and formulations were stable after 3 months of accelerated stability studies.

Keywords: Extended release; Controlled release; Glipizide; Osmotic pressure; Osmotic pump; Stability

1. Introduction

Osmotically controlled oral drug delivery systems (OCODDS) utilize osmotic pressure as the energy source for the controlled delivery of drugs. Drug release from these systems is independent of pH and hydrodynamic conditions of the gastro-intestinal tract (GIT) to a large extent, and release characteristics can be easily adjusted by optimizing the parameters of the delivery system [1–3].

Glipizide, an oral hypoglycemic agent, is one of the most commonly prescribed drugs for the treatment of patients with type II diabetes mellitus [4]. It is practically water-insoluble, but the absolute bioavailability is close to 1. Thus, it belongs to class 2 of Biopharmaceutic Classification System (BCS) [5]. Glipizide has a relatively short elimination half-life (2–4 h), thereby requiring twice daily dosing in large number of patients [6,7], which often leads to non-compliance. Thus, there is a strong clinical need and market potential for a dosage form that will deliver glipizide in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance.

The present study was aimed towards the development of extended release formulations of glipizide based on osmotic technology. Different formulation variables were studied and optimized to achieve the desired release profile. The manufacturing procedure was standardized and the stability of the formulations evaluated after 3 months of storage at accelerated stability conditions.

2. Materials and methods

2.1. Materials

Glipizide (99.79% purity), a gift sample from USV Limited, India, was characterized against the Chemical Reference Standard of glipizide (European Pharmacopoeia Commission Secretariat, France). Samples of Glucotrol

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XL® (Pfizer Inc., USA) were obtained from retail pharmacy. Following chemicals and excipients were purchased from commercial sources and used as such.

Cellulose acetate (Fluka, Switzerland), colloidal silicon dioxide (Aerosil 200®, Degussa AG, Germany), tromethamine GR (Loba Chemie, India), mannitol (Pearlitol SD-200®, Roquette, France), sodium chloride AR (Loba Chemie, India), polyvinyl pyrrolidone (Plasdone K-29/32®, ISP, USA), talc (Panacea Biotech, India), and magnesium stearate (Mallinckrodt, USA). Dichloromethane-GR (Merck, India) and methanol-GR (Merck, India) were used for the preparation of coating solutions.

2.2. Formulation development

Before initiating formulation development, compatibility of glipizide with different excipients was tested using the techniques of DSC and isothermal stress testing [8]. Excipients used in the final formulation were found to be compatible with glipizide.

Core tablets of glipizide were prepared by wet granulation and the batch size was kept as 500 tablets. Glipizide was mixed with all the excipients and passed through 30-mesh sieve. The blend was mixed for 10 min and PVP was added. The mixture was granulated with ethanol and the resulting wet mass passed through 18-mesh sieve. The granules were dried at 50 °C (approximately 10 min) to get a loss on drying (LOD) value between 0.9 and 1.1%, after which they were passed through 22-mesh sieve. These sized granules were then blended with magnesium stearate, talc, and colloidal silicon dioxide (all 60-mesh passed) and compressed into tablets having an average weight of 360–400 mg using a single stroke tablet-punching machine (CMS-25, Cadmach, India) fitted with 10 mm round standard concave punches. Formulae of different core formulations of glipizide are listed in Table 1. The core tablets of glipizide were coated in an automated perforated pan (GAC-250, Ganscoater, India). The composition of coating solution used for coating of glipizide tablets is given in Table 2. Various components of the coating solution were added to the solvent mixture in a sequential manner. The component added first was allowed to dissolve before the next component was added. Core tablets of glipizide were placed in the coating pan along with 200 g of filler tablets (tablets made using 7.00 mm round deep concave punches and containing microcrystalline cellulose, starch, dibasic calcium phosphate, magnesium stearate, and colloidal silicon dioxide). Initially, pan was rotated at low speed (2–5 rev./min) and heated air was passed through the tablet bed. Coating process was started once the outlet air temperature reached 28 °C. The revolutions per minute of the pan was kept in the range of 15–20 and coating solution was sprayed at the rate of 5–8 ml/min. Atomization pressure was kept at 1 kg/cm^2 and the outlet temperature was maintained above 28 °C by keeping the inlet air temperature in the range of 50–55 °C. Coating was continued until desired weight gain was obtained on the active tablets. In all the cases, active tablets were dried at 50 °C for 16 h before further evaluation.

Table 1
Core formulations of glipizide

Ingredients	Core code			
	I	II[a]	III	IV
Glipizide	2.78	2.78	2.78	2.78
Tromethamine	–	–	25.02	48.61
Sodium chloride	9.72	12.22	9.72	9.72
Fructose	–	81.00	–	–
Mannitol	78.50	–	53.48	29.89
PVP	5.00	–	5.00	5.00
Magnesium stearate	1.50	1.50	1.50	1.50
Talc	2.00	2.00	2.00	2.00
Colloidal silicon dioxide	0.50	0.50	0.50	0.50

Compositions given in terms of % w/w. Each tablet contained 10 mg of glipizide; average tablet weight was 360 mg.

[a] Core tablets prepared by the process of direct compression. Average tablet weight was 400 mg.

Table 2
Coating compositions for glipizide core formulations

Ingredients	Coat code		
	A	B	C
Cellulose acetate	2.58	3.08	2.22
PVP	0.64	–	1.11
Triacetin	0.26	0.31	0.22
PEG-400	0.52	0.62	0.44
Methanol	24.00	24.00	24.00
Dichloromethane	72.00	72.00	72.00

Compositions given in terms of % w/w. Total solids in the coating composition: 4.0%.

2.3. Evaluation of the developed formulations

IR moisture balance (PM 480, Mettler Toledo, Switzerland) was used to determine LOD of the powder blend. To determine bulk and tapped density of the powder blend, USP method II on a tap density tester (ETD-1020, Electrolab, India) was used. From the data obtained, compressibility index and Hausner Ratio were calculated.

The core and coated tablets were evaluated for weight variation. Thickness and diameter of the core and coated tablets was measured using a thickness gauge (Digimatic, Mitutoyo, Japan). Hardness of the randomly selected tablets was tested using hardness tester (TBH-20, Erweka, Germany). Friability of the core tablets was carried out on a friabilator (EF-2, Electrolab, India) for which 20 accurately weighed tablets were used.

The developed formulations of glipizide ($n = 6$) were subjected to release studies using USP-I dissolution

apparatus (Electrolab, India) at 100 rev./min. Dissolution medium used was simulated intestinal fluid (SIF, pH 6.8, 1000 ml) maintained at 37 ± 0.5 °C, which was found to provide sink conditions (solubility of glipizide in SIF was determined to be 0.078 mg/ml). The samples were withdrawn (10 ml) at different time intervals and replaced with an equivalent amount of fresh medium. The dissolution samples, after filtration through 0.45-μm nylon membrane filters, were analyzed using a validated UV spectroscopic method at 276 nm [8]. However, as the excipients present in Glucotrol XL® interfered with the UV method, it was ruled out for analysis. HPLC method was developed and used for the analysis of dissolution samples of Glucotrol XL®. For HPLC analysis, Shimadzu HPLC system equipped with LC-10 AT VP pump, DGU-14 AM on-line degasser, SIL-10 AD VP autoinjector, CTO-10 AS VP column oven, and SPD-10 AVP UV-VIS detector was utilized. Chromatographic separation of glipizide in dissolution samples of Glucotrol XL® was performed on a C_{18} Symmetry column (4.6 × 250 mm, 5 μm particle size) fitted with a C_{18} Nucleosil guard cartridge. Mobile phase used was acetonitrile–methanol–phosphate buffer (10 mM, pH 7.0) in the ratio of 20:30:50 v/v, at a flow rate of 0.5 ml/min. Temperature of the column oven was maintained at 35 °C. The method was validated for specificity, range and linearity, accuracy, precision, and solution state stability. Standard solutions and dissolution samples were analyzed at 225 nm using a UV detector [8]. After analyzing the drug content in the dissolution samples, corrections were made for the volume replacement and the graph of cumulative percentage of drug release versus time was plotted. Release profiles of various formulations were compared using model independent pair-wise approach, which included the calculation of 'difference factor' f_1 and 'similarity factor' f_2. The two release profiles were considered to be similar, if f_1 value was lower than 15 (between 0 and 15) and f_2 value was more than 50 (between 50 and 100). For the calculation of f_1 and f_2 values, only one data point was taken into consideration after 85% of the drug was released.

Release profiles were also compared using mean dissolution time or MDT, which was calculated using following equation

$$\mathrm{MDT} = \frac{\sum_{j=1}^{n} \hat{t}_j \Delta M_j}{\sum_{j=1}^{n} \Delta M_j} \quad (1)$$

where j is the sample number, n the number of dissolution sample times, $\hat{t}_j$ the time at midpoint between t_j and t_{j-1}, and ΔM_j the additional amount of drug dissolved between t_j and t_{j-1}. One-way analysis of variance test (ANOVA) was performed to check whether there is significant difference among the different formulations.

For content uniformity testing, one accurately weighed tablet ($n = 5$) was added in 100 ml of methanol. The sample was sonicated for 30 min and filtered through 0.45-μm nylon membrane filter. The filtered solutions, after appropriate dilution with methanol, were analyzed by UV spectroscopy at 276 nm.

In addition, the developed formulations were subjected to various tests.

2.3.1. Effect of pH

To study the effect of pH and to assure a reliable performance of the developed formulations independent of pH, release studies of the optimized formulations were conducted according to pH change method. The release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by SIF (pH 6.8) for the remaining period of 24 h. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45-μm nylon membrane filters.

2.3.2. Effect of agitational intensity

In order to study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus at various rotational speeds. Dissolution apparatus used was USP-I (rotating basket) at 50, 100, and 150 rev./min. In another experiment, stirred and stagnant conditions were induced in a single run using USP-I apparatus. The rotational speed was kept at 100 rev./min (stirred conditions), which, however, was stopped intermittently to induce the stagnant conditions. The protocol used was stirred conditions for first 3 h (0–3 h), stagnant conditions for next 2 h (3–5 h), stirred condition for next 3 h (5–8 h), and stagnant condition for next 2 h (8–10 h). Samples were withdrawn at predetermined intervals and analyzed after filtration through 0.45-μm nylon membrane filters.

2.3.3. Effect of osmotic pressure

In order to confirm the mechanism of drug release, release studies of the optimized formulation were conducted in media of different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride (osmotically effective solute) was added in SIF [9,10] and the pH was adjusted to 6.8 ± 0.05. Release studies were carried out in 1000 ml of media using USP-I dissolution apparatus (100 rev./min). To avoid any interference in the analysis by sodium chloride, residual drug analysis methodology was utilized for construction of release profile [11,12]. At predetermined time points, specified numbers of tablets (one or two) were withdrawn from each vessel, cut open, and the contents dissolved in 250–500 ml of SIF. The samples were analyzed to determine the residual amount remaining in each tablet. Accuracy of this method was checked in SIF, where results after direct measurement of glipizide into the release media were similar to the results of residual drug analysis method.

2.4. Osmotic pressure and pH measurement

Saturated solution was prepared for the measurement of osmotic pressure of the core formulation. Excess drug and the components of the core formulation (in the weight ratio that was present in the formulation) were added in 5 ml of water (in 30 ml of glass vials). The vials were screw capped tightly and kept for shaking (at 200 rev./min) on a shaking water bath at 37 °C for 24 h [1,13]. The samples were filtered through 0.45-μm nylon membrane filter and osmolality measured ($n = 3$) after suitable dilutions, if required, using a vapor pressure osmometer (Vapro, 5520 XR, Vapor pressure osmometer, Wescor, USA). Before measurement, osmometer was calibrated using calibration standards of 100, 290, and 1000 mmol/kg. The osmotic pressure of the dissolution media was also measured in a similar manner.

Saturated solutions were centrifuged (15 min at 3000 rev./min) and supernatant liquid was taken for measurement of pH of core formulation.

2.5. Burst strength

Burst strength of the exhausted shells, after 24 h of dissolution, was determined to assure that the tablets would maintain their integrity in the GIT. Burst strength was determined as the force required to break/rupture the shells after dissolution studies. The texture analyzer (TAX T2i, Stable Micro systems, England) with a 5 kg load cell and 25 mm aluminum cylindrical probe was utilized for this purpose. Test speed of 0.8 mm/s was selected and the distance moved was set at 2 mm.

2.6. Scanning electron microscopy studies

In order to elucidate the mechanism of drug release from *in house* formulations, surface of coated tablets, both before and after dissolution studies, was studied using scanning electron microscope (SEM). The samples were placed on a spherical brass stub (12 mm diameter) with a double backed adhesive tape. The tablets (coated tablets before dissolution studies) were mounted as such on the specimen stub. On the other hand, small sample of the coating membrane was carefully cut from the exhausted shells (after 24 h of dissolution studies) and dried at 50 °C for 12 h. The mounted samples were sputter coated for 5 to 10 min with gold using fine coat ion sputter (JFC-1100, Jeol, Japan) and examined under SEM (JSM-6100, Jeol, Japan).

2.7. Accelerated stability studies

Optimized formulations of glipizide were packed in strips of 0.04 mm thick aluminum foil laminated with PVC. The packed formulations were stored in ICH certified stability chambers (KBF 720, Binder, Germany) maintained at 40 °C and 75% RH for 3 months. The samples were withdrawn periodically and evaluated for drug content, hardness, burst strength, and release studies.

Table 3
Important pharmacokinetic parameters of glipizide

Pharmacokinetic parameter	Value	Reference
Fraction of drug absorbed (f)	1	[37]
Elimination half-life ($t_{1/2}$)	3.3 h	[37]
Terminal disposition rate constant (k_{el} or β)	0.21 h^{-1}	[37]
Apparent volume of distribution (V_d)	0.17 l/kg	[38]
Minimum effective concentration ($C_{ss\ min}$)	20 ng/ml	[36]
Maximum effective concentration ($C_{ss\ max}$)[a]	300 ng/ml	[6]
Clearance (CL)	0.52 ± 0.18 ml min^{-1} kg^{-1}	[38]

[a] No well-defined upper limits reported for therapeutically effective plasma concentration. However, threshold concentration of 300 ng/ml has been suggested above which no additional glucose-lowering effect is likely to be achieved.

2.8. Prediction of in vivo performance

Known pharmacokinetic properties of drugs (Table 3) and various drug release parameters (R^0 and t_{Del}), which were calculated from in vitro release data, were used to predict blood levels of drugs [14]. It was assumed that after the administration of a test dose of formulation, the drug would be released at a release rate (R^0) for a period of time (t_{Del}) shorter than the selected dosing interval (τ). Time of delivery, t_{Del}, is the time taken to deliver 90% of the total drug within a selected dosing interval ($\tau = 24$ h). The predicted plasma levels of *in house* formulations were compared with those of innovator product by calculating the percent-predicted error (% PD) in C_{max}, C_{min}, T_{max}, and $AUC_{0-\tau}$. Bioequivalence was anticipated [15,16] if the average % PD was less than 15% for C_{max} and $AUC_{0-\tau}$. The % PD was calculated using the following equation:

$$\%PD = \frac{\text{predicted value} - \text{reference value}}{\text{reference value}} \times 100 \qquad (2)$$

3. Results and discussion

3.1. Formulation development

The dosage form developed was designed as a tablet core coated with a rate controlling membrane. Tablet core

consists of drug along with solubility modifier, osmagent, and other conventional excipients to form the core compartment. Solubility modifiers used in the formulations are alkalinizing agents that are in immediate contact with the drug and capable of modifying the microenvironmental pH of the core above the p*K*a of drug. The core compartment is surrounded by a membrane consisting of a semipermeable membrane-forming polymer, water-soluble additives, and at least one plasticizer capable of improving film-forming properties of the polymers. The semipermeable membrane-forming polymer is permeable to aqueous fluids but substantially impermeable to the components of the core. In operation, the core compartment imbibes aqueous fluids from the surrounding environment across the membrane. After coming into contact with the aqueous fluids, the solubility modifier dissolves and elevates the microenvironmental pH of the tablet core above the p*K*a of the drug, thus increasing its solubility. The dissolved drug is released through the pores created after leaching of water-soluble additive(s) in the membrane. Cellulose acetate and PVP were used as water-insoluble polymer and water-soluble additive, respectively. PEG-400 and triacetin were used as water-soluble and water-insoluble plasticizers, respectively.

Formulation development involved trials with different types of polymers, water-soluble additives, etc.

Following parameters were studied.

3.1.1. Effect of level of solubility modifier

In the initial trial, core tablets of glipizide (core code: I) were coated with coating composition A (formulation code: GLOP-I/A). However, no drug was released till 24 h. This phenomenon could be expected either because of low osmotic pressure of the core formulation or due to poor water solubility of glipizide. To increase the osmotic pressure of core compartment, fructose (osmotically effective agent) was added (formulation code: GLOP-II/A). This approach was also unsuccessful, as there was no drug release till 24 h.

Osmotic pumps per se are suitable for delivery of drugs having intermediate water solubility [2,17]. It has been reported [3] that in case of water-insoluble drugs, meaningful release rates may not be obtained using elementary osmotic pump (EOP) or controlled-porosity osmotic pump (CPOP). This is because the kinetics of osmotic drug release is directly related to the solubility of drug within the core. Assuming a tablet core of pure drug, the fraction of drug released with zero-order kinetics is given by

$$F(z) = 1 - \frac{S}{\rho} \tag{3}$$

where $F(z)$ is the fraction released by zero-order kinetics, S the drug's solubility (g/cm^3), and ρ the density (g/cm^3) of the core tablet [17]. Drugs with a solubility of ≤ 0.05 g/cm^3 would be released with $\geq 95\%$ zero-order kinetics according to Eq. (3). However, the zero-order release rate would be slow according to Eq. (4), due to the small osmotic pressure gradient

$$\frac{dM}{dt} = \frac{A}{h} K \pi C \tag{4}$$

Eq. (4) describes drug release from osmotic pumps, where dM/dt is the drug delivery rate; A and h the membrane area and thickness, respectively; K constant; π the osmotic pressure of the core; and C the concentration (or the solubility, when excess of drug is present in the core) of drug in the dispensed fluid [18].

According to Eq. (3), highly water-soluble drugs would demonstrate a high release rate that would be zero-order for a small percentage of the initial drug load. Thus, the intrinsic water solubility of many drugs might preclude them from incorporation into an osmotic pump. However, it is possible to modulate the solubility of drugs within the core, and thus extend this technology for delivery of drugs, which otherwise may be poor candidates for osmotic delivery [2,3,19].

Glipizide is a weakly acidic drug that is practically insoluble in water and buffer media of acidic pH [8]. Tromethamine was added as a solubility modifier to increase the microenvironmental pH of the core above the p*K*a of glipizide. Tromethamine has been used as a buffering agent to increase the dissolution rate [20,21]. Inclusion of tromethamine as alkalinizing agent in the developed formulations was expected to increase the solubility of glipizide and hence, its release from the developed systems [19]. Two batches were prepared, in which the concentration of tromethamine was varied. Batches GLOP-III/A and GLOP-IV/A were prepared that contained 25 and 48.61% w/w of tromethamine, respectively. It is clearly evident from Fig. 1 that the concentration of tromethamine has a direct effect on drug release. Table 4 shows osmotic pressure, pH data, and MDT of these formulations. The difference in MDT between GLOP-III/A and GLOP-IV/A was found to be statistically significant ($P < 0.001$).

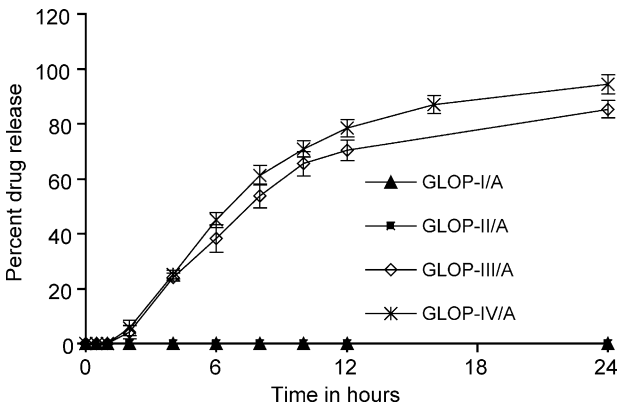

Fig. 1. Effect of concentration of tromethamine on drug release from the developed formulations.

Table 4
Osmotic pressure and pH data of selected core formulations and their effect on mean dissolution time (MDT)

Code	Core composition	Osmotic pressure (atm.)[a]	pH[b]	$MDT_{50\%}$ (h)[c]	$MDT_{75\%}$ (h)[c]
I	0% Tromethamine + mannitol	109.33	4.31	–[d]	–[d]
II	0% Tromethamine + fructose	119.47	5.48	–[d]	–[d]
III	25% Tromethamine + mannitol	134.13	9.68	4.56	5.75
IV	48.61% Tromethamine + mannitol	173.17	10.07	3.69	5.18

[a] Osmotic pressure of the saturated solution as measured by vapor pressure osmometer.
[b] pH of the saturated solution.
[c] Mean dissolution time of the coated tablets.
[d] Not achieved.

3.1.2. Effect of weight gain

To study the effect of weight gain of the coating on drug release, core tablets of glipizide (core code: IV) were coated (coating composition A) so as to get tablets with different weight gains (12, 13, and 15% w/w). Release profile of glipizide from these formulations is shown in Fig. 2. It is clearly evident that drug release decreases with an increase in weight gain of the membrane. $MDT_{75\%}$ between the different formulations (5.70, 7.64, and 8.06 h for formulations with weight gain of 12, 13, and 15% w/w, respectively) was found to be statistically significant ($P < 0.001$). No bursting of the systems was observed during the dissolution run in any of the formulations. In addition, exhausted tablets (after 24 h of dissolution studies) were evaluated for burst strength to assure that the tablets maintain their integrity in GIT and do not lead to dose dumping [11,12,22]. Fig. 3 shows the dependence of burst strength of the exhausted shells on weight gain. The strength of mechanical destructive forces in the GIT of humans and dogs has been reported to be 1.9 N (approximately 190 g) and 3.2 N (approximately 320 g), respectively [23,24]. In a previous study, it has been reported that osmotic pumps having the burst strength in the range of 500–600 g were intact in the GIT of dogs while those having burst strength of around 200 g were compromised [12]. In all cases, the value is much higher than the mechanical destructive forces in GIT, thus assuring that the formulations can be expected to remain intact in GIT without any incidence of dose dumping.

3.1.3. Effect of level of pore former

To study the effect of level of pore former (PVP), core formulations of glipizide were coated with coating compositions containing 0 and 50% w/w (of cellulose acetate) level of PVP (GLOP-IV/B and GLOP-IV/C, respectively). Release profile from these formulations, in comparison with GLOP-IV/A (containing 25% w/w of PVP), is shown in Fig. 4. It is clearly evident that the level of PVP had a direct effect on drug release. As the level of pore former increases, the membrane becomes more porous after coming into contact with the aqueous environment, resulting in faster drug release. Other workers have also obtained similar results [11,25,26]. Another parameter affected by the level of pore former was burst strength of the exhausted shells. The burst strength was inversely related to the initial level of pore former in the membrane. With the increase in level of PVP, the membrane became more porous after exposure to water, leading to a decrease in its strength. The results in the present study are consistent with other reports [11,22,26]. Effect of level of PVP on burst strength is shown in Fig. 5.

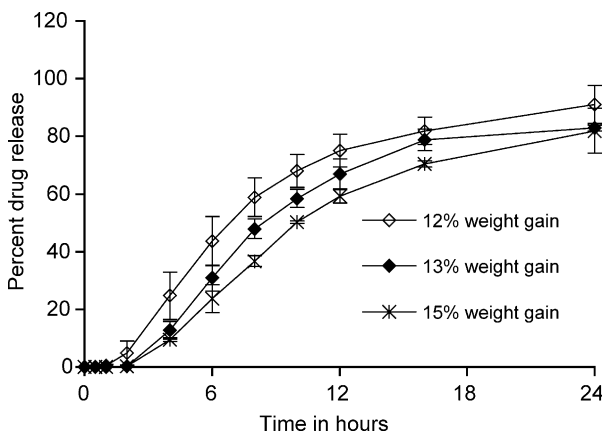

Fig. 2. Effect of weight gain on glipizide release from the developed formulations.

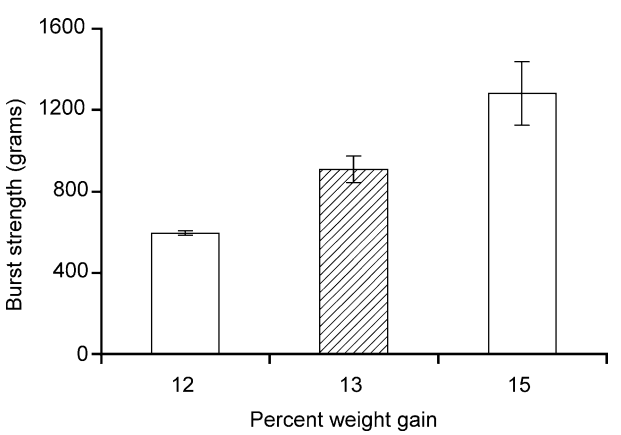

Fig. 3. Dependence of burst strength on weight gain of the membrane containing 25% w/w of pore former.

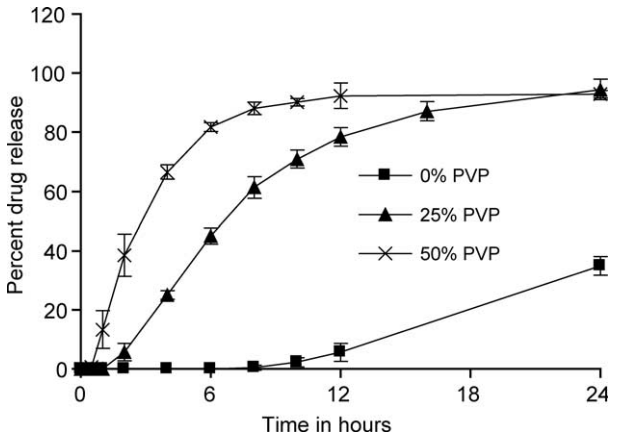

Fig. 4. Effect of concentration of PVP (at 15% weight gain of the membrane) on drug release from the developed formulations.

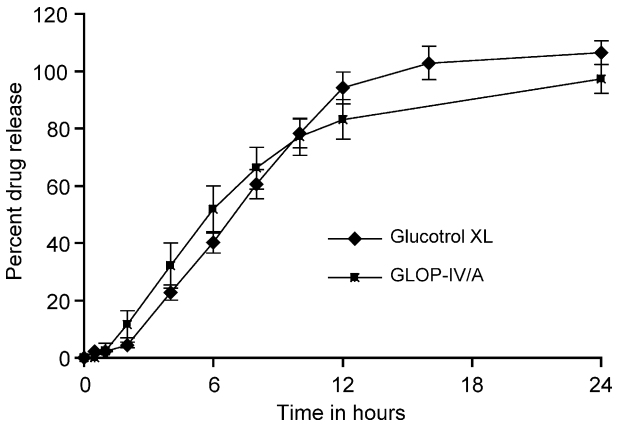

Fig. 6. Release profile of GLOP-IV/A formulation in comparison with Glucotrol XL® (Pfizer Inc., USA) in simulated intestinal fluid (pH 6.8) using USP-1 apparatus at 100 rev./min.

To evaluate the performance of the developed formulations, release profile was compared with a marketed innovator product. Glucotrol XL® marketed by Pfizer Inc., USA is based upon push–pull osmotic pump technology and is listed as a reference-listed drug [27]. It is a bilayer tablet coated with a semipermeable membrane. Drug along with osmagents is present in the upper compartment whereas lower compartment consists of polymeric osmotic agents. The drug compartment is connected to the outside environment via a delivery orifice. After coming into contact with the aqueous environment, polymeric osmotic layer swells and pushes the drug layer, thereby delivering the drug in the form of a fine dispersion via the orifice. The advantages of the *in house* developed system the are that it is simpler in design (single layer vs. bilayer), requires less number of manufacturing steps (no need for laser drilling), economical, and easily amenable to mass production. Fig. 6 shows release of glipizide from the formulation IV/A in comparison with Glucotrol XL®. The f_1 and f_2 values were found to be 13.97 and 56.55, respectively, taking the release profile of Glucotrol XL® as reference. This formulation was selected as the optimized formulation and evaluated further.

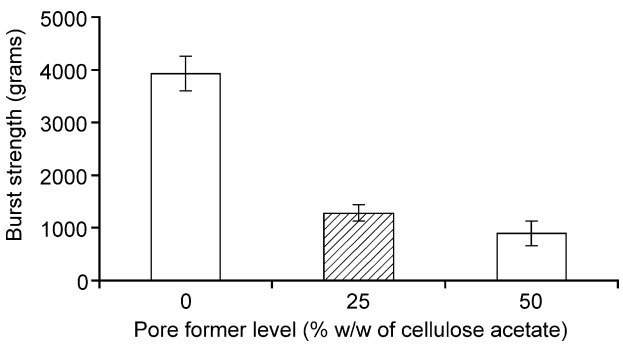

Fig. 5. Burst strength of membranes (at 15% weight gain) as a function of level of pore former.

3.2. Performance evaluation of the optimized formulation

The optimized formulation was evaluated for various pharmacopoeial and non-pharmacopoeial tests, results of which are listed in Table 5. The ready for powder blend was free flowing as demonstrated by the values of compressibility index (less than 15) and Hausner ratio (less than 1.25). Other parameters for the uncoated and coated tablets were also within limits. Exhausted shells, after dissolution, were visually observed for any imperfection or cracks in the coating. There were no visible cracks in the coating and it was found to be intact in all the batches after 24 h of

Table 5
Properties of the powder blend, core tablets, and final coated tablets of the optimized formulation

Parameter	Value
LOD (%)[a]	0.99
Bulk density[a] (gm/cm^3)	0.540
Tap density[a] (gm/cm^3)	0.578
Compressibility index[a] (%)	6.57
Hausner ratio[a]	1.07
Tablet weight (mg, $n = 20$)	
Core tablets	363.00 ± 7.89
Coated tablets	409.17 ± 7.35
Thickness (mm, $n = 20$)	
Core tablets	4.62 ± 0.06
Coated tablets	4.97 ± 0.07
Diameter (mm, $n = 20$)	
Core tablets	10.02 ± 0.01
Coated tablets	10.33 ± 0.04
Hardness (kp, $n = 10$)	
Core tablets	13.56 ± 2.30
Coated tablets	25.72 ± 1.95
Friability[b] (%)	0.096
Weight gain[c] (% of the core, w/w)	13
Content uniformity[c] (%, $n = 5$)	104.60 ± 2.44

[a] Properties of the granules.
[b] Properties of the core tablets before coating.
[c] Properties of the final coated tablets.

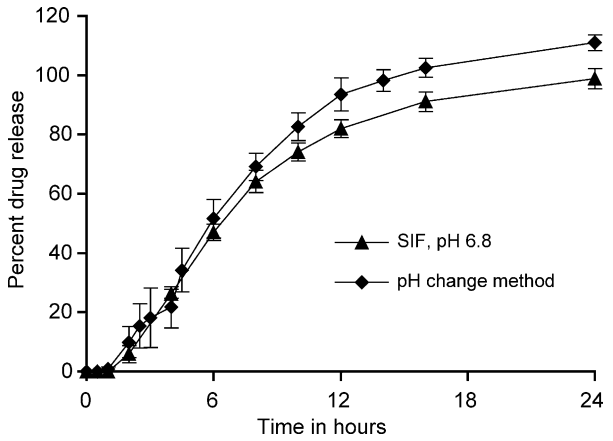

Fig. 7. Effect of pH on glipizide release from the developed formulations.

dissolution studies. The burst strength of the exhausted shell was found to be much more than the reported mechanical destructive forces in the GIT of humans [23,24], assuring that the formulation would be intact in GIT.

In order to study the effect of pH on drug release, release studies were conducted according to pH change method. Release studies of the optimized formulation (GLOP-IV/A) were conducted according to pH change method to assure a reliable in vivo performance and also to study the effect of pH on drug release. Fig. 7 shows release of glipizide from GLOP-IV/A formulation and it is clearly evident that the release profile is similar in both the media. The f_1 and f_2 values were found to be 13.05 and 56.77, respectively, taking the release profile in SIF as the reference.

Drug release from osmotic pumps, to a large extent, is independent of agitational intensity of the release media [2,18,28]. Two experiments were conducted to study this parameter. In the first experiment, release studies of GLOP-IV/A formulation were carried out in USP-I dissolution apparatus at varying rotational speed (50, 100, and 150 rev./min). Fig. 8 shows that the release profile of glipizide from the developed formulations is fairly

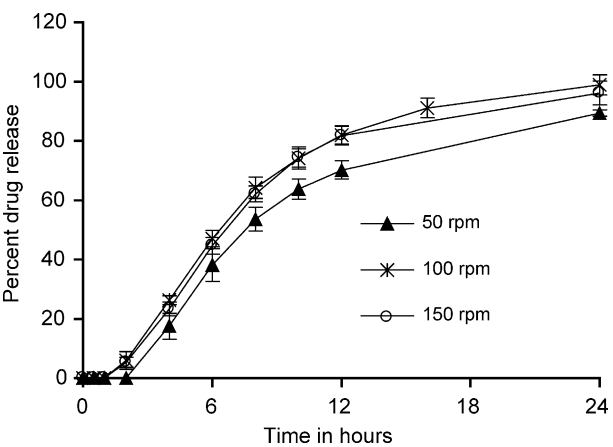

Fig. 8. Effect of agitational intensity of the release media on glipizide release from GLOP-IV/A formulation.

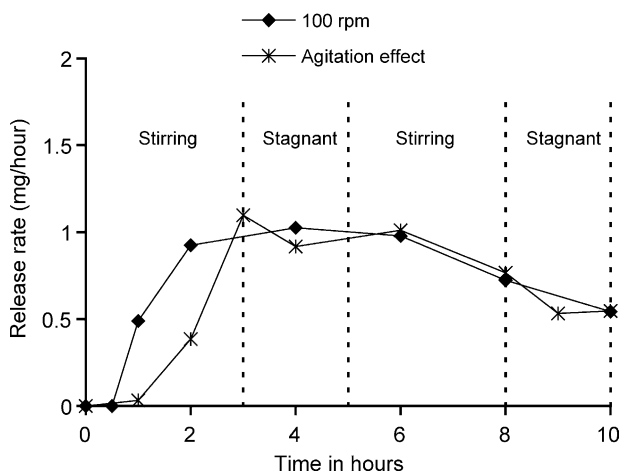

Fig. 9. Effect of agitational intensity of the release media on glipizide release rate—release from GLOP-IV/A formulation.

independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulations will be independent of the hydrodynamic conditions of the body. The f_1 and f_2 values were

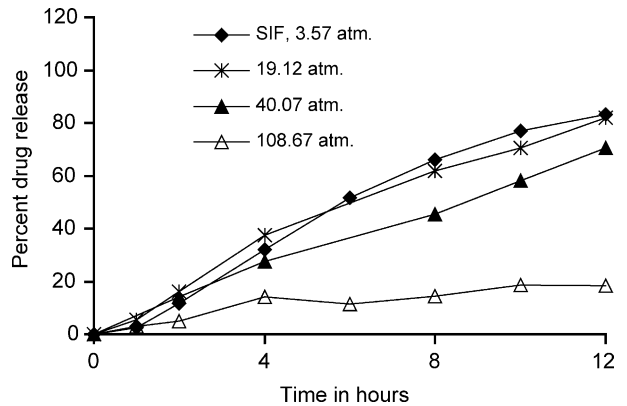

Fig. 10. Effect of osmotic pressure of the release media on glipizide release from GLOP-IV/A formulation.

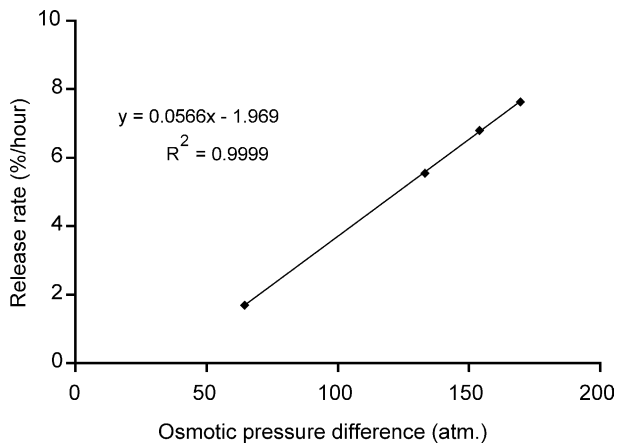

Fig. 11. Glipizide release rate from GLOP-IV/A formulation—effect of osmotic pressure difference across the membrane.

Table 6
Fitting of drug release data of the optimized formulation according to various mathematical models

Model	Parameters used to assess the fit of model						
	R^2	r	Intercept	Slope	k	SSR	AIC
Zero-order	0.9714	0.9856	−0.5603	7.6345	0.7635	173.29	38.08
First-order	0.9952	−0.9976	4.8127	−0.1641	−0.1641	70.32	31.78
Higuchi	0.9232	0.9608	−18.2650	26.7570	26.7570	638.76	53.68

R^2, goodness of fit; r, correlation coefficient; SSR, sum of squared residuals; AIC, Akaike information criterion; and k, release rate constant for respective models (k_0 in mg/h, k_1 in h^{-1}, and k_H in $\%/h^{1/2}$ for zero-order, first-order, and Higuchi rate equations, respectively).

found to be 16.54 and 54.02 (between 100 and 50 rev./min), 2.76 and 83.09 (between 100 and 150 rev./min), and 16.52 and 54.24 (between 50 and 150 rev./min), respectively. In the second experiment, stirred and stagnant conditions were induced in the same run. Release studies of GLOP-IV/A formulations were carried out in USP-I apparatus (at 100 rev./min). The stirring, however, was stopped after fixed time intervals so as to induce stagnant conditions. Release rates were calculated and are shown in Fig. 9 in comparison with those obtained at 100 rev./min (stirred conditions). It is clearly evident that the release rate is similar in both the experiments. Finally, it was concluded that drug release from the developed osmotic pumps is independent of the agitational intensity of the release media.

To study the effect of osmotic pressure, release studies of the optimized formulation (GLOP-IV/A) were conducted in media of different osmotic pressure. The results of release studies in media of different osmotic pressure showed that the drug release is highly dependent on the osmotic pressure

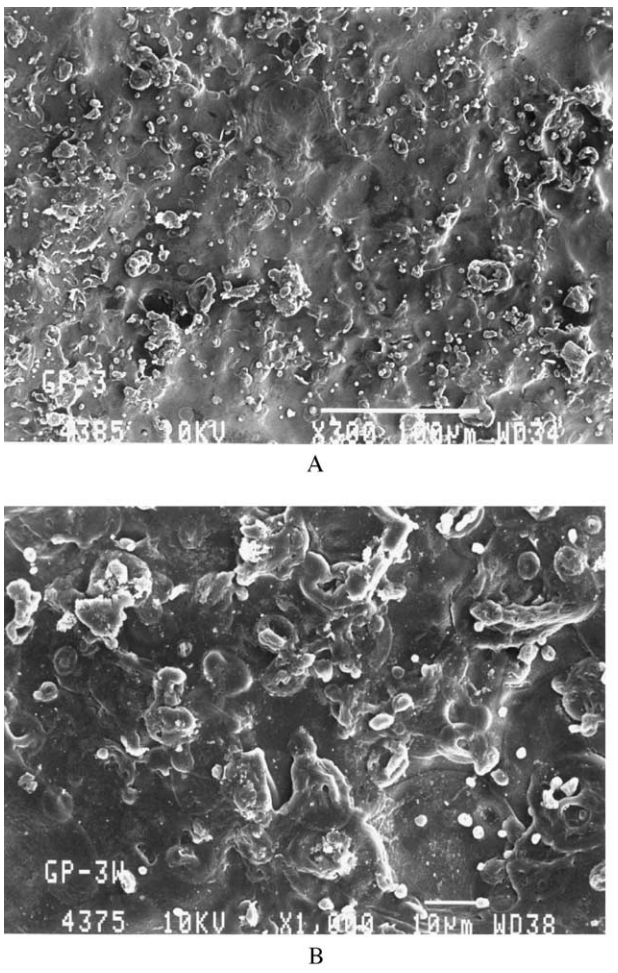

Fig. 12. SEM micrograph showing the membrane structure of formulation GLOP-IV/B before (A) and after dissolution studies (B).

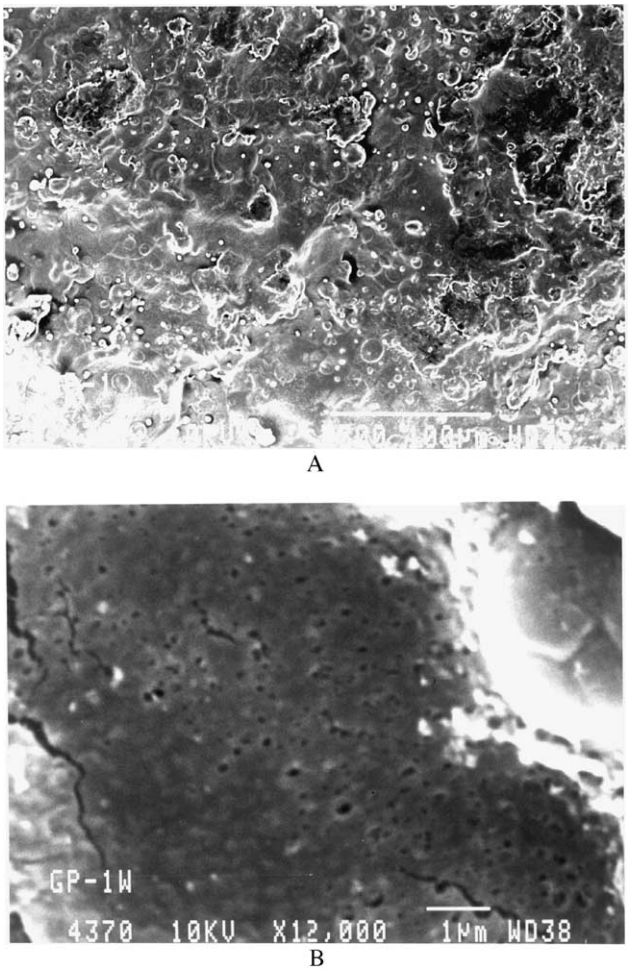

Fig. 13. SEM micrograph showing the membrane structure of formulation GLOP-IV/A before (A) and after dissolution studies (B).

of the release media. Glipizide release from the formulations decreased as the osmotic pressure of the media increased (Fig. 10). When the release rates obtained were plotted against the osmotic pressure difference across the membrane wall of the developed systems (osmotic pressure of the core formulation was determined to be 173.17 atm.), a linear relationship was obtained (Fig. 11). It was concluded that osmotic pumping is the major mechanism governing drug release from developed formulations [11,12,26,29].

3.3. Kinetics and mechanism of drug release

Dissolution data of the optimized formulation was fitted to various mathematical models (zero-order, first-order, and Higuchi) in order to describe the kinetics of drug release. Smallest value of sum of squared residuals (SSR) and Akaike information criterion (AIC) and best goodness-of-fit test (R^2) were taken as criteria for selecting the most appropriate model [30]. Drug release from *in house* formulations (GLOP-IV/A) fitted well into first-order kinetics (Table 6), while the second best model describing the release was zero-order model. The reason for first-order release from the *in house* formulations could be because of the presence of solubility modifier in the core formulation, which was necessary to modulate the solubility of glipizide. Since no attempts were made to control the release of solubility modifier from the formulations, majority of it must be releasing before the entire drug release took place and thus, drug release showed first-order release. The results are consistent with the earlier reports [17,19,31–35].

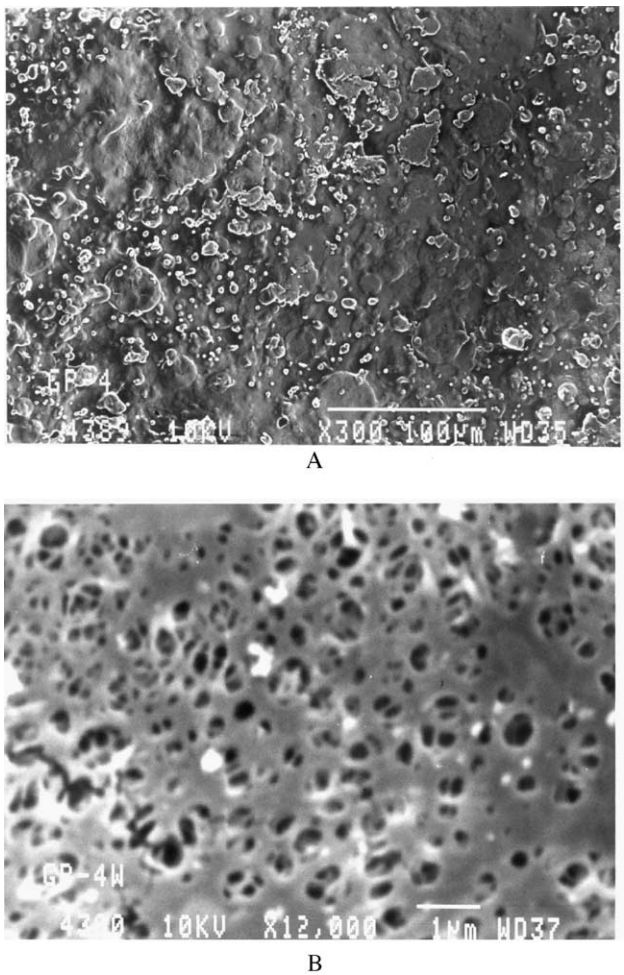

Fig. 14. SEM micrograph showing the membrane structure of formulation GLOP-IV/C before (A) and after dissolution studies (B).

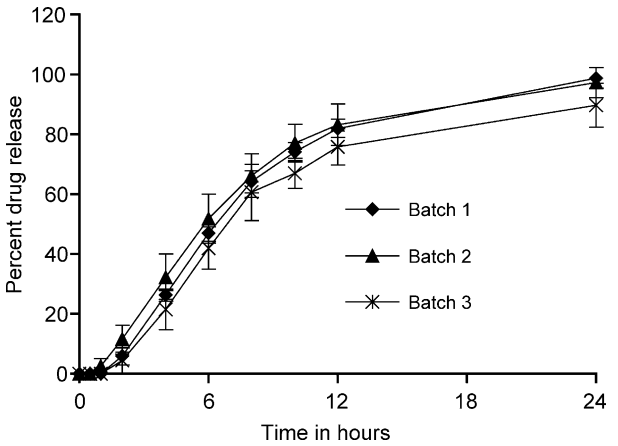

Fig. 15. Reproducibility of the manufacturing procedure—glipizide release from three repeat batches of GLOP-IV/A.

To investigate the changes in the membrane structure, surface of coated tablets (both before and after dissolution studies) was studied using SEM. Figs. 12–14 show SEM micrographs of membrane surface of *in house* formulations (GLOP-IV/B, GLOP-IV/A, and GLOP-IV/C containing 0, 25, and 50% w/w of PVP, respectively) both before and after dissolution studies. After dissolution studies, coating was intact without any cracks. However, there was formation of channels/pores in the membrane, which possibly acted as exit ports for the drug. When comparison

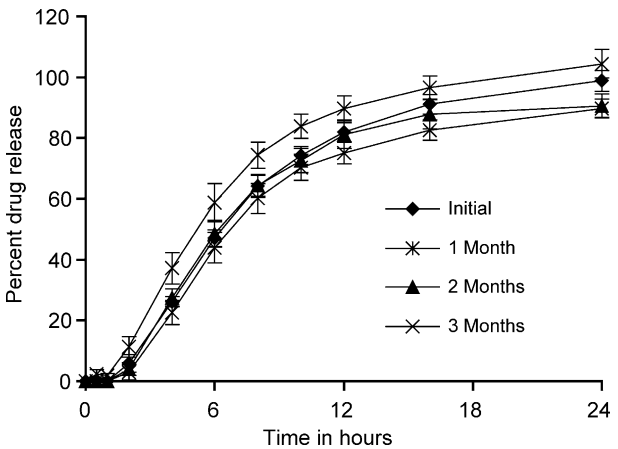

Fig. 16. Dissolution stability of GLOP-IV/A formulation in 0.04 mm thick aluminum foil after 3 months of storage at 40 °C and 75% RH.

Table 7
Evaluation of GLOP-IV/A formulation after 3 months of storage at 40 °C and 75% RH

Parameter	Initial	1 month	2 months	3 months
Drug content (%)[a]	104.60 ± 2.44	106.71 ± 2.90	101.35 ± 1.64	102.16 ± 2.07
Hardness (kp)[a]	25.72 ± 1.95	28.70 ± 2.30	28.86 ± 2.19	28.58 ± 2.13
Burst strength (g)[a]	857.88 ± 64.45	796.00 ± 91.82	956.50 ± 104.02	894.43 ± 96.04
f_1 value[b]	–	8.63	3.85	14.52
f_2 value[b]	–	61.62	72.73	54.50
$MDT_{75\%}$ (h)[c]	5.19	5.27	5.29	4.71

[a] Values expressed as average ± standard deviation.
[b] Initial sample (0-month) was taken as reference to calculate f_1 and f_2 values.
[c] Mean dissolution time.

was made among the membranes containing different levels of pore formers, it was found that the membrane that initially contained higher level of pore former becomes more porous after the dissolution studies. Moreover, as the level of pore former in the membrane increases, the size and number of pores increases. The membrane becomes more porous, presumably because of leaching of pore former from the membrane. In Figs. 12–14, top panel 'A' shows the membrane structure before dissolution studies. In all the cases, no significant difference was observed due to the presence of different levels of pore former (PVP). The surface of coated tablet was smooth before coming into contact with the aqueous environment and the coats appeared to be free of point defects. Fig. 12B shows SEM micrograph of an excised section of the top surface of membrane (after dissolution studies) containing 0% level of PVP (GLOP-IV/B). It exhibits a surface morphology similar to that of Fig. 12A, suggesting that there is no evidence of development of pores in the membrane. On the other hand, after dissolution studies, there was formation of pores in the membranes that contained 25 and 50% level of PVP (GLOP-IV/A and GLOP-IV/C, respectively). Fig. 13B shows SEM micrograph of the membrane of GLOP-IV/A formulation, in which pores were formed after exposure to the release media. The membrane that contained 50% level of PVP (GLOP-IV/C) showed significant porosity after dissolution studies (Fig. 14B). Finally, it can be concluded that leaching of pore former from the membrane (after coming into contact with the aqueous environment) leaves behind the porous membrane from where the drug release takes place. The numbers of pores are directly proportional to the initial level of pore former in the membrane.

3.4. Reproducibility of manufacturing procedure

The reproducibility of the manufacturing procedure was confirmed by preparing three repeat batches (batch size of 500 tablets each) of the final optimized formulation on three different occasions. Release studies were conducted in SIF and similar release profiles were obtained (Fig. 15) demonstrating that the manufacturing procedure is reproducible. The f_1 and f_2 values were found to be 6.67 and 70.51 (between batches 1 and 2), 9.39 and 61.46 (between batches 1 and 3), and 14.42 and 54.65 (between batches 2 and 3), respectively.

3.5. Accelerated stability studies

GLOP-IV/A formulations were packed in strips of 0.04 mm thick aluminum foil laminated with PVC and stored in ICH certified stability chambers maintained at 40 °C and 75% RH for 3 months. The tablets were withdrawn periodically and evaluated for drug content, hardness, burst strength, and release studies. The formulations were found to be stable in terms of drug content and dissolution stability (Fig. 16 and Table 7). In all the cases, the burst strength was higher than the reported values of mechanical destructive forces in the GIT [23,24], ensuring the formulations to be intact in GIT without any incidence of dose dumping.

3.6. Prediction of in vivo performance

Plasma levels of glipizide were predicted by the superposition method [14] using the known pharmacokinetic parameters of drug (Table 3) and various drug release parameters (R^0 and t_{Del}) calculated from in vitro release data. Fig. 17 shows predicted plasma levels after administration

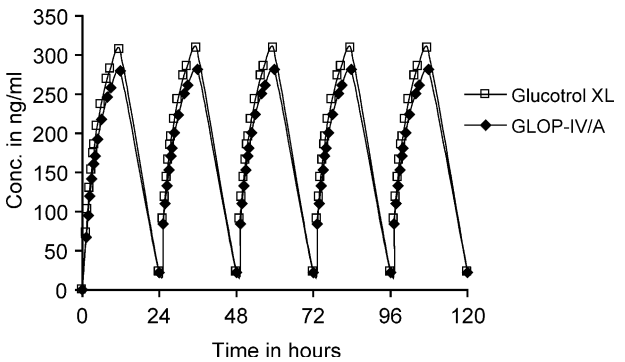

Fig. 17. Predicted steady-state plasma levels of glipizide after administration of a test dose (10 mg) of GLOP-IV/A formulation in comparison with Glucotrol XL®.

Table 8
Predicted in vivo performance of different products

Predicted parameters[a]	Glucotrol XL®	GLOP-IV/A	% PD[b]
C_{max} (ng/ml) after a single dose study	306.66	280.02	−8.69
C_{max} (ng/ml) at steady state	308.66	281.85	−8.69
T_{max} (h)	11.59	11.86	2.33
C_{min} (ng/ml) after a single dose study	22.64	21.88	−3.36
C_{min} (ng/ml) at steady state	22.79	22.02	−3.36
$AUC_{0-\tau}$ (ng h/ml) after a single dose study	4469.78	4111.70	−8.01
$AUC_{0-\tau}$ (ng h/ml) at steady state	4582.69	4220.43	−7.91

[a] Predicted from drug release studies using the method of superposition [14]. The drug release parameters from in vitro release studies were calculated using linear regression. Glucotrol XL®: $R^0 = 0.840$ mg/h, $t_{Del} = 11.59$ h. GLOP-IV/A: $R^0 = 0.763$ mg/h, $t_{Del} = 11.86$ h.
[b] % Predicted error from the innovator.

of a test dose (10 mg) of Glucotrol XL® and GLOP-IV/A formulation. It is clearly evident that both the products are able to maintain plasma levels within the therapeutic range (20–300 ng/ml) [6,36]. Table 8 lists various predicted parameters after a single dose and at steady state for the developed formulation. As can be seen, absolute % PD was found to be less than 15%. Thus, it can be concluded that the developed formulation should produce plasma levels that are well within the therapeutic range and similar to those produced by the marketed formulations [15,16].

4. Conclusions

Extended release formulations of glipizide were developed based on osmotic technology. The effect of different formulation variables was studied to optimize release profile. Level of solubility modifier (tromethamine) affected the release from the developed formulations. Drug release was directly proportional to the initial level of pore former, but inversely related to the membrane weight. The release from the developed formulations was independent of pH and agitational intensity of the release media, assuring the release to be fairly independent of pH and hydrodynamic conditions of the body. Glipizide release from the developed formulations was inversely proportional to the osmotic pressure of the release media, confirming osmotic pumping to be the major mechanism of drug release. Results of SEM studies showed the formation of pores in the membranes after coming into contact with the aqueous environment, the number of pores being dependent on the initial level of pore former in the membrane. The manufacturing procedure was standardized and found to be reproducible. Developed formulations were found to be stable after 3 months of storage at accelerated stability conditions. The predicted steady-state plasma levels of *in house* formulations were found to be within desired range and comparable with that of innovator.

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