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RESEARCH ARTICLE

Inlay osmotic pump tablets containing metformin and glipizide

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Abstract

The goal of diabetes therapy today is to achieve and maintain as near normal glycemia as possible to prevent the long-term microvascular and macrovascular complications of an elevated blood glucose. A newly developed inlay osmotic pump tablet (IOPT) can deliver glipizide (GLZ) and metformin HCl (MET) gradually in controlled manner. The aim of present investigation was to prepare the IOPT that can deliver >75% of GLZ in 2 h, whereas MET released after 2 h and sustained up to 12 h. In the present work, HP-β-CD was used to modify the solubility of GLZ before incorporating in the osmotic system and MET was spray-dried with HPMC A15C to modify its release profile, flow property, and compressibility. Various parameters mainly $G_{75\%}$ (75% GLZ release), t_{LMET} (lag time of MET release from device), $Q_{10\,h}$ (percent of MET released within 10 h), and RSQ_{ZERO} (R^2 of release data fitted to zero-order equation) were used to compare different formulations. The effects of different formulation variables, that is, osmagents, concentration of hydrophilic polymer, diameter of drug releasing orifice, and coating composition on the drug release profile were investigated. The release rate of GLZ could be effectively modified by the addition of sodium carbonate and sodium chloride, whereas the release rate of MET was adjusted by dual-coating system and by addition of hydrophilic polymer. The developed inlay osmotic system could be effective in the multidrug therapy of diabetes by delivering both drugs in a controlled manner.

Keywords: Inlay tablet, osmotic pump, metformin HCl, glipizide, controlled drug delivery

Introduction

The diagnosis and management of type 2 diabetes mellitus is rapidly undergoing progressive changes. Type 2 diabetes is characterized by abnormalities in insulin secretion and insulin sensitivity. About 80% to 90% of subjects with type 2 diabetes exhibit insulin resistance together with features of the metabolic syndrome. Insulin resistance is closely associated with excess fat and redistribution, abnormal adipocytokine secretion, and the deregulation of intramyocellular fatty acid metabolism. The goal of diabetes therapy today is to achieve and maintain as near normal glycemia as possible to prevent the long-term microvascular and macrovascular complications of an elevated blood glucose[1]. Type 2 diabetes is a progressive illness and most patients will eventually need more than two oral agents to maintain adequate glucose control[2]. Switching from one drug to another in a patient with poorly controlled glycemia or maximizing the dosage of an existing drug is only rarely hopeful. Adding medications from different groups to the existing regimen often provides more effective glycemic control. Several of the available oral agents have been studied in combination and have been shown to further improve glycemic control when compared with monotherapy[3].

In 1995, metformin (MET) was added to sulfonyl urea therapy in patients who had not achieved glycemic control with sulfonyl urea as monotherapy, although the two agents were found to have a remarkable effect on glycemic control or lowering of hemoglobin-A1c. Prescription data reveals ~60% of MET use is in combination with a sulfonyl urea[1].

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A glipizide (GLZ) and MET combination is used to treat high blood sugar levels that are caused by type 2 diabetes.

The concept of multicomponent therapy is beneficial when the selected agents posses differing mechanism of actions that provide additive or synergistic efficacy, reducing the required doses of individual agents as compared with monotherapy and potentially limiting side effects. Multicomponent therapy may seem costlier than monotherapies in the short term, but causes significant savings, lower treatment failure rate, lower case fatality ratios, reduction in development of resistance, and consequently less money needed for the development of new products in long-term therapy[4].

Conventional tablets containing a fixed dose of MET and GLZ are widely available in the market. SR microcapsules of MET by ethyl cellulose are described by Balan et al.[5], where MET gave *in vitro* release for up to 22 h. Defang et al.[6] formulated MET and GLZ into extended release formulations exhibiting comparable *in vitro* release profiles using two formulation principles, that is, elementary osmotic pump tablets and bilayer hydrophilic matrix tablet. Both the drug released from the osmotic system in sustained manner and independent of *in vitro* and *in vivo* conditions. An alternative approach for effective control of blood glucose is to manufacture oral dosage forms delivering both immediate release (IR) and sustained release (SR) antidiabetic drugs from single-dosage form. Based on this concept, one patent was filed where tablets containing 500 mg MET as SR and 2.10 mg of glimepiride as IR were made. Torrent Pharmaceutical Ltd. (Gujarat, India) developed inlay tablet for antidiabetic drugs containing rosiglitazone in IR layer and MET in SR form.

Inlay tablet is a type of layered tablet in which instead the core tablet being completely surrounded by coating, top surface is exposed. During the preparation, only the bottom of the die cavity is filled with coating material and core is placed upon it. When compression force is applied, some coating material is displaced to form the sides and compresses the whole tablet[7].

A newly developed inlay osmotic system that can deliver GLZ and MET gradually for extended period of time was characterized in a view to reduce the problems associated with the multidrug therapy of diabetes. In the preparation of IOPT, GLZ layer was compressed on 5-mm diameter punch and instead of coating material the MET layer was compressed with GLZ tablet (core tablet) on 13-mm punch to produce final tablet.

In the present study, an IOPT system that could deliver GLZ and MET with predefined objective was developed and evaluated to reduce the problems associated with the multidrug therapy of type 2 diabetes mellitus. It is an objective of this research to provide a novel pharmaceutical composition in the form of IOPT tablet that could deliver not less than 75% of GLZ in 2 h, whereas MET could give SR effect, which started release after 2 h and delivered up to 12 h.

MET is highly soluble and high-dose drug (500 mg), whereas GLZ is water-insoluble and low-dose drug (5 mg). It is a great challenge for pharmacists to use less excipient and provide satisfactory extended release of MET and GLZ. In this article, HP-â-CD was used to improve the solubility of GLZ within the core and a MET composite with hydrophilic polymer was used to improve the flow property, compressibility and prevent the immediate burst release of MET.

Materials

GLZ, MET, polyethylene glycol 400 (PEG 400), Eudragit L100, cellulose acetate (CA), microcrystalline cellulose phosphate (MCCP), dibasic calcium phosphate (DCP), polyvinyl pyrrolidone (PVP) K30, mannitol, magnesium stearate, and talc were received as gift sample by Sword and Shield Pharmaceutical Ltd. (Chhatral, India). The samples of HP-β-CD with an average molecular weight of 15,000 Da were generous gift from Roquette (France). Sodium chloride, sodium bicarbonate, and potassium chloride were purchased from S.D. Fine Chem. Ltd. (India). Different grades of HPMC were gifted by Colorcon Asia Pacific Pvt. Ltd. (India). The other chemicals used were of analytical grade.

Experimental

Drug analysis

Phenomenex C_{18} (2) column (250 mm × 4.6 mm i.d., 5 µm particle size) was used at ambient temperature. The mobile phase comprised of 0.01 M pH 6.5 phosphate buffer:methanol:acetonitrile (30:40:30 v/v/v) and final pH adjusted to 6.5 ± 0.02 with 0.2 M NaOH and 0.2 M H_2SO_4 and was pumped at a flow rate of 1 mL/min. The mobile phase was filtered through nylon 0.45 µm–47 mm membrane filter. The elution was monitored at 225 nm. The injection volume was 20 µL. A calibration curve was plotted over a concentration range of 10–50 µg/mL and 1–10 µg/mL for MET and GLZ, respectively.

Preparation and optimization of OPT

For the formulation of IOPT, GLZ layer was separately compressed on 5-mm round concave punch and instead of coating material the MET layer was compressed with GLZ tablet (core tablet) on 13-mm concave punch to produce inlay tablet.

The GLZ layer was prepared by the wet granulation method and the batch size of 100 tablets was kept. GLZ complex was mixed with all excipients except magnesium stearate and talc and passed through 80# sieve. IPA was added to make granules and lump mass was passed through 20# sieve. The granules were dried at 60°C for 2 h and finally passed through 40# sieve. The magnesium stearate and talc were mixed with dried granules. The lubricated mass was compressed on laboratory model Rimek tablet press fitted with 5-mm round standard concave punches to get average weight of 100 ± 7.5 mg. The average hardness of compressed tablets was 3.0 ± 0.5 kg/cm^2.

For the formulation of MET layer, spray-dried MET composite was mixed uniformly with other excipients. For the formulation of inlay tablet, MET layer was compressed with GLZ tablet by direct compression technique. The GLZ tablet was placed on cavity of 13-mm standard concave punch. Then MET layer was filled and compressed to get inlay tablet with average weight of 690 ± 15 mg. The average hardness of compressed tablets was 6.5 ± 1.5 kg/cm^2. The formulations of inlay tablets are depicted in Table 1.

Various mathematical parameters were analyzed to optimize the both layer. Various parameters mainly $G_{75\%}$ (75% of GLZ release), t_{LMET} (lag time of the MET release from device), $Q_{10\ h}$ (percent of MET released within 10 h), and RSQ_{ZERO} (R^2 of release data fitted to zero-order equation) were used to compare different formulations. Formulations with acceptable $G_{75\%}$ (i.e. $G_{75\%} \geq 2$ h) were adopted for further evaluations for GLZ layer. Amongst the other formulations, those with t_{LMET} (i.e. $t_{LMET} < 2$ h for >10% release) were selected for further optimization. The defined range of $Q_{10\ h}$ was 70% < $Q_{10\ h}$ > 90%.

Coating and drilling

The inlay tablets were prepared with dual-coated systems to get the desired release profile. First, it was coated with enteric coated polymer (2.5% w/v Eudragit L 100 in methanol) and water-insoluble plasticizer. Further, the tablets were coated with 2.5% w/v CA in acetone:water (95:05) using castor oil or PEG 400 as plasticizer. Conventional laboratory model coating pan (SS, 30-cm pear shaped, baffled, 25 rpm) was used for coating. Inlay tablets were placed in the coating pan along with 50 g of dummy tablets (tablets made using 9.6-mm round concave punches and containing lactose, DCP, starch paste, magnesium stearate, and talc). The inlet air temperature was about 60–70°C. The manual coating procedure was used based on an intermittent spraying and drying technique. The coated tablets were dried overnight at 50°C to remove the residual solvent.

An orifice of 1-mm size was made through the membrane by a mechanical driller. To check the effect of orifice size, the best batch among the preliminary trial batches was selected. To check the influence of membrane variation on drug release profile, various combinations were used, which are depicted in Table 2.

Table 1. Formulae for inlay tablet (%/tablet).

Ingredients	I1	I2	I3	I4	I5
GLZ layer					
Complex of GLZ (≈5 mg of GLZ)	39	39	39	39	39
NaCl	40	30	20	10	00
$NaHCO_3$	0	10	20	30	40
PVP-K30	5	5	5	5	5
Mannitol	14	14	14	14	14
IPA	q.s	q.s	q.s	q.s	q.s
Mg stearate	1	1	1	1	1
Talc	1	1	1	1	1
MET layer					
MET composite (≈500 mg of MET)	79	79	79	79	79
NaCl	10	10	10	10	10
MCCP	10	10	10	10	10
Mg stearate	01	01	01	01	01

In vitro drug release profile

In vitro drug release was tested according to USP XXX NF XXV-modified release products in apparatus II at 37 ± 0.5°C and 50 rpm using 750 mL of 0.1 N HCl for the first 2 h then added 250 mL of 0.20 M tribasic sodium phosphate that had been equilibrated to 37 ± 0.5°C. If necessary, the solution was adjusted with 2 N hydrochloric acid or 2 N sodium hydroxide to a pH of 6.8 ± 0.05. A sample (10 mL) of the solution was withdrawn at different time intervals from the dissolution apparatus for 12 h, and the samples were replaced with fresh dissolution medium. The samples were filtered through Whatman filter paper #1 and the solutions were analyzed by HPLC method at 225 nm. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

Accelerated stability studies

Optimized formulations of IOPT were packed in aluminum strips laminated with PVC. According to ICH guideline, the packed formulations were stored in stability chambers (Cintex humidity oven; Cintex Industrial Corporation, Dadar, Mumbai) maintained at 40°C and 75% relative humidity for 3 months. The samples were withdrawn and evaluated for drug content and drug release studies.

Table 2. Coating composition for IOPT.

	Enteric coat		Semipermeable coat		
Batch No.	% Weight gain	Plasticizer	% Weight gain	Plasticizer	Pore former
I6	—	—	5%	PEG 400 (20% w/w)	Eudragit L 100 (20% w/w)
I7	—	—	5%	Castor oil (20% w/w)	Eudragit L 100 (20% w/w)
I8	2%	PEG 400 (20% w/w)	5%	PEG 400 (20% w/w)	—
I9	2%	Castor oil (20% w/w)	5%	PEG 400 (20% w/w)	—
I10	1%	Castor oil (20% w/w)	5%	PEG 400 (20% w/w)	—
I11	1%	Castor oil (20% w/w)	7.5%	PEG 400 (20% w/w)	—
I12	1%	Castor oil (20% w/w)	5%	PEG 400 (40% w/w)	—
I13	1%	Castor oil (20% w/w)	5%	Castor oil (20% w/w)	—

Scanning electron microscopic studies

In order to elucidate the surface of coated tablets, both before and after dissolution studies, scanning electron microscope (SEM) was used. The sample tablets (coated tablets before dissolution studies) were examined for surface morphology by a SEM (JSM-5600, Jeol, Japan). On the other hand, small sample of the coating membrane was carefully cut from the exhausted shells (after 12 h of dissolution studies) and dried at 50°C for 12 h, and examined under SEM for surface morphology changes after dissolution.

Results and discussion

Drug analysis

To determine the linearity of the HPLC detector response, standard solutions of GLZ and MET were prepared. Linear correlation was obtained between peak area versus concentration of GLZ and MET in the range of 1 to 10 μg/mL and 10 to 50 μg/mL, respectively. Each measurement represented the average of three replicates. The regression equations for GLZ and MET were Absorbance = 19,510 × concentration– 12,576 and Absorbance = 97,994 × concentration + 19,990, respectively, and the correlation coefficients for the same were 0.998 and 0.996, respectively.

Formulation development

In general, both highly water-soluble and poorly water-soluble drugs are not good candidates for osmotic delivery. However, MET is highly soluble and high-dose drug (500 mg), whereas GLZ is water-insoluble and low-dose drug (5 mg). It is a great challenge to design a formulation containing these types of drugs. From our previous study carried out to improve the dissolution of GLZ, the complex of GLZ with HP-â-CD was prepared. The optimization, characterization, and stability study of complex was carried out in our previous work[8]. Inclusion complex of HP-β-CD:GLZ (2:1) showed better *in vitro* dissolution profile, which was selected for further studies.

On the other hand, high-dose MET was difficult to formulate into a tablet dosage form due to its poor compressibility and compactibility[9]. Difficulty was overcome by utilizing spray-dried MET composite with hydrophilic polymer to prepare the tablet core.

MET composite was prepared by preparing aqueous solutions of 10% w/v MET and 0.5% w/v HPMC K4M. The prepared solutions were subsequently spray-dried using spray-dryer (Labultima, Mumbai, India). The spray-drying was carried out at following conditions: inlet temperature, 150°C; pump setting, 2 mL/min; aspirator setting, 35 Nm^3/h. These conditions resulted in an outlet temperature of 60–70°C. The prepared MET composite exhibited good flow and high compressibility than the pure MET crystals. The value Carr's index for MET composites (around 17%) was less than the pure MET (40.66%). The value of Carr's index should be <20% for better compressibility. The result of angle of repose for pure MET (47.18°) was more than the MET composites (21.78°). So, spray-drying improves the flow properties and compressibility of powder. The MET composites restrict the initial burst release and retarded the release up to 60 min.

Optimization of GLZ layer

In order to get desired release profile from osmotic devices, various excipients were incorporated in the core formulation of GLZ layer. The results (Figure 1A and 1B) show that the osmotic devices containing only NaCl as osmogents released GLZ after 1 h of exposure to the dissolution medium with an exceptions of the devices containing $NaHCO_3$ (effervescent-generating agent) because it produced effervescent when reacted with an acid. In first 2 h, the tablets were placed in dissolution medium containing gastric fluid with pH 1.2. The relatively vigorous effervescent effect might be responsible for the initial 2 h faster release rate. It was indicated that the incorporation or effervescent-generating agent into the GLZ core tablet improved the drug release from IOPT. In other words, effervescent helped to produce desired $G_{75\%}$ value. Incorporation of more amount of effervescent-generating agent improved the drug release profile of GLZ but it also reduced the t_{LMET} values. So, the batch I3 containing 20% of effervescent-generating agent ($NaHCO_3$) and 20% of NaCl was selected as an optimized batch for GLZ layer, which produced desired $G_{75\%}$ without affecting MET release (i.e. t_{LMET}).

Influence of coating and drilling on in vitro drug release profile

Based on the above results, tablet formulation I3 was adopted in the following study. The membrane was also an important factor for the release profile of IOPT. Therefore, the following studies were carried out to investigate the influence of coating compositions and membrane thickness on drug release profiles. Plasticizers modify the physical properties of polymers and improve their film-forming characteristics by changing their viscoelastic behavior. Plasticizers turn a hard and brittle polymer into a softer, more pliable material and possibly make it more resistant to mechanical stress. These changes also affect the aqueous permeability of polymer films. The water permeability of CA film is relatively high and can be easily adjusted by selecting the proper concentration and type of plasticizer. The enteric coat retarded the MET release due to restriction of drug release through the membrane. The water-soluble plasticizer present in the membrane creates the pores after contact with dissolution medium, which provide the release of MET through the membrane.

Figure 2A and 2B clearly indicates that the membrane variables have significant effect on *in vitro* drug release profile of drug form IOPT.

Table 3. Influence of hydrophilic polymer on formulation of IOPT (%/tablet).

Ingredients	I16	I17	I18	I19	I20	I21
GLZ layer						
Complex of GLZ (≈5 mg of GLZ)	39	39	39	39	39	39
NaCl	20	20	20	20	20	20
$NaHCO_3$	20	20	20	20	20	20
PVP-K30	5	5	5	5	5	5
Mannitol	14	14	14	14	14	14
IPA	q.s	q.s	q.s	q.s	q.s	q.s
Mg stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
MET layer						
MET composite (≈500 mg of MET)	79	79	79	79	79	79
NaCl	10	10	10	10	05	00
HPMC K4M	10					
HPMC K15M		10		05	10	10
HPMC K100M			10			
MCCP	q.s	q.s	q.s	q.s	q.s	q.s
Mg stearate	01	01	01	01	01	01

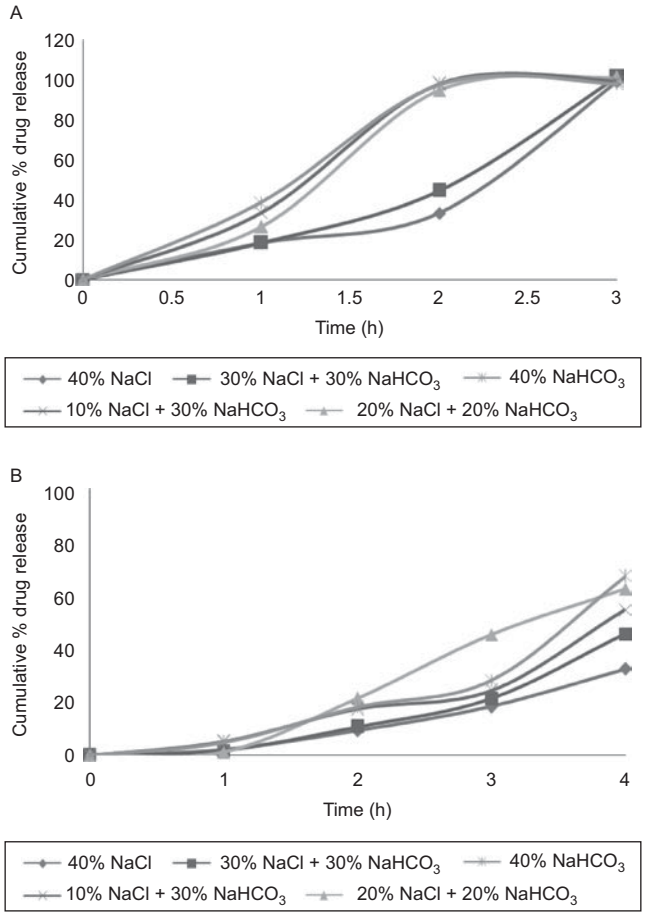


Figure 1. (A) *In vitro* GLZ release profile. (B) *In vitro* MET release profile.

To study the influence of pore former in SIF, the inlay tablets were film-coated with semipermeable membrane of 2.5% w/v CA with castor oil as plasticizer or with a microporous membrane consisting of PEG 400 as plasticizer. The CA membrane was composed of Eudragit L100 (20% w/w, total weight of CA) with castor oil and PEG 400 in concentration of 20% w/w (total weight of CA). Incorporation of Eudragit L100 in CA solution with PEG 400 was not enough to prevent MET release from IOPT in GF due to pore created by dissolving PEG 400 after contact with dissolution medium. Although the Eudragit L100 with castor oil restricted the release of MET in GF, it did not retard the MET release over an extended period of time. This is due to the coating of Eudragit L 100 was dissolved in SIF and created porous structure. To get desired release profile, further batches were dual-coated, which was first coated by enteric coating and further coated by semipermeable membrane.

Enteric coating showed significant effect on *in vitro* drug release profile for both drugs. At higher weight gain (2%), the drug release rate was slower than the 1% weight gain. Enteric coating decreased the drug release rate of MET and GLZ from IOPT. Although the thickness of CA membrane had no effect on *in vitro* drug release profile of GLZ, it retarded the MET release from IOPT. Figure 2A and 2B depicts that increase in PEG 400 level in both coating membranes led to an increase of drug release rate. Since PEG 400 incorporated into the membrane, the more void space formed after leaching and as a result higher the permeability of membrane and the drug release rate. In case of castor oil, it was found that the release rate of drugs was inversely proportional to the concentration. Hydrophilic plasticizers such as PEG 400 were found to increase drug release, whereas hydrophobic plasticizers like castor oil were found to decrease drug release from IOPT.

Based on the above results, batch I10 was selected to check the effect of orifice on *in vitro* drug release profile. Three different sizes of orifice were made for batch I10. Once the tablet formulation and membrane variables were chosen, the orifice size was key factor for drug release. Figure 3 shows the influence of orifice size on *in vitro* release profile of GLZ and MET.

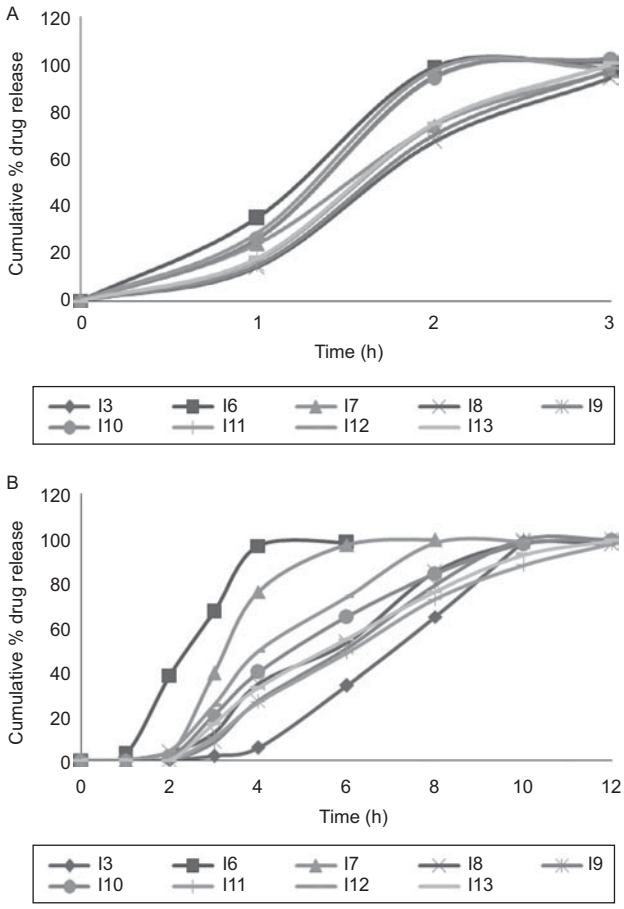


Figure 2. (A) Influence of membrane composition on *in vitro* GLZ release profile. (B) Influence of membrane composition on *in vitro* MET release profile.

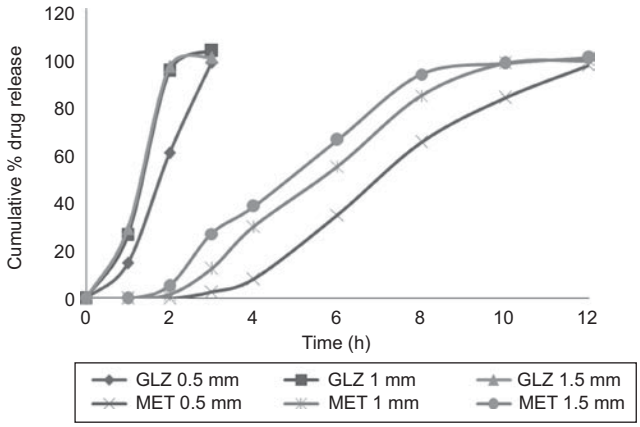


Figure 3. Influence of drilling orifice on *in vitro* drug release.

The size of orifice had significant difference in the release profile. The smaller orifice (0.5 mm) gives low drug release rate, whereas tablet drilled with larger orifice (1.5 mm) gives high drug release rate. So the orifice size had direct effect on *in vitro* drug release profile. GLZ release also depended on the dissolution medium penetration from orifice, so the small orifice had low capacity of penetration whereas large orifice had higher. During *in vitro* drug release study, there was no burst effect observed; it can be inferred that the selected orifice size (0.5mm, 1.0mm, and 1.5mm) successfully prevented the membrane from rupturing by effectively releasing the hydrostatic pressure developed inside the system and delivered the drug from IOPT.

Optimization of MET layer

As per the above results, the GLZ layer was optimized to get desired dissolution parameters, but it was not possible to retard the MET release according to the requirements. In order to make drug release slightly slow, the excipients named release retarder were added to form MET layer. Li et al.[10] used ethyl cellulose, HPMC, and PEO as release retarder; amongst these, HPMC showed zero-order drug release profile in osmotic pump tablet. To retard the MET release form IOPT, different grades of HPMC (HPMC K4M, HPMC K15M, and HPMC K100M) were used as release retarder.

Figure 4A and 4B shows the drug release profile of formulations containing constant amounts of different grades of HPMC (I16, I17, and I18 contained HPMC K4M, HPMC K15M, and HPMC K100M, respectively).

As shown in figure, the polymer had markedly affected the drug release from the osmotic devices. $Q_{10\ h}$ were 100.28%, 89.53%, and 66.34% for the formulation containing HPMC K4M, HPMC K15M, and HPMC K100M, respectively. $Q_{10\ h}$ for I18 formulation was considerably lower than the acceptable range. Low $Q_{10\ h}$ of I18 was probably due to the presence of polymer with higher viscosity. This indicated that the release of water-soluble drug may alter by incorporating polymer with high viscosity in osmotic devices. The concentration of polymer may also produce significant effect on *in vitro* drug release rate. At higher concentration the drug release rate was lower, whereas at low concentration it was higher. So the hydrophilic polymer had inverse effect on *in vitro* drug release profile (Figure 4A and 4B).

The release profiles of batches that contained HPMC did not produce desire value of $Q_{10\ h}$, which was due to the presence of higher amount of NaCl. As MET was not only an active ingredient but also an osmotic agent, the concentration of NaCl may alter the drug release profile of MET. Figure 4B shows the effect of NaCl on MET release profile. The release rate was decreased as the amount of NaCl decreased. $Q_{10\ h}$ were 88.28% and 75.29% for the formulation containing 5% and 0% of NaCl, respectively. It was found in the range of predefined limit of $Q_{10\ h}$. It was clearly indicated that the concentration of HPMC K15M and NaCl had marked effect on *in vitro* drug release profile of MET release form IOPT.

To identify GLZ release, the photographs were taken at different time interval in dissolution medium. The tablets were placed on wire mesh and the mesh was placed in 1000 mL dissolution medium on magnetic stirrer. During study, gentle stirring was applied to mix the content.

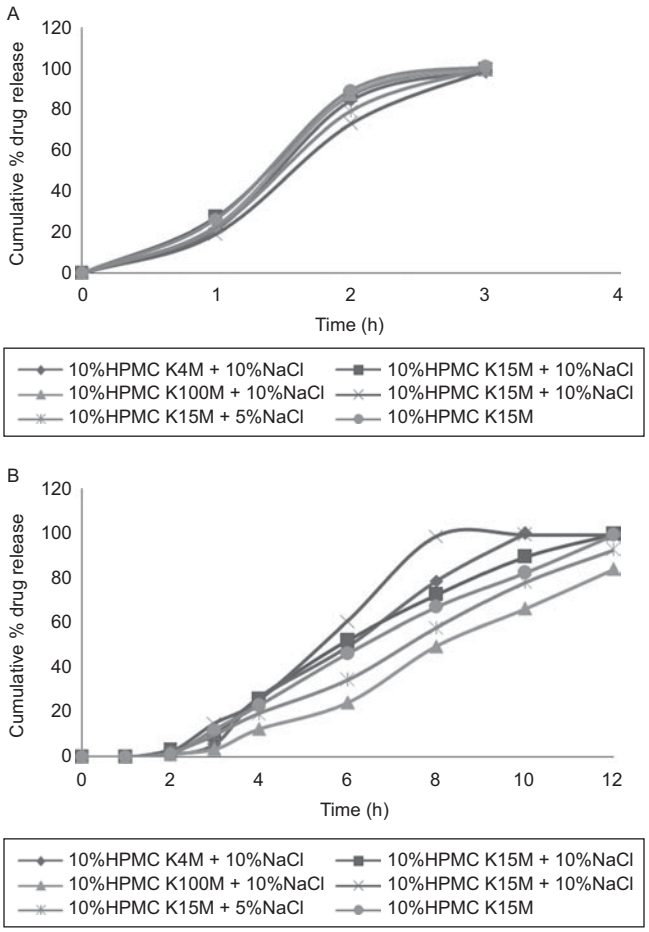


Figure 4. (A) Influence of hydrophilic polymer on *in vitro* GLZ release. (B) Influence of hydrophilic polymer on *in vitro* MET release.

The captured photograph of IOPT showed the pink-colored layer (i.e. GLZ layer). The effervescent was observed after 1 h, which was due to the presence of $NaHCO_3$. GLZ layer was completely disappeared after 3 h. This indicated that the GLZ was completely released within the prescribed time.

Accelerated stability studies

An ethical drug manufacturer is committed to provide his consumers with drug products that are both efficacious and safe. This can only be ensured by instituting a program to study the stability of a product during its various phases of development and to use proper storage conditions and comply with the expiry period under those conditions. This is a requirement in most countries and is stipulated by the regulatory agencies of those countries. These studies will very quickly identify the need, if any, to stabilize the active substance or the formulation, and save any waste of time and effort on an unmarketable formulation. With the recent trend toward globalization of manufacturing operations, it is imperative that the final product is sufficiently robust for marketing worldwide under a variety of climate conditions, including tropical, subtropical, and temperate. The optimized formulation of IOPT containing GLZ and MET subjected to accelerated stability studies in an aluminum/aluminum strips is considered to be the best protecting packaging materials, and it is used as packing material in the present study.

Batch no. I20 was packed in an aluminum/aluminum strip and subjected to short-term stability studies at 40 ± 2°C and 75 ± 5% relative humidity for 90 days. Samples withdrawn after each month showed no significant change in physical appearance, drug content, and *in vitro* drug release characteristics. So, the formulations were found to be stable in terms of drug content and *in vitro* drug release (Figure 5A and 5B). After stability study, the *in vitro* drug release profiles of tablets are compared for various dissolution parameters (Table 4) for GLZ and MET release.

The values of different dissolution parameters showed that there was no more difference between *in vitro* drug release profile of initial and after stability batch. The values of $G_{75\%}$, t_{LMET}, and $Q_{10\,h}$ were found to be in limit.

SEM studies

To investigate the changes in the membrane structure, surface of coated tablets was studied using SEM. Figure 6A and 6B shows SEM micrographs of membrane

surface of batch I20 before and after dissolution studies, respectively.

Figure 6A shows the membrane structure of batch I20 before dissolution studies. 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. Figure 6B shows SEM micrograph of an excised section of the top surface of membrane after dissolution study. It exhibits a surface morphology completely different to that of Figure 6A. Formation of pore like structure was observed due to incorporation of water-soluble plasticizer in the coat, suggesting that the pores were formed in the membrane and become intake during the *in vitro* drug release profile.

Conclusion

The present study aimed to develop an oral osmotic system, which delivered the GLZ within 2 h and MET with controlled rate up to 12 h. The release rate of GLZ can be effectively modified by the addition of sodium carbonate, which can manipulate pH within the tablet, whereas the release rate of MET can be controlled by dual-coating system and by addition of hydrophilic polymer. Results of SEM studies showed the formation of pores in the membranes after coming into contact with the aqueous environment. The inlay osmotic system could be effective in the multidrug therapy of diabetes by delivering both drugs in a controlled manner. The prototype design of the system could be applied to other combinations of drugs used in cardiovascular diseases, asthma, tuberculosis, diabetes, and so on.

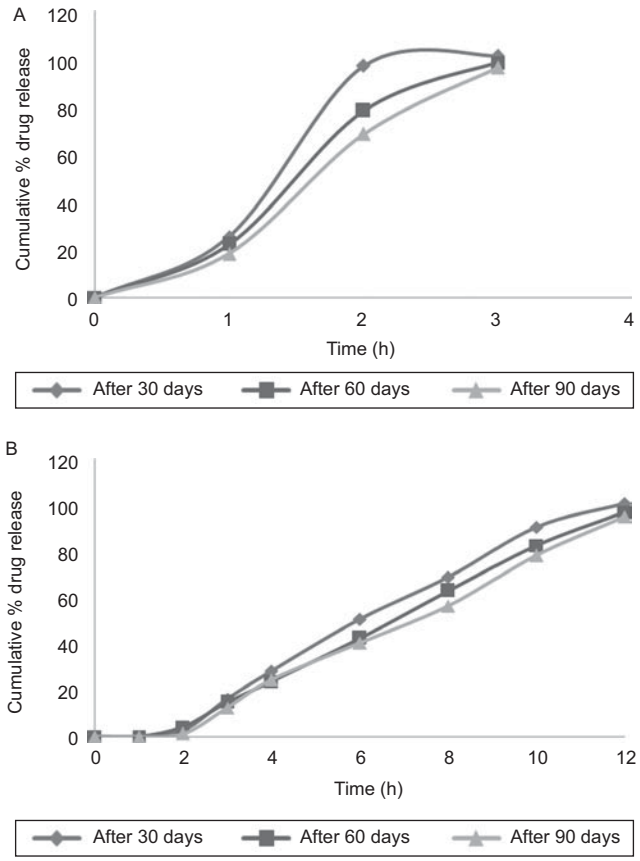
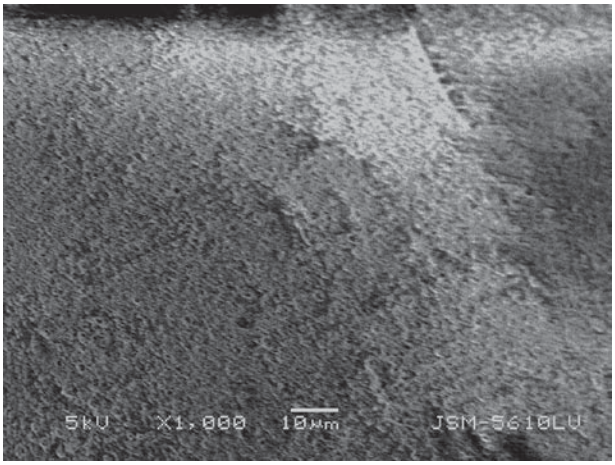


Figure 5. (A) *In vitro* GLZ layer after stability study. (B) *In vitro* MET layer after stability study.

A: Membrane structure of batch I20 before dissolution studies



B: Membrane structure of batch I20 after dissolution studies

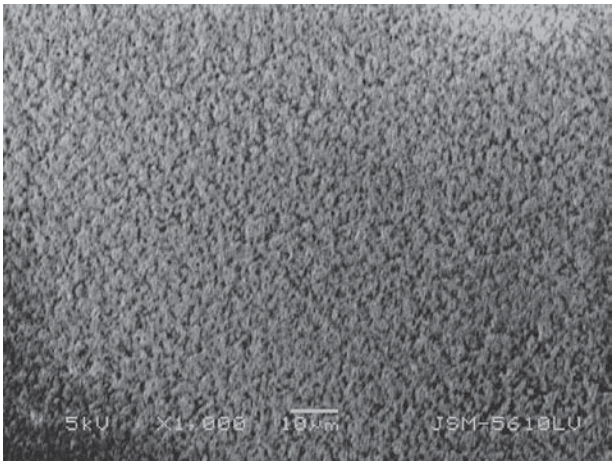


Figure 6. (A) Membrane structure of batch I20 before dissolution studies. (B) Membrane structure of batch I20 after dissolution studies.

Table 4. Comparison of dissolution parameter after stability study.

	Assay of GLZ	Assay of MET	$G_{75\%}$	t_{LMET}	$Q_{10\,h}$	RSQ_{ZERO}
Initial	101 ± 2.04	99 ± 2.74	—	>2 h	87.88	0.987
After 30 days	100 ± 1.86	100 ± 3.02	<2 h	>2 h	90.54	0.984
After 60 days	101 ± 2.21	99 ± 2.50	<2 h	>2 h	82.56	0.988
After 90 days	101 ± 2.14	99 ± 2.42	>2 h	>2 h	78.27	0.983

Declaration of interest

There is no interest of all authors in financial and personal relationship with any other people or any organization for publishing this research article or financial support for research work.

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