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Research Article

Controlled Porosity Solubility Modulated Osmotic Pump Tablets of Gliclazide

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Abstract. A system that can deliver drug at a controlled rate is very important for the treatment of various chronic diseases such as diabetes, asthma, and heart disease. Poorly water-soluble drug with pH-dependent solubility such as gliclazide (GLZ) offers challenges in the controlled-release formulation because of low dissolution rate and poor bioavailability. Solid dispersion (SD) of GLZ consisted of hydroxypropyl cellulose (HPC-SSL) as a polymeric solubilizer was manufactured by hot melt extrusion (HME) technology. Then, controlled porosity osmotic pump (CPOP) tablet of gliclazide was designed to deliver drug in a controlled manner up to 16 h. The developed formulation was optimized for type and level of pore former and coating weight gain. The optimized formulation was found to exhibit zero order kinetics independent of pH and agitation speed but depends on osmotic pressure of dissolution media indicated that mechanism of drug release was osmotic pressure. The *in vivo* performance prediction of developed formulation using convolution approach revealed that the developed formulation was superior to the existing marketed extended-release formulation in terms of attaining steady state plasma levels and indicated adequate exposure in translating hypoglycemic response. The prototype solubilization method combined with controlled porosity osmotic pump based technique could provide a unique way to increase dissolution rate and bioavailability of many poorly water-soluble, narrow therapeutic index drugs used in diabetes, cardiovascular diseases, etc.

KEY WORDS: convolution approach; gliclazide; hot melt extrusion (HME); hydroxypropyl cellulose; solid dispersion.

INTRODUCTION

Diabetes is a serious condition with potentially devastating complications that affects all age groups worldwide. According to the International Diabetes Federation, the prevalence of diabetes is likely to increase from 382 million in 2013 to 592 million by 2035 (1). Type 2 diabetes is the most common form of the disease making up about 90% of diabetes cases (2). The growing impact of the obesity epidemic promises that type 2 diabetes will remain a public health burden well into the future (3). Prevention of type 1 diabetes has not yet been successful; however, the evidence indicates that preventing type 2 diabetes would result in significant public health benefits, including lower rates of cardiovascular disease, renal failure, blindness, and premature mortality (4), and hence, novel therapeutic strategies aimed at reducing diabetes risk are badly needed. There are several classes of antidiabetic medications available. Sulfonylureas have represented the backbone of oral therapy in type 2 diabetes for more than 30 years (5). Gliclazide (GLZ) is a second-generation sulfonylurea derivative, widely used for the treatment of type 2 diabetes (6). It acts by stimulating insulin secretion from pancreatic beta cells (7). Prior research work revealed that it has good general tolerability, low incidence of hypoglycemia, and low rate of secondary failure (8,9). In addition, it has the potential for slowing the progression of diabetic retinopathy (10). For these reasons, gliclazide appears to be a drug of choice in long-term sulfonylurea therapy for the control of type 2 diabetes (7). In general, rapid gastrointestinal (GI) absorption is required for oral hypoglycemic drugs, in order to prevent a sudden increase in blood glucose level after food intake in patients with diabetes mellitus (11). However, the GI absorption rate of gliclazide, in conventional dosage form, appears to be rather slow. Several studies using healthy volunteers or patients revealed that the time to reach peak serum GLZ concentration ranged from 2 to 8 h following oral administration of a conventional tablet (12,13). Slow absorption of a drug usually originates from either its poor dissolution from the formulation or poor permeability across the GI membrane. This eventually limits its oral bioavailability and therapeutic efficacy (14). These facts justify the rationale for the development of controlled-release dosage form. Osmotic drug delivery was attempted since, though a number of design options are available to control the drug release from a dosage form, majority of the oral dosage form fall in the category of matrix, reservoir, or osmotic systems. Drug release from osmotic system is independent of pH and

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gastrointestinal motility to a large extent (15). The development of oral osmotic systems has a strong market potential, as evident from the marketed products and number of patents granted in the last few years (16). Instead, an attempt was made to develop CPOP to circumvent the need for a laser or mechanical drilling. In CPOP, the orifice through which drug is released are formed by incorporation of a leachable water-soluble component in the coating material (17). The CPOP has an advantage as drug is released from the whole surface of device rather than from the single hole which may reduce stomach irritation problem. Preparation of CPOP is simple; it is not necessary to consider complicated side drilling, and compared to other osmotic pump systems, less excipients are required. The coating composition of CPOP includes pore-forming agent, which generates pores in contact with aqueous media (18). Although controlled porosity osmotic pump tablet could be prepared simply, they were usually applicable for soluble drugs. However, the drawback of this potentially useful hypoglycemic agent is that it is highly hydrophobic and practically insoluble in water (19). Therefore, there was a need to modulate the solubility of the drug using suitable solubility enhancement techniques. Various techniques to increase solubilization of gliclazide have been explored including formulation of complexes of gliclazide with ß-cyclodextrin (20–22), complexes of gliclazide with ß-cyclodextrinhydroxypropyl methylcellulose (23), gliclazide suspension in PEG 400 (24), solid dispersions of gliclazide in PEG 6000 (25), solid dispersion of gliclazide in polyvinylpyrrolidone K90 (26), etc. Although a number of methods are available to improve the solubility and or dissolution rate of poorly soluble drugs, the most promising method for promoting dissolution rate is formation of SDs (27). Lately, the melt extrusion technology has evolved as an efficient manufacturing technique, to disperse or dissolve the drug in molten polymer, forming a solid dispersion or solid solution (28). The interest in hot melt extrusion for pharmaceutical applications is growing rapidly with over 100 scientific publications over the last decade (29), and only a few drug products based on this technology are available in the market (30,31). This technology shows numerous benefits over traditional/classical methods including shorter processing time due to continuous downstream processes, environmental advantages due to elimination of solvents, and increased efficiency in delivering the drug to the patients (32). Although HME exhibits numerous advantages and applications, its limitations include low amorphous conversion efficiency and poor dispersion of higher melting drugs, as well as potential thermal degradation of API's and polymers at operating temperatures. In such cases, plasticizers are required to reduce the polymer glass transition temperature (*T*g) and melt viscosity. However, their inclusion may lead to drug–polymer immiscibility and re-crystallization (33,34). Noorullah et al. evaluated hydroxypropyl cellulose (Klucel EF and ELF) polymers for immediate-release oral dosage forms prepared by melt extrusion technology for solubility enhancement of Ketoprofen (35). Recently, Ashish et al. evaluated the utility of low-viscosity hydroxypropyl cellulose (HPC-SL and SSL) polymers for the first time as HME excipients as compared to other polymers for dissolution enhancement of BCS class II drugs with high melting point (Tm) and different chemical properties. HPC is a semi-crystalline polymer with low Tg which may be used to manufacture SDs of high melting drugs without the use of plasticizers (36). HPC depicts higher molecular mobility and plasticity due to a high degree of amorphous content with a low Tg (37).

Based on this report, an attempt was made to improve the delivery of low soluble drug GLZ by formation of solid dispersion with HPC-SSL using HME technology and subsequently fabrication and evaluation of controlled porosity osmotic pump system. It was observed that most of the core content releases through pores at a constant rate, where the release mechanism primarily was osmotic with simple diffusion playing a minor role. A zero-order delivery pattern was designed to produce plasma levels within studied and optimized to achieve the desired release profile. Besides, the *in vivo* performance of the optimized formulation was predicted.

MATERIALS AND METHODS

Materials

Gliclazide was a gift sample from Bal Pharma Limited, Bangalore, India. Hydroxypropyl cellulose (HPC-SSL) was a gift sample from Nippon Soda, Japan. Sodium chloride was obtained from RFCL Ltd. Lactose anhydrous was a gift sample from Kerry Bioscience, USA. Hydroxypropyl methyl cellulose (Methocel E5 Premium LV) was gift sample from Dow Chemical Company, USA. Colloidal silicon dioxide (Aerosil Pharma 200) was obtained from Evonik Degussa, GmbH, Germany. Magnesium stearate (Hyqual, Vegetable source) was obtained from Avantor Performance Materials Inc., USA. Cellulose acetate (CA) was obtained from Eastman Chemical Ltd., USA. Polyethylene glycol-400 (PEG-400) was obtained from Clariant, GmbH, Germany. Mannitol was obtained from Signet Chemical Company, Mumbai. Hydroxypropyl cellulose was obtained from Aqualon Co., USA. Triethyl cellulose (TEC) was obtained from Vertellus Performance Materials Inc., USA. All other solvents and chemicals used were of the analytical grade.

Methods

Preparation of Solid Dispersion

Solid dispersions (SDs) of GLZ-HPC were prepared in various ratios (1:0.5, 1:1, 1:2 and 1:3) by Hot melt extrusion technique.

Polymer and drug were mixed in a bin blender (Tapasya Engineering Co./Lab model, Piller type) at 25 rpm for 10 min. The blended material was extruded on a co-rotating twin screw extruder (Nano-16, Leistriz, Germany) utilizing a round-shaped die to yield extrudate rods. The temperature of the barrel was maintained at 100°C to 140°C, and screw speeds of 150 to 200 rpm were utilized. The extruded rods were milled using quadro co-mill, and the size fractions sieved between US mesh nos. 40 and 60 (250–420 μm) were stored in a desiccator and used in subsequent studies.

Solubility Study

Solubility studies were performed for solid dispersions by taking solid dispersions of drug and various carrier ratios in 250 mL of water and were subjected to mechanical shaking at 200 rpm for 24 h. The resultant dispersions were collected and filtered through 0.45-μ filters, and the concentration of drug was analyzed by UV spectrophotometers at absorbance of 226 nm.

Thermal Analysis (DSC)

The thermal analysis of pure drug, HPC and SD were investigated using differential scanning calorimeter (Mettler Toledo, DSC822^e, Greifensee, Switzerland). About 2–3 mg of sample was weighed in a round bottomed aluminum pan (40 μl), whereas an empty pan of same type was used as a reference. The heat run for each sample was set from 25 to 300°C at a linear heating rate of 10°C/min, under an inert environment of nitrogen.

Powder X-ray Diffraction

Powder X-ray diffraction (PXRD) studies for pure drug, HPC and SD were performed on a D-8 Advance X-ray diffractometer (Bruker, Germany). The pattern was collected with a tube voltage of 40 kV and a tube current of 40 mA over a range of 2θ values from 3 to 45° with a step size of 0.01° 2θ and time per step of 0.1 s.

Preparation of CPOP Tablet Containing SD

Tablet Core. Core tablets were prepared by direct compression, and the composition is given in Table I. GLZ-HPC SD was blended with sodium chloride, lactose anhydrous, hydroxypropyl cellulose, and colliodal silicon dioxide already passed through 40 sieve for 10 min. The prelubricated blend was then blended with magnesium stearate (60 sieve passed) for 5 min and compressed into tablets using a rotary tablet compression machine (Cadmach CMD4-16, India) fitted with 10.5 mm, round, standard concave punches.

Functional Coating. The core tablets were coated in an automated perforated pan (O'Hara Technologies Inc., LC-M, Canada). The composition of coating solution used for coating tablets is given in Table II. Coating solution was prepared by dissolving accurately weighed quantities of water insoluble polymer, pore formers, and plasticizer in the solvent mixture (acetone and water mixture) using a mechanical stirrer. Coating process was started once the outlet air temperature reached 30–35°C. Coating pan rpm was kept in the range of 16–18, and coating solution was sprayed at the rate of 5–7 g/min. Coating was continued until desired weight gain was obtained on the active tablets. In all the cases, active tablets were dried at 50°C in a tray dryer for 2 h before further evaluation.

Table I. Composition of Core Tablets of CPOP

Ingredients	Amount (mg per tablet)
GLZ-HPC SD	240
Sodium chloride	80
Lactose anhydrous	80
Hydroxypropyl cellulose	20
Colloidal silicon dioxide	5
Magnesium stearate	5

Evaluation of the Developed Formulations

The developed formulations were subjected to release studies using USP-II dissolution apparatus (Distek Evolution 6300, USA) at 100 rpm. Dissolution medium was pH 6.8 phosphate buffer and dissolution volume was 900 ml maintained at 37±0.5°C. The samples were withdrawn (10 ml) at specified time intervals. The dissolution sample after filtration through 0.45 μm PVDF filter were analyzed using a validated UV spectrophotometric method at 226 nm. Each study was done on six units, and the mean values±SD were reported. A simple model independent approach based on two fit factors, the similarity factor (f_2), and the difference factor (f_1) (38), were used for comparing the dissolution profiles of a pair of formulations. According to the FDA's guidelines, f_1 values lower than 15 (0–15) and f_2 values greater than 50 (50–100) show the similarity of the dissolution profiles.

Formulation Variables

In order to optimize the formulation to release the drug at a constant zero-order release rate independent of hydrodynamics of the body, different formulation variables such as level of pore former, type of pore former, and coating thickness were optimized (39).

Effect of Type and Level of Pore Former

To study the effect of pore former on the drug release, different hydrophilic pore formers such as HPMC, Mannitol, and PEG 400 were used at the level of 12.5, 25, and 37.5% (*w*/*w*) of CA, respectively.

Effect of Weight Gain

To study the effect of weight gain of the coating on drug release, core tablets were coated so as to get tablets with different weight gains (8, 10, and 12% *w*/*w* of tablet weight).

Burst Strength

Burst strength of the exhausted shells, after complete dissolution of the core was determined to assure that the tablets would maintain their integrity *in vivo*. Burst strength is the force required to rupture the shells after dissolution

Table II. Formulation Variables of Controlled Porosity Osmotic Pump Tablet

	Formulation code							
Coating components	CF1	CF2	CF3	CF4	CF5	CF6	CF7	CFW
CA (% *w/v*)	5	5	5	5	5	5	5	5
HPMC (% *w/w* of CA)	12.5	25	37.5	–	–	25	25	0
PEG 400 (% *w/w* of CA)	–	–	–	25	–	–	–	–
Mannitol (% *w/w* of CA)	–	–	–	–	25	–	–	–
Triethyl citrate (% *w/w* of CA)	7.5	7.5	7.5	7.5	7.5	7.5	7.5	7.5
Thickness (%)	10	10	10	10	10	8	12	10

studies. The texture analyzer (TAX T2i, Stable micro system, 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 with a distance of 2 mm was selected.

Scanning Electron Microscope

To study the morphology and the porous structure of the developed formulations, coating surface of tablets before and after complete dissolution studies was examined using scanning electron microscope (JSM-6360, Jeol, Japan). Small portion of the coating membrane was carefully cut from the exhausted shells after dissolution studies and dried at 50°C for 12 h and stored in a dessicator until examination.

Effect of pH

To study the effect of pH on the performance of the developed formulation, release studies of the optimized formulations were conducted in media of different pH, such as pH 1.2, pH 6.8, and pH change method [the dissolution media was 0.1 N HCl (pH 1.2) for first 2 h, acetate buffer (pH 4.5) for next 2 h, followed by phosphate buffer (pH 6.8) for the remaining period of 16 h]. Release studies were carried out in 900 ml of media using USP II dissolution apparatus at rotation speed of 100 rpm. The sampling was done at predetermined intervals and analyzed after filtration through 0.45 μm PVDF filter using UV spectrophotometer at 226 nm.

Effect of Agitational Intensity

To study the effect of agitational intensity of the release media, dissolution studies of the optimized formulations were carried out in pH 6.8 phosphate buffer using USP II (Paddle) apparatus at various rotational speeds (50, 100, and 150 rpm). Sampling was done at predetermined intervals and analyzed after filtration through 0.45 μm PVDF filter using UV spectrophotometer at 226 nm.

Effect of Osmotic Pressure

To confirm the mechanism of drug release, release studies of the optimized formulations were conducted in media of different osmotic pressure. An osmotically effective solute (sodium chloride) was added in pH 6.8 phosphate buffer (40) in order to increase the osmotic pressure of the media, and osmotic pressure was measured (Advanced® Model 3320 μ-Osmometer, USA). Release studies were carried out in 900 ml of media using USP II dissolution apparatus at rotation speed of 100 rpm. Sampling was done at pre-determined intervals and analyzed after filtration through 0.45 μm PVDF filter using UV spectrophotometer at 226 nm.

Kinetic and Mechanism of Drug Release

Dissolution data of optimized formulation was applied to different mathematical models in order to establish the kinetics and mechanism of drug release. Selection of most appropriate model was based on best goodness of fit test (R^2) (41).

Prediction of In Vivo Performance

Plasma drug concentration of the optimized CPOP formulation was predicted by numerical convolution method. The convolution method uses *in vitro* dissolution data to derive plasma drug levels using reported pharmacokinetic (PK) parameters of a test product. This convolution method is very useful for designing and selection of formulation before animal and human studies (42).

Steady-state simulations of gliclazide plasma concentration time data were performed using nonparametric superposition. Nonparametric superpositioning analysis was performed using validated Phoenix WinNonlin (Version 6.3) software to generate $C_{max,\ ss}$, $C_{min,\ ss}$, and time to reach steady state (43).

In addition, the formulation was characterized by population PK-PD modeling. The population PK-PD model provides the opportunity to study the relationship between the pharmacokinetics (PK) of gliclazide and its long-term pharmacodynamic (PD) effect. This PKPD analysis leads to a

better understanding of the kinetics of the hypoglycaemic effect of gliclazide and of its intersubject variability (44).

Accelerated Stability Studies

The optimized formulation of GLZ was packed in HDPE bottle and PVC blister packs and charged on ICH specified accelerated stability condition of 40°C and 75% relative humidity (RH) for 3 months (Stability chamber, Thermolab Scientific equipment Pvt. Ltd, Mumbai, India). The samples were withdrawn at specified time intervals and evaluated for drug content, hardness, burst strength, and release studies. Samples were withdrawn at pre-determined intervals and analyzed after filtration through 0.45 μm PVDF filter using UV spectrophotometer at 226 nm.

RESULTS AND DISCUSSION

Formulation Development

The compatibility of selected excipients with GLZ API was evaluated using differential scanning calorimetry (DSC). The changes in the endotherm observed in case of physical mixture of CPOP tablet (melting endotherm at 160.14°C, Fig. 1) compared to the original melting endotherm of GLZ at 171.61°C (Fig. 2) was insignificant when exposed at 40±2°C/75±5% RH for 4 weeks. Hence, it was concluded that the selected excipients were compatible with the drug substance.

GLZ belongs to BCS class II drug and not a good candidate for osmotic delivery. Therefore, an attempt was made to prepare solid dispersion of GLZ and HPC in various ratios (1:0.5, 1:1, 1:2, and 1:3) using hot melt extrusion technology to improve the solubility and thereby dissolution rate of GLZ. Solubility studies of GLZ-HPC SD systems in water at 25°C revealed that the solubility of GLZ increased linearly with the increase in the concentration of HPC with maximum solubility observed in case of 1:3 ratio. Solubility of pure GLZ in purified water was 47 μg/ml whereas the solubility of prepared solid dispersion (1:3) was found to be 675 μg/ml. Therefore, SD with 1:3 ratio of drug and polymer was selected for further characterization.

Physical Characterization of SD

The physical properties of SD were examined using differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). It has been widely known that the SD can

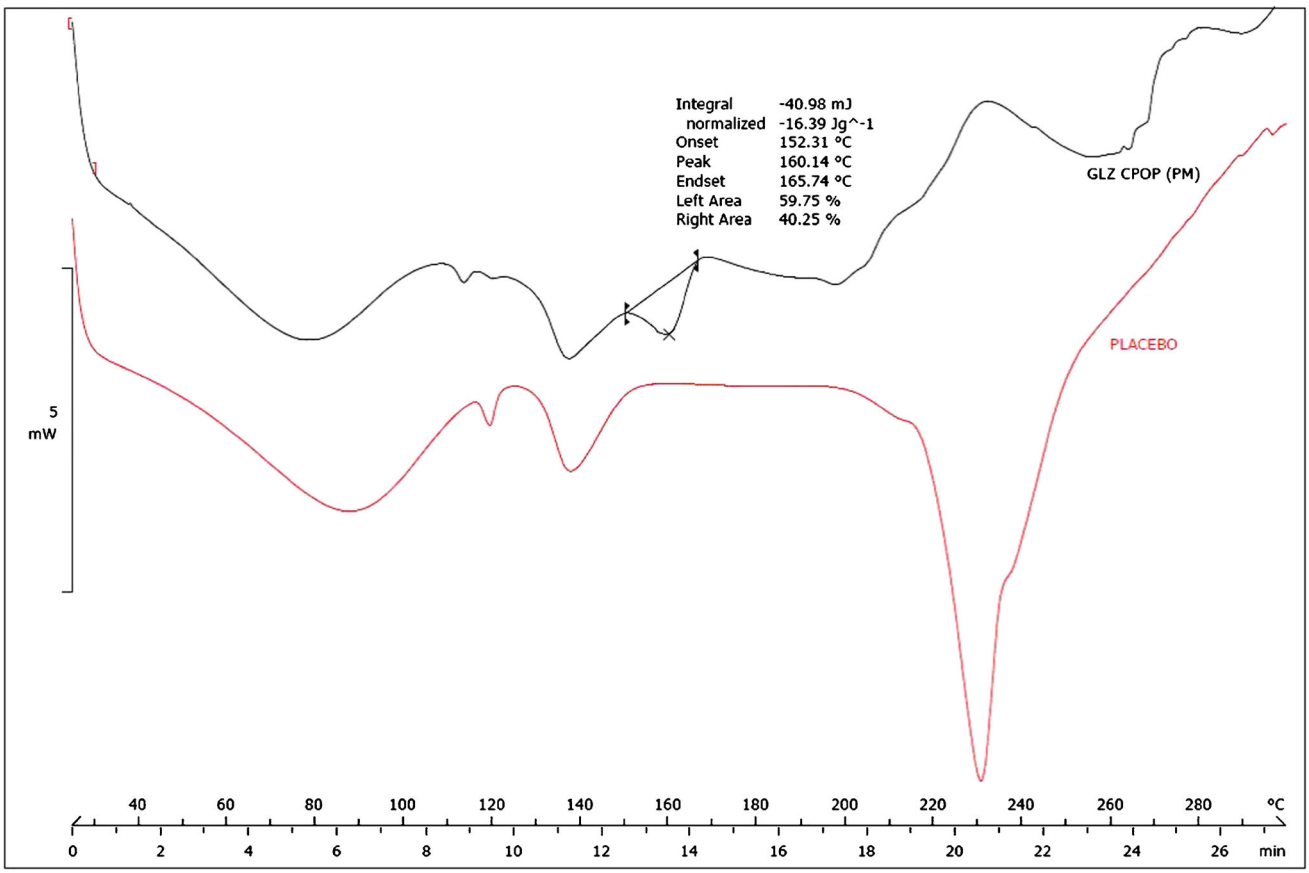

Fig. 1. DSC thermogram showing drug excipient compatibility study

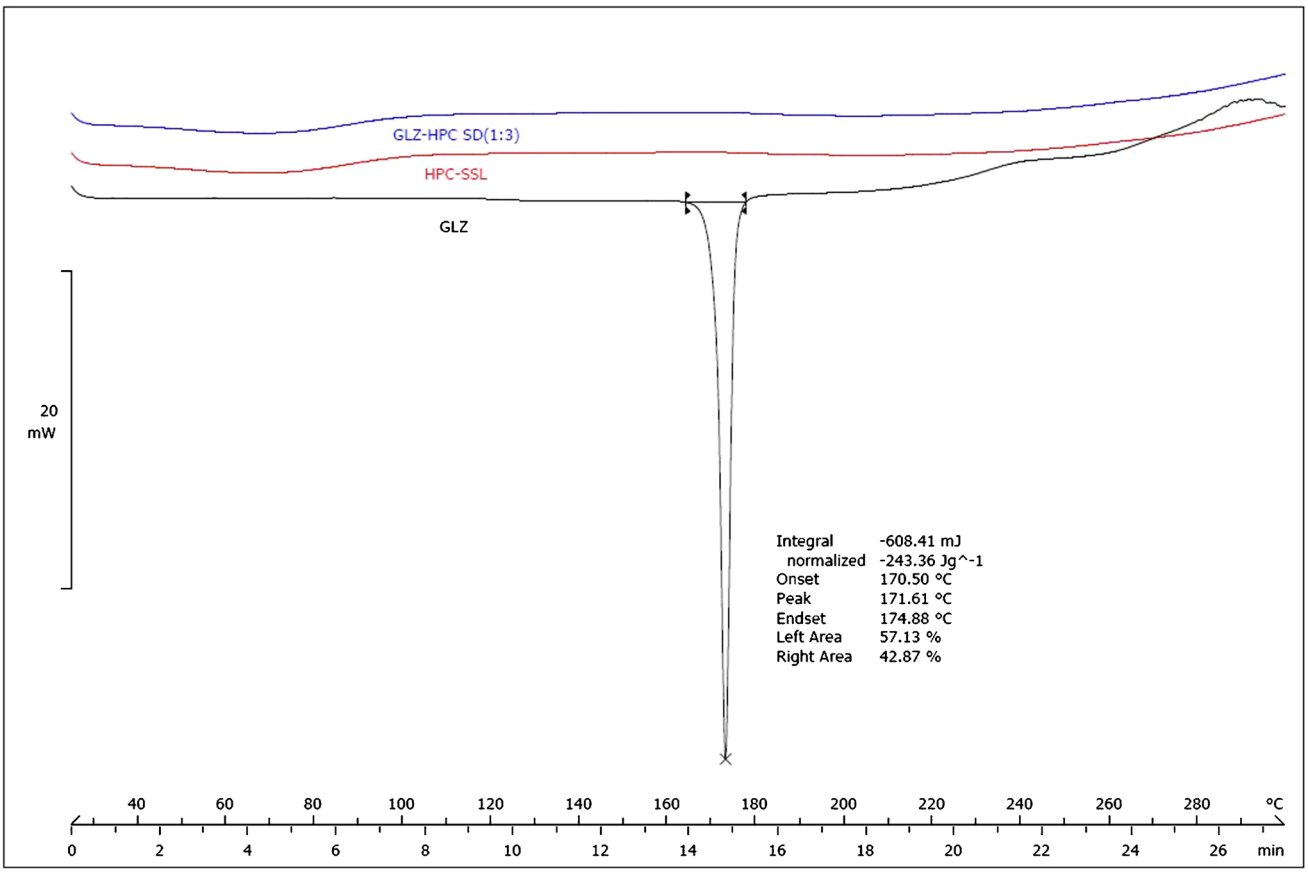

Fig. 2. DSC thermogram of gliclazide-HPC solid dispersion

improve the dissolution rate of poorly water soluble drugs by changing the crystalline structure of the drug into amorphous state. DSC thermogram of SD was compared with the pure drug and HPC in Fig. 2. Pure GLZ exhibited single endothermin peak at 171°C, which corresponds to the intrinsic melting point of drug. In contrast, the sharp crystalline characteristic peak of drug disappeared in the thermogram of SD indicated the crystalline drug changed into its amorphous structure (45). This fact was attributed to be a factor-enhancing drug release.

The PXRD pattern of SD was also compared with the pure drug and HPC in Fig. 3. Diffractrogram of pure drug reveals the highly crystalline nature through its numerous distinct high intensity peaks at 2θ of 10.59, 14.98, 17.21, 17.85, 18.15, and 22.07°. HPC alone exhibited no peaks in the diffractrogram indicating its amorphous nature. Moreover, numerous distinctive peaks of the drug in the SD disappeared, indicating that the high concentration of the drug was dissolved in the solid state carrier matrix in an amorphous structure (46,47).

The developed formulation consists a core of GLZ-HPC SD along with osmogen and other excipients. The core compartment is coated by a membrane consisting of a water-insoluble semipermeable membrane which is permeable to aqueous fluids but impermeable to the components of the core, water-soluble pore-forming additives capable of generating *in situ* pores and a plasticizer capable of providing flexibility to the polymers film. When placed in aqueous environment, the water-soluble additives dissolves results in *in situ* formation of microporous structure through which drug release takes place. CA and triethyl citrate (TEC) were used as semipermeable membrane and plasticizer, respectively. HPMC, mannitol, and PEG 400 were tried as pore formers.

Influence of Tablet Formulation Variables on GLZ Release

To study the effect of formulation variables on drug release, tablets with various formulations were prepared, subsequently coated with the coating thickness of 10% and plasticized with 7.5% TEC.

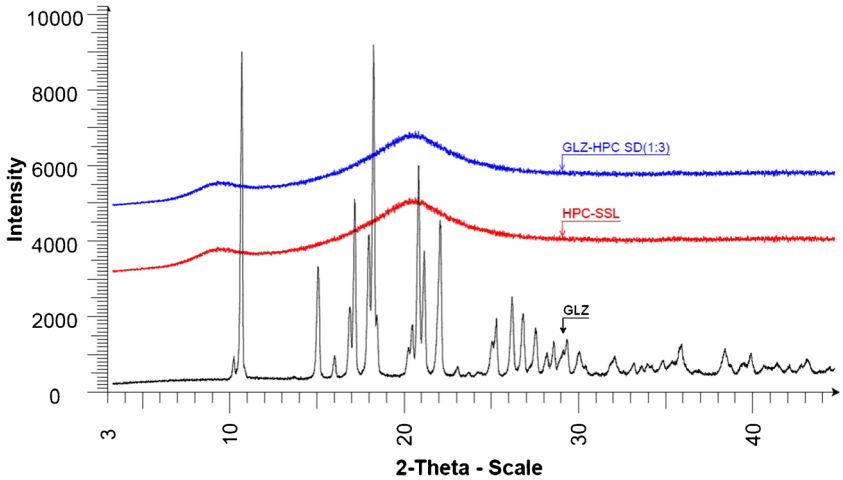

Fig. 3. PXRD diffractogram of gliclazide-HPC solid dispersion

Effect of Level of Pore Former

To study the effect of level of pore former (HPMC), core tablets were coated with polymer-coating composition containing different level of pore former such as 12.5, 25, and 37.5% *w*/*w* (of cellulose acetate) level of HPMC (formulations: CF1, CF2, and CF3, respectively). A linear correlation was observed between the drug release and the level of pore former (Fig. 4) attributable to more porous membrane structure at higher level of pore former, resulting in faster drug release. Similar results were also reported by Zentner and Appel (48,49). The drug release was found to be significant between 12.5 and 25% (*w*/*w*) levels of pore former. However, the drug release was found to be faster with higher level of pore former [37.5% (*w*/*w*)] because of increase in number of open pores and void volume. The level of pore former also affects the burst strength of the exhausted shells. The burst strength was found to decrease with increase in the level of pore former (HPMC) in the membrane (Fig. 5) as less resistance imposed by highly porous structure after exposure to water, leading to decrease in its strength. Effect of level of HPMC on burst strength is shown in Table III. Since the formulation (CF2) with 25% pore former exhibited satisfactory drug release and adequate burst strength, this level of pore former was selected for further studies.

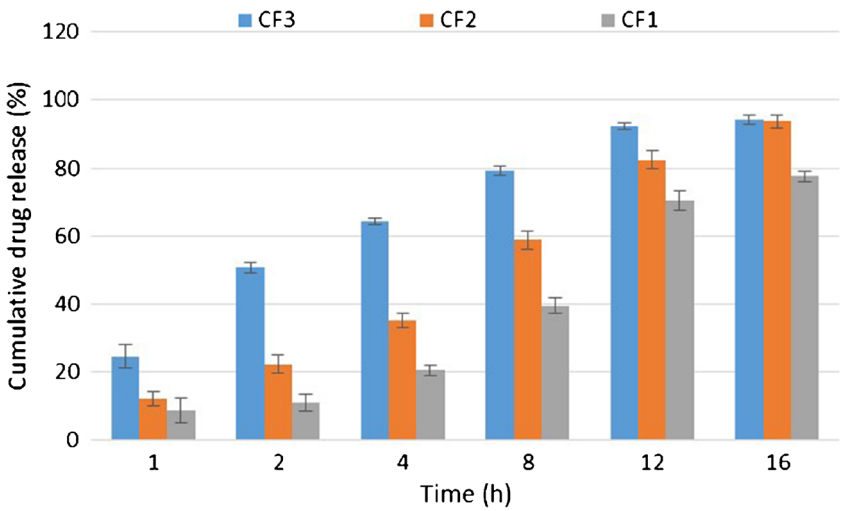

Fig. 4. Effect of level of pore former on release of GLZ

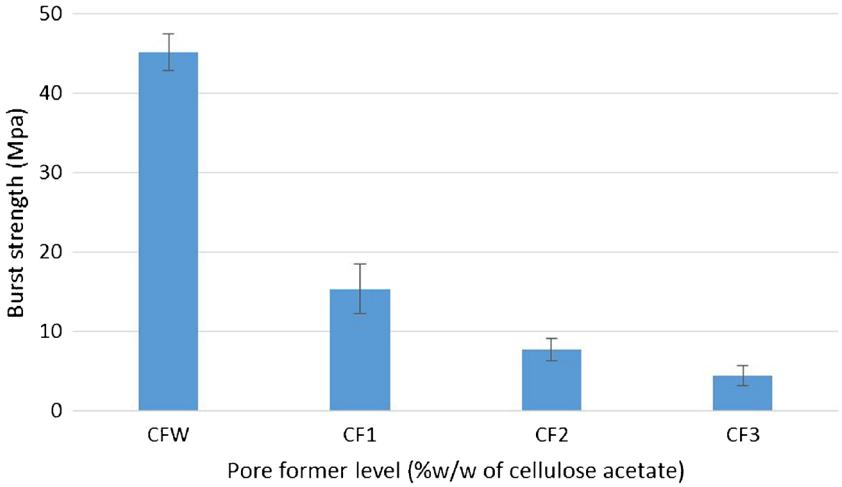

Fig. 5. Burst strength of the membrane as function of level of pore former

Effect of Type of Pore Former

To study the effect of type of pore former, CPOP formulations CF2, CF4, and CF5 were prepared by incorporating GLZ in tablet core followed by coating with cellulose acetate solution containing various types of pore formers [HPMC 25% (CF2), Mannitol 25% (CF4) and PEG-400 25% (CF5)]. As revealed from Fig. 6, drug release rate was directly proportional to the type and concentration of pore formers, and it was possible to modulate release rate by choosing appropriate type of pore former. The percentage drug release was more in case of HPMC as pore former, since it swelled and dissolved quickly to give a solution of both increased viscosity and expanding force (50) and hence the drug release rate. It has also been reported that water-soluble polymers such as HPMC may leach out of the coating, forming a porous film with increased permeability or produce hydrated water-filled HPMC regions within the membrane that allow drug transport across the film (51). Moreover, Burst strength of exhausted shells are also affected by the type of pore former (Table III), and this parameter should also be focused in the selection of appropriate pore former. The formulation containing HPMC as pore former (CF2) exhibits satisfactory drug release pattern and burst strength, hence this formulation was selected for further evaluation.

Table III. Effect of Level and Type of Pore Former on Burst Strength

S. No	Pore former (% *w/w* of CA)	Burst strength (MPa)
1	HPMC (0)	45.12
2	HPMC (12.5)	15.31
3	HPMC (25)	7.65
4	HPMC (37.5)	4.37
5	Mannitol (25)	16.12
6	PEG-400 (25)	6.85

Effect of Weight Gain

To study the effect of weight gain of the membrane, the core tablets of GLZ were coated with cellulose acetate as semipermeable membrane to get tablets with different weight gain of 8 (CF6), 10 (CF2), and 12% (CF7). Figure 7 depicts the release profile of GLZ as a function of weight gain of the membrane. Drug release was inversely related to the weight gain of the membrane. Though CF2 and CF6 showed higher drug release pattern, an approximate zero order release pattern and better burst strength was observed with CF2 in comparison to CF6. Drug release was observed to be slower in case of 12% weight gain (CF7) compared to 8% (CF6) and 10% (CF2) weight gain. The lag time was also found to be increased with increase in weight gain. In order to ensure the integrity of tablets in the GIT and devoid of dose dumping incidence, exhausted tablets after complete dissolution studies were evaluated for burst strength (Fig. 8). The strength of mechanical destructive forces was reported to be 1.9 N (approximately 190 g) and 3.2 N (approximately 320 g) in the GIT of humans and dogs, respectively, by Kamba *et al.* (52,53). The value of burst strength is found to be much higher than the reported mechanical destructive forces in GIT of human in all the formulations developed in the current study, indicating that all the formulations were robust and expected to retain their integrity in the GIT environment without any scope of dose dumping. It was found that an approximate zero order release rate pattern up to 16 h and sufficient burst strength was obtained in the

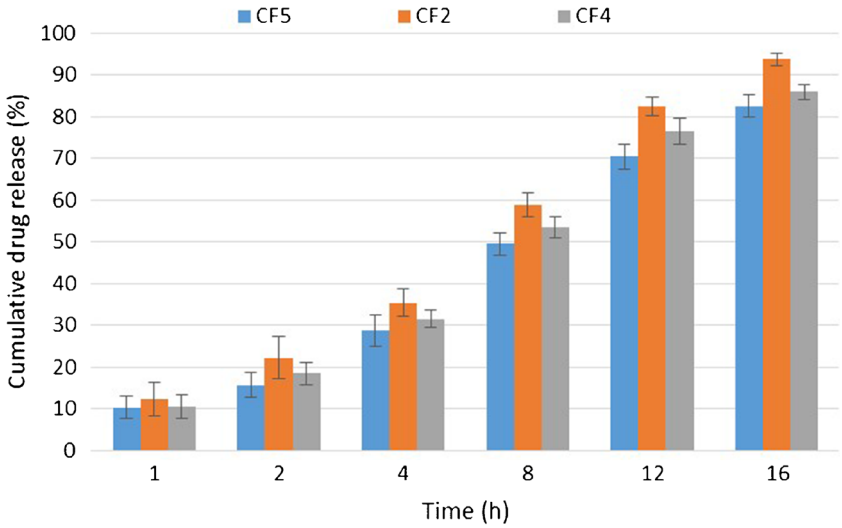

Fig. 6. Effect of type of pore former on release of GLZ

case of the 10% coating thickness. Hence, CF2 with HPMC at 25% level and weight gain of 10% was used as optimized formulation for further evaluations.

Kinetics and Mechanism of Drug Release

Based on the best goodness of fit obtained from in vitro drug release data of the optimized formulation (Table IV), it was concluded that kinetics of CF2 formulations was zero order with higher sum of correlation coefficient for zero order compared to first order and Higuchi model. The diffusion exponent of release profile (slope) has a value of (n>0.5>1), which indicates a zero order release controlled by non-Fickian diffusion (anomalous transport).

Scanning Electron Microscope

To understand the morphology of the coating membrane, coating surface was studied before and after dissolution study using SEM. Figure 9 showed SEM micrographs of membrane surface of optimized formulations (CF2) containing 25% of HPMC before and after dissolution studies. After dissolution studies, coating was

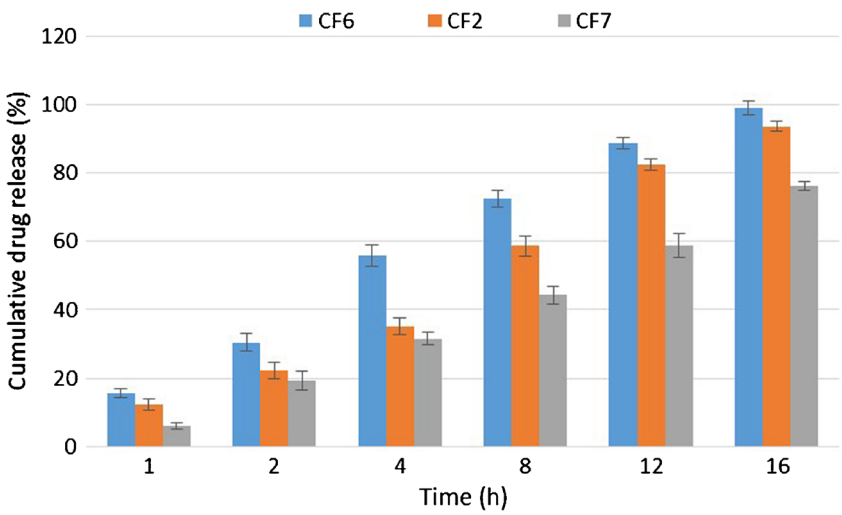

Fig. 7. Effect of weight gain on release of GLZ

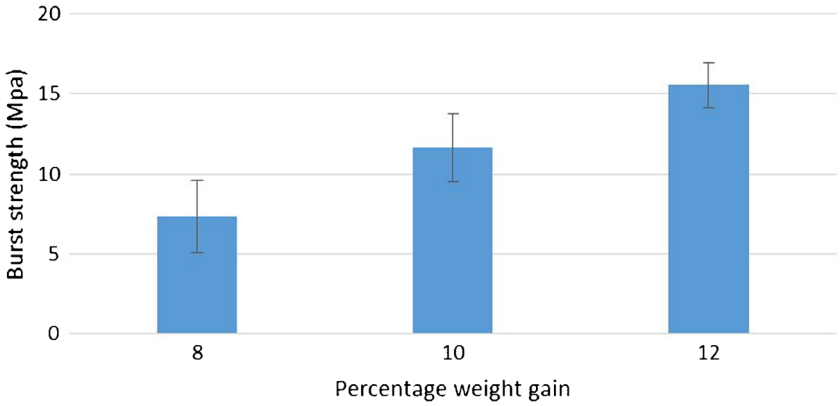

Fig. 8. Burst strength of the membrane as function of weight gain

found to be intact with small pores in the membrane, which would possibly acted as delivery ports for the release of the drug in the aqueous environment. The surface of coated tablet was smooth before coming into contact with the aqueous environment, and the coats appeared to be devoid of any distortion.

Morphology of membrane containing HPMC revealed to contain more number of pores with bigger pore size compared to membrane containing mannitol and PEG-400 which could be due to quick dissolution followed by leaching of HPMC from the membrane (figure not shown for mannitol and PEG-400).

Effect of pH

To assure the consistent release of the drug irrespective of the pH of the dissolution media, release study of the optimized formulation was conducted in media of different pH and compared with release profile of pH 6.8. Release profile of optimized formulation (CF2) in pH 6.8, pH 1.2, and pH change method were reported in Table V. The f_2 values were found to be 76 (between pH 6.8 and pH 1.2) and 85 (between pH 6.8 and pH change method), respectively. The dissolution data of Table V clearly depicted pH-independent and congruous release profile of optimized formulation.

Effect of Agitational Intensity

To confirm the uniform release of drug independent of agitation intensity of the release media, release studies of the optimized formulation (CF2) were carried out in USP II dissolution apparatus at different agitation speed (50, 100, and 150 rpm). The dissolution data of Table VI clearly indicated rotational speed independent release profile of optimized formulation. The f_2 values were found to be 74 (between 100 and 50 rpm) and 75 (between 100 and 150 rpm), respectively. Hence, it can be anticipated that the optimized formulation will exhibit uniform *in vivo* drug release independent of the hydrodynamic conditions of the GIT.

Effect of Osmotic Pressure

To study the effect of osmotic pressure on the drug release of optimized formulation, release studies of the optimized formulation (CF2) were carried out in media of different osmotic pressure. The release profile of Table VII prominently reflected that the drug release was highly dependent and inversely related to the osmotic pressure of the release media. This study distinctly supports that the mechanism of drug release is by the osmotic pressure.

Table IV. Kinetics of GLZ Release from the Optimized Formulation (CF2)

Models	Zero Order	First order	Higuchi	Hixson Crowell	Koresmeyer-Peppas		Best fit model
	R^2	R^2	R^2	R^2	n	R^2	
	0.9742	0.9638	0.9640	0.912	0.6604	0.9948	Zero Order

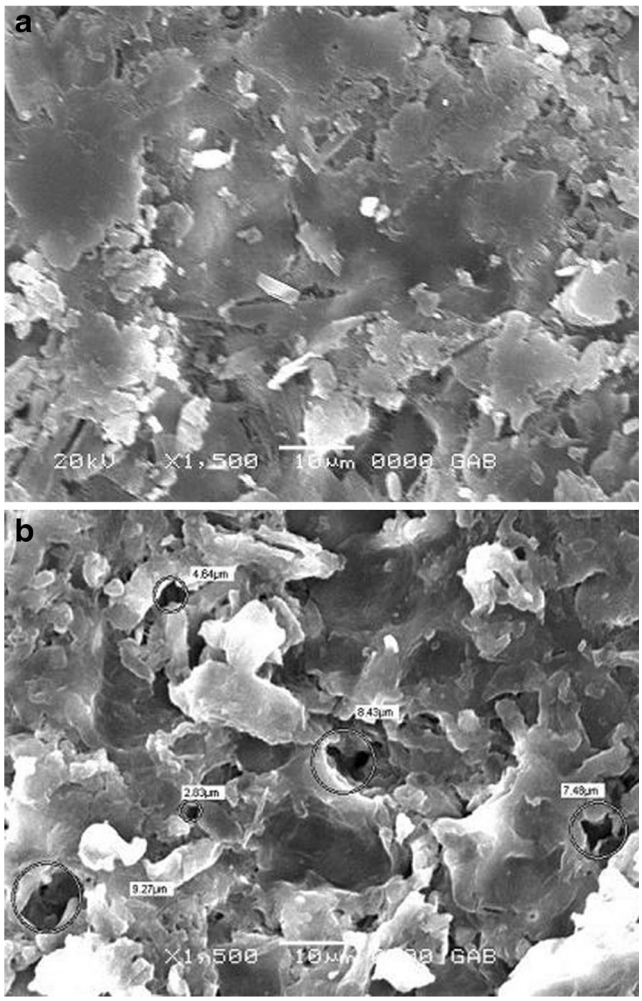

Fig. 9. SEM micrograph of 25% HPMC **a** before and **b** after dissolution studies

Table VI. Effect of Agitational Intensity on Release of GLZ from CF2 (n=6)

	Cumulative % release ±SEM		
Time (h)	50 rpm	100 rpm	150 rpm
0	0.00±0.00	0.00±0.00	0.00±0.00
1	13.25±0.68	15.01±0.71	16.20±1.42
2	20.24±1.23	25.32±1.12	25.54±2.80
4	39.30±1.50	42.28±1.54	45.21±2.37
8	55.77±1.91	59.10±2.31	63.38±1.98
12	80.54±0.21	84.08±3.02	88.49±2.63
16	93.58±1.10	94.09±2.86	96.80±2.12

Prediction of *In Vivo* Concentration-Time Profile from *In Vitro* Data

With the current *in vitro* dissolution profile of gliclazide's CPOP formulation (CF2), convolution was performed taking the input parameters from the mean pharmacokinetic (PK) profile of gliclazide bioequivalence study involving Diamicron® 80 mg (immediate release tablets) (54) to get an estimated pharmacokinetic profile of new CPOP formulation. For consideration of input parameters from 60 mg and with the information of linear pharmacokinetics (PK) of Diamicron MR formulation (55), the 80-mg profile was simulated to 60 mg's profile. Convolution was performed taking the input parameters or model parameters (PK coefficients and rate parameters) describing the 60-mg PK profile of Diamicron MR formulation, with the help of Phoenix Winnonlin professional software (version 6.3, product of Certara^{TM}). The input parameters used in convolution were derived from modeling the pharmacokinetic profile of the Diamicron® 80-mg tablets with the help of Phoenix Winnonlin. The PK profile can be well described by a 2-compartment body model with a lag time (t_{lag}) of about 18 min in absorption.

Table V. Effect of pH on Release of GLZ from CF2 (n=6)

	Cumulative % release ±SEM		
Time (h)	pH 6.8	pH 1.2	pH change
0	0.00±0.00	0.00±0.00	0.00±0.00
1	15.01±0.71	12.12±1.30	14.25±1.40
2	25.32±1.12	22.22±1.89	23.24±1.51
4	42.28±1.54	40.10±2.80	45.30±2.01
8	59.10±2.31	55.66±2.30	58.77±1..74
12	84.08±3.02	80.81±2.67	82.49±2.65
16	94.09±2.86	91.80±1.80	96.68±2.33

Table VII. Effect of Osmotic Pressure on Release of GLZ from CF2

	Cumulative % release			
Time (h)	CF2	1.5 atm	3.0 atm	4.5 atm
0	0.00	0.00	0.00	0.00
1	15.01	12.25	9.80	4.41
2	25.32	22.24	15.12	7.36
4	42.28	35.30	24.34	15.24
8	59.10	58.77	38.17	21.15
12	84.08	82.49	53.88	33.18

Table VIII. Pharmacokinetics Parameters of the Developed Formulation (CF2) at Single Dose

PK parameters	Kel (1/h)	$t_{1/2}$ (h)	Tmax (h)	Cmax (ug/ml)	AUClast (ug.h/ml)	AUCinf (ug.h/ml)
	0.047	14.7	14.4	1.4	38.6	40.2

The equation of the model can be described as:

$$C_t = \left\{ A.\exp\left(-\alpha.\left(t-t_{lag}\right)\right) + B.\exp\left(-\beta.\left(t-t_{lag}\right)\right) - C.\exp\left(-k_{01}.\left(t-t_{lag}\right)\right)\right\},$$

where C_t is conc. at time t, A, B, and C are coefficients derived from dose, volume of distribution, disposition rate constants, and bioavailability factor, α, β are hybrid rate constants of disposition, and k_{01} is the absorption rate constant.

Through convolution, a single-dose PK profile distinct of the new CPOP formulation was estimated. The estimated PK parameters were, C_{max} of about 1.4 μg/mL, $AUC_{0\text{-}inf}$ of about 40 μg.h/mL, time to reach C_{max} (T_{max}) was 14 h (Table VIII, Fig. 10).

Since diabetic type-II patients require anti-hyperglycemic(s) in a chronic regimen to effectively control plasma glucose levels, therefore, the single dose PK profile was replicated to steady state assuming a once-daily regimen of gliclazide. The steady state levels were estimated through non-parametric superposition principle considering linear PK of Diamicron MR within the therapeutic dosage range of 30 to 120 mg (55). Steady state level was achieved within 4 days of drug initiation. The maximum plasma levels ($C_{max,\ ss}$) achieved was 2 μg/mL and the trough level ($C_{min,\ ss}$) was about 1.2 μg/mL (Table IX). The % fluctuation under steady state was about 50%, which should be acceptable in terms of maintaining the steady state levels (trough levels) and also not attaining high peak levels, especially for a non-narrow therapeutic index drug like gliclazide. Besides, in clinical studies, gliclazide is associated with a relatively low incidence of hypoglycemia (56).

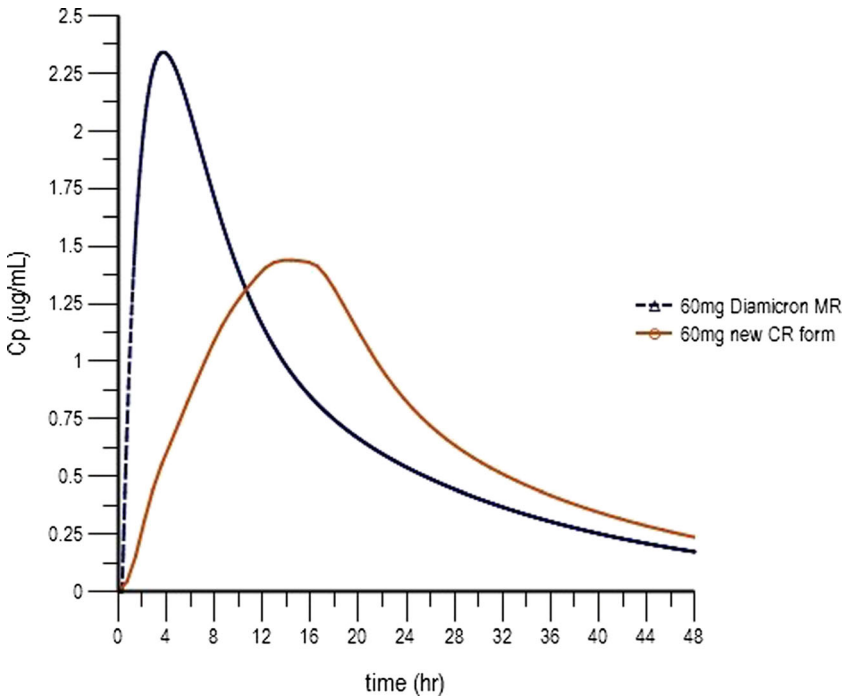

Fig. 10. Predicted steady-state concentration of GLZ in comparison with the marketed formulation

Table IX. *In vivo* Performance Comparison of the Developed Formulation (CF2) with Marketed Formulation at Steady Sate (at day 7)

Pharmacokinetic parameters, at day 7					
Formulation Code	Tmax, ss (h)	Cmax, ss (ng/ml)	Cmin, ss (ng/ml)	AUC0-24 (ng h/ml)	AUCtau (ng h/ml)
CF2	157	2.02	1.17	24.3	40.2
Diamicron MR 60 mg	148	3.01	0.80	29.7	41.0
CF2/Diamicron MR ratio		0.67	1.47	0.82	0.98

In one study, there was evidence that a serum gliclazide concentration of 1.5 μg/mL represents the threshold for maximal hypoglycemic effect (57). In the case of the new CPOP formulation, the estimated steady state peak and trough levels of gliclazide are in close proximity to the threshold level observed (1.5 μg/mL). Therefore, it can be well assumed that the new formulation could have adequate effectiveness based on the steady state plasma levels and the threshold level of gliclazide for maximum hypoglycemic effect.

In a study involving population PK-PD analysis, an E_{max} relationship was established between the plasma AUC of gliclazide (Diamicron MR) and the decrease in fasting plasma glucose (FPG) (58). The population AUC_{50} (AUC that induces 50% of maximal effect) was found to be 20 μg.h/mL which was just below the mean AUC of the 30-mg MR dose, which is the initial dose of gliclazide MR dosing regimen. It was the highest tested dose of 120 mg that was predicted to produce 87% of the maximum hypoglycemic effect. The hypoglycemic efficacy (E_{max}) of gliclazide was found to be directly related to the baseline FPG level; the higher the FPG level, the higher its decrease from the baseline. Moreover, the estimated plasma AUC (40 μg.h/mL) from the new CPOP formulation (60 mg dose) was well above the population AUC_{50} observed from the population PK-PD study indicating adequate exposure of CPOP formulation in translating the required hypoglycemic response.

Accelerated Stability Studies

The stability samples of optimized formulation (CF2) showed no significant changes in drug content and drug release profile compared to the initial samples (Table X). The burst strength of stability samples was also exhibited no change compared to the initial samples. Hence, it was concluded that the product was stable in HDPE bottle and PVC blister packs at 40±2°C/75±5%RH for 3 months with respect to all physical and chemical attributes studied.

CONCLUSION

Hot melt extrusion technology in the preparation of SD could be a useful approach to enhance *in vitro* dissolution and *in vivo* bioavailability of a thermostable, poorly water-soluble drug like GLZ. The dissolution enhancement in SD system was attributed to polymorphic change of drug from crystalline into amorphous state and the formation of microenvironment to dissolve GLZ by incorporating formulations. This SD system was formulated into CPOP-based tablet that can deliver GLZ in a controlled manner for 16 h. This study suggests that drug release from these systems is controlled by osmotic pressure as the major mechanism; release pattern followed zero order kinetics controlled by non-Fickian diffusion and independent of environmental medium and the mobility of the gastrointestinal tract. The CPOP formulation was found to be stable when exposed to accelerated stress condition of 40°C/75%RH for 3 months. The CPOP formulation was found to attain desired plasma level for a longer period of time compared to marketed modified release formulation and predicted to provide adequate exposure in translating hypoglycemic response. The prototype solubilization method using HME combined with controlled porosity osmotic pump-based technique could provide desirable zero order release profile with improved bioavailability which is significant in case of sulfonylurea class of drugs which sometimes leads to hypoglycemic shocks in hyperglycemic patients.

Table X. Stability Study Data of Optimized Formulation (CF2) in HDPE and PVC Blister Packs

Parameter	Drug content (%)	Hardness (Kp)	Burst strength (MPa)	Drug release f_2 value (initial vs stability sample)
Initial	99.82±1.23	8.6	7.65±0.96	–
3 months (HDPE bottle)	98.64±1.21	9.5	6.85±0.68	78
3 months (PVC blister)	98.75±1.17	8.1	6.75±0.65	75

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