Formulation and Optimization of Controlled Porosity Osmotic Pump Tablet for Oral Administration of Glipizide

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Abstract

Aim: Glipizide (GZ) which is oral hypoglycemic drug belongs to BCS Class II was selected as a model drug to prepare controlled porosity osmotic pump (CPOP) tablet. **Materials and Methods:** The solubility of GZ was increased by forming its solid dispersion (SD) with polyvinylpyrrolidone (PVP). The GZ–PVP SD (GZ-SD) systems were prepared by physical mixing and spray drying method, and characterized by differential scanning calorimetry, powder X-ray diffraction analysis, Fourier transform-infrared spectroscopy, and scanning electron microscopy (SEM). **Results and Discussion:** The effect of different formulation variables - such as the 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 present in the core. GZ release was inversely proportional to the membrane weight but directly related to the initial level of pore former (PVP, sorbitol) in the membrane. Drug release from the developed formulations was independent of pH and agitational intensity, but dependent on the osmotic pressure of the dissolution media. **Conclusion:** Results of SEM studies confirmed the formation of pores in the membrane from where the drug release occurred. The formulations were stable after 3 months of accelerated stability studies. The results indicated that CPOP tablet developed using spray dried GZ–SD had excellent zero-order release characteristics *in vitro*.

Keywords: Controlled porosity osmotic pump, glipizide, osmotic pressure, polyvinylpyrrolidone, solid dispersion

INTRODUCTION

In the recent years, considerable attention has been focused on the development of novel drug delivery system (NDDS).[1] Among the various NDDS available in market, per oral controlled release (CR) systems hold the major market share because of their obvious advantages ease of administration and better patient compliance.[2] CR delivery systems provide desired concentration of drug at the absorption site which allows to maintain plasma concentrations within the therapeutic range and reduces dosing frequency.[3] Various dosage forms are available to control the release of drug such as matrix, reservoir or osmotic systems. However, osmotic systems are most promising than conventional CR dosage forms because these systems utilize osmotic pressure as an energy source to release drug. Drug release from these systems is independent of pH, other physiological parameters to a large extent and it is possible to modulate the release characteristics by optimizing properties of drug and system.[4]

Two problems that are frequently encountered with many active substances: Their low degree of solubility in water and their limited bioavailability. One simple method to improve solubility is to incorporate a solubilizer such as povidone.[5] Povidone forms soluble complexes with many

active substances. In some cases, a physical mixture (PM) of an API and povidone is quite enough. Apart from that, several methods have been proposed to increase the surface interface between active substance and solubilizer. In such cases, solid dispersions (SDs) systems are more suitable. Povidone is suitable for the manufacture of SDs as it hydrophilic in nature, available in various molecular weights and viscosities, forms water-soluble complexes with many active substances, and is almost universally soluble.[6]

In the present investigation, controlled porosity osmotic pump (CPOP) system of glipizide (GZ) was developed since preparation of CPOP is simple; it is not necessary to have complicated side drilling and compared to other osmotic pump systems, it required less excipients for its formulation. The coating composition of CPOP includes pore forming agent, which generates pores after coming in contact with aqueous media and core content releases through pores at a constant rate, where the release mechanism primarily is osmotic with simple diffusion playing a minor role.[7-9] Different formulation variables were studied and optimized to get the desired release profile.

MATERIALS AND METHODS

Materials

GZ and PVP were obtained from Watson Pharmaceuticals, Goa, India, as a gift sample. Sodium carbonate, lactose, sodium lauryl sulfate, magnesium stearate, cellulose acetate, sorbitol, PEG-400, and triacetin was procured from S.D. Fine Chemicals, Mumbai, India. Acetone, ethanol, methylene chloride were purchased from Unichem Biological sciences, Kolhapur. All chemicals and solvents used are of analytical grade.

Methods

Phase solubility

According to the Higuchi and Connors method, solubility studies were carried out. Accurately weighed sample of GZ in quantities exceeding its aqueous solubility was taken into vials to which 15 mL of distilled water added, containing various concentration of PVP (0-2%). The suspension was shaken at room temperature for 48 h to reach equilibrium and then filtered through a 0.45 μm membrane and analyzed at 276 nm using UV-visible spectrophotometer (Shimadztu Corp, Japan).[10,11]

PMs

PMs were obtained by homogeneous blending of previously sieved and weighed GZ and PVP in tumble mixer for 15 min. For forming PMs, drug and polymer were taken in three different ratios (1:4, 1:5, 1:6 w/w).[12]

Preparation of SD using spray drying

The suspensions of GZ with PVP was taken into three different ratios (1:4, 1:5, 1:6 w/w) and were dried using (LSD-48; JISL Pvt. Ltd., Mumbai) spray dryer. GZ and PVP were dissolved in minimum amount of ethanol and methylene chloride to form solution. The spray dryer was equipped with a fluid nozzle and operated in a cocurrent mode (the feeding suspension and the drying air flow in the same direction). The drying was performed using the following parameters: Inlet temperature 80°C, outlet temperature in a range from 40°C, air pressure 2 bar, air flow rate: 20 m³/h, flow rate of the solution: 20 mL/min and the nozzle orifice size: 0.8 mm. aspirator setting 95% and pump setting 18%. The feeding suspension was mixed continuously during the drying process using a magnetic stirrer to prevent sedimentation of the suspended cellulose fibers. The spray dried powder were collected from the dryers' collection vessel and stored in closed vials at room temperature.[12-15]

In vitro dissolution studies of GZ, PMs, and SD

Preliminary dissolution tests of pure GZ, its PM and SD were intended for selecting the SD system, performed using the USP dissolution apparatus II at 50 rpm. At appropriate intervals, samples from the dissolution medium were withdrawn filtered, and concentrations of GZ were determined spectrophotometrically at 276 nm maintained at temperature of 37°C ± 0.5°C.[16-18]

Characterization of PM and SD of GZ

Differential scanning calorimetry (DSC) analysis

The thermal analysis was carried out with DSC (Lab. Mettler) for pure drug, polymer and their PM and SD. All samples were placed in sealed aluminum pans and heated at a rate of 10°C/min in 0-300°C temperature range under a nitrogen flow of 20 mL/min.[19]

Fourier transform infra-red (FT-IR) spectroscopy

FT-IR spectra of pure drug, polymer and their PM and SD was recorded using FT-IR spectrophotometer (Agilent). These spectrums were recorded in scanning range of 400-4000/cm with resolution of 4/cm.

Powder XRD

The powder XRD patterns of pure drug, polymer and their PM and SD were collected with an XRD (D8 advanced Bruker AXS) at 2θ angle.[20]

Scanning electron microscopy (SEM)

The surface morphology of the SD of GZ was analyzed by a SEM model JEOL-JSM-6360 coupled with energy dispersive

X-ray analysis. The micrographs were used for morphological characterization and particle size determination.[21] SEM micrographs of pure drug, polymer and their PM and SD were taken. The samples were coated with a thin layer of gold, before scanning.[22]

Preparation of core tablets

Core tablets of GZ were prepared by wet granulation technique. All the excipients except GZ SD were mixed and passed through 30-mesh sieve. The blend was mixed for 10 min and PVP was added and granulated with ethanol. The resulting wet mass was passed through 18-mesh sieve, and granules were dried at 50°C for 10 min. The granules were passed through sieve 22 and obtained uniform sized granules were mixed with GZ-SD with blending of magnesium stearate and talc (all 60-mesh passed).[23-26] The resultant homogenized mixture were compressed into tablets having an average weight of 400 mg using a multistation rotary machine (CIP-Ahmadabad, D-8, India) fitted with 10 mm round standard concave punches [Table 1].

Coating of core tablets

The core tablets of GZ were coated in an automated perforated pan (VJ instruments, R and D coater). To have a constant zero-order release, the level of pore former, type of pore former and coating thickness were used as formulation variables [Table 2]. Various components of the coating solution were added to the coating solvent in a sequential manner, component which was added first was allowed to dissolve before the next component was added. Core tablets of GZ were placed in the coating pan along with 200 g of filler, tablets which were made using 7.00 mm round deep concave punches and containing microcrystalline cellulose, starch, magnesium stearate, and colloidal silicon dioxide.[27,28]

Initially, pan was rotated at low speed (2-5 rev/min) and heated air was passed allowed to pass through the tablet bed. Coating process was started when the outlet air temperature reached 28°C. The pan was kept rotating in the range of 15-20 revolutions per minute and coating solution was sprayed at the rate of 5-8 ml/min. Atomization air pressure was kept at in the range 6-10 psi and the outlet temperature was maintained above 28°C by keeping the inlet air temperature in the range of 50-55°C. The coating was continued until desired weight gain was obtained. In all the cases, tablets were dried at 50°C for 16 h before further evaluation.

Characterization of CPOP tablet

The core and coated tablets were evaluated for various physicochemical parameters.

Table 1: The formulation of core tablets of GZ

Sr. No.	Ingredients (mg)	F1	F2	F3
1	Glipizide SD*	30	30	30
2	Sodium carbonate	0	5	10
3	Lactose	350	350	350
4	SLS	10	10	10
5	Magnesium stearate	3	3	3
6	Talc	5	5	5
7	PVP K30	q.s.	q.s.	q.s.
8	Isopropyl alcohol	q.s	q.s	q.s.

*30 mg of GZ SD is equivalent to 5 mg of GZ. GZ: Glipizide, SD: Solid dispersions, PVP: Polyvinylpyrrolidone

Table 2: The solution for coating core tablets of glipizide

Ingredients	A1	A2	A3	B1	B2	B3
CA (% w/v)	4	4	4	4	4	4
PVP %w/w of CA	30	40	50	-	-	-
Sorbitol %w/w of CA	-	-	-	30	40	50
PEG-400 %w/w of CA	12.5	12.5	12.5	12.5	12.5	12.5
Triacetin %w/w of CA	6.25	6.25	6.25	6.25	6.25	6.25

Coating solvent: Acetone:water [95:5]. GZ: Glipizide, PVP: Polyvinylpyrrolidone

Effect of pH

To assure that release from developed formulations is independent of pH, release studies of the optimized formulations were conducted in dissolution media of different pH and according to pH change method in which release media was simulated gastric fluid (SGF, pH 1.2) for first 2 h and followed by SIF (pH 6.8) for the remaining hours. The samples (10 ml) were withdrawn at predetermined intervals and analyzed after filtration through 0.45 mm cellulose membrane filters.[21]

Effect of agitational intensity

To study the effect of agitational intensity of the release media, release studies of the optimized formulation were carried out in dissolution apparatus which was kept rotating at various rotational speeds. Dissolution apparatus used was USP-II (paddle type) which was rotated at 50, 100, and 150 rpm. Samples were withdrawn at specified time intervals and analyzed using UV-visible spectrophotometer at 276 nm after filtration through 0.45 mm cellulose membrane filters.[29,30]

Effect of osmotic pressure

To confirm the drug release mechanism, release studies of the optimized formulation were conducted in media having different osmotic pressure. To increase the osmotic pressure of the release media, sodium chloride was added to dissolution medium which acts as osmotically effective solute. The pH was adjusted to 6.8 ± 0.05. Release studies were carried out in 900 ml of media using USP II dissolution test apparatus (100 rpm) and analyzed using UV-visible spectrophotometer at 276 nm.[31]

In vitro dissolution

The developed formulations were subjected to release studies using USP-II dissolution apparatus (Veego, India) which was kept rotating at speed 100 rpm. Dissolution medium used was simulated intestinal fluid (SIF, pH 6.8, 900 ml) and maintained at $37°C \pm 0.5°C$. The samples were withdrawn (10 ml) at specified time intervals and replaced with an equivalent amount of fresh medium. After filtration through 0.45 µm membrane filters, the dissolution samples were analyzed using a validated UV spectroscopic method at 276 nm.[32-35] Release profiles of various formulations were compared using model independent pair-wise approach, viz., calculation of "difference factor" f1 and "similarity factor" f2.

$$f_1 = \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \times 100$$

$$f_2 = 50 X \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum_{t=1}^{n} w_f |R_t - T_t|^2\right]^{-0.5} \times 100\right\}$$

According to the FDA guidance, in both equations, R and T represent the dissolution measurements at P time points of the reference and test, respectively. f1 values of 0-15 and f2 values of 50-100 ensure sameness or equivalence of the two dissolution profiles.[36-38]

Release kinetics

To elucidate the mechanism of release and release rate kinetics of the dosage form, the release data obtained were fitted into zero order, first order, Higuchi matrix, Peppas, and Hixson-Crowell model. The highest value of R^2 was taken as criteria for selection of the best-fit model.[39,40]

SEM

To reveal the mechanism of drug release from the developed formulations, surface of coated tablets before and after dissolution studies was studied using SEM.

A small sample of the coating membrane was carefully cut from the exhausted shells (after dissolution studies) and dried at 50°C for 2 h. The mounted samples were sputter coated for 2 min with gold using fine coat ion sputter with the pressure of 8 kg Pascal and examined under SEM (JSM-6360, JEOL Ltd.).[40]

Accelerated stability studies

Optimized formulations of GZ were packed in aluminum foil strips of 0.04 mm thick which is laminated with PVC. The packed formulations were stored in ICH certified stability chamber which was 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.[41,42]
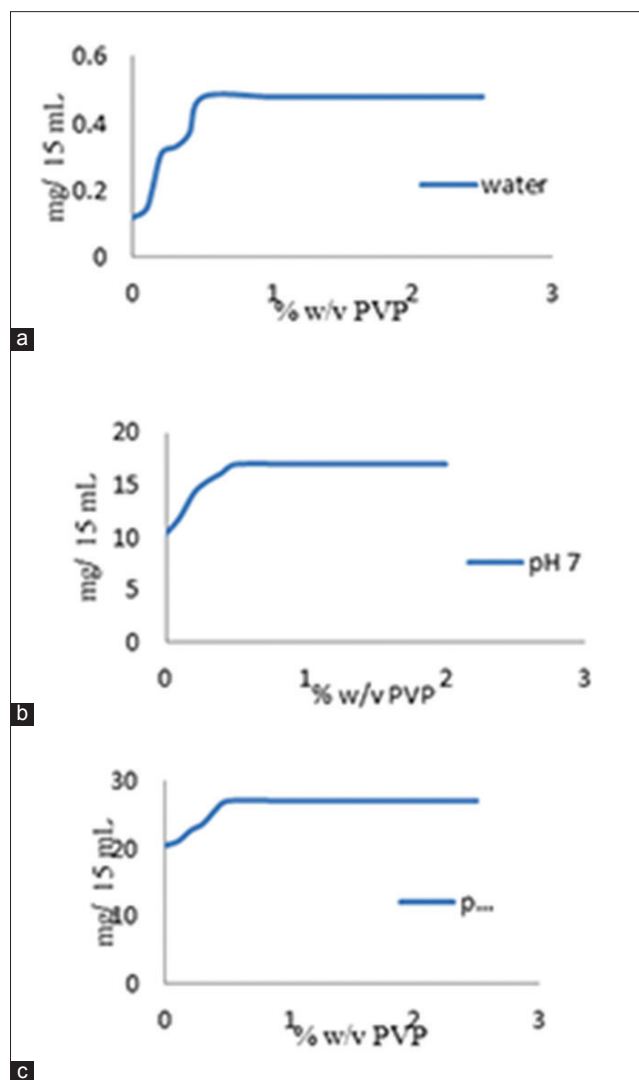
Figure 1: Phase solubility diagrams for glipizide in the presence of polyvinylpyrrolidone in water (a), phosphate buffer pH 7 (b) and phosphate buffer pH 9 (c) at 25°C ± 0.5°C ($n = 3$)
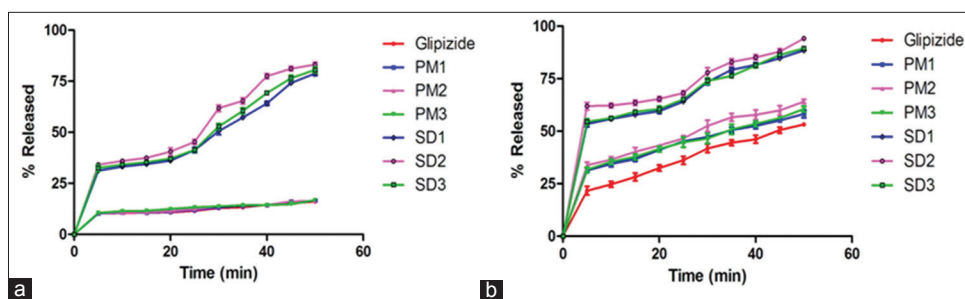
Figure 2: Dissolution study of glipizide alone and its physical mixtures, solid dispersions with polyvinylpyrrolidone K90 in (a) 0.1 N HCl and (b) phosphate-buffered saline of pH 6.8, data is represented as mean ± standard deviation, *n* = 3

RESULT AND DISCUSSION

Phase solubility

The solubility of GZ in water, PBS pH 7 and PBS pH 9 were 8.42 ± 0.54, 691 ± 17.54 and 1371 ± 20.59, respectively. It is evident that the pH of solutions has a pronounced effect on the solubility of GZ. The effect of PVP concentration increasing on the GZ solubility in water and buffer solutions with different pH values at 25°C [Figure 1]. It is clearly observed that the apparent solubility of GZ continually increased as a function of polymer concentration up to 0.5% w/v of PVP and then remained constant.[2]

In vitro dissolution of GZ, PMs, and SDs

The percentage drug release versus time for pure GZ; PMs (PM1, PM2, PM3) and SDs (SD1, SD2, SD3) in a volume of 900 mL in the two different media: 0.1 N HCl SGF (IP) and phosphate buffer solution at pH 6.8 (IP), respectively [Figure 2]. GZ powder showed poor dissolution in both media with release of 16.04% ± 0.06% in 0.1 N HCl and 53.23% ± 0.76% in phosphates buffer solution at pH 6.8 after 50 min. PMs resulted in a slight enhancement of drug dissolution which may be attributed to the superficial complexation exists between GZ and hydrophilic polymer PVP as a particle carrier [Figure 2]. PVP can reduce the interfacial tension between the poorly soluble drug and the dissolution medium. Spray drying of GZ results into increased surface area and due to this reason GZ released from SDs exhibited faster dissolution rate in both media as compared with the pure GZ and PMs.

Characterization of PM and SD of GZ

DSC analysis

DSC curves of pure GZ, polymer and their corresponding PM and SD were [Figure 3] obtained using DSC, Mettler. The DSC curve of GZ shows sharp melting endothermic peak (T onset = 211.57°C, T peak = 213.19°C) which confirms that the drug is in crystalline form. A large endothermal effect ranging from 80°C to 120°C associated with water
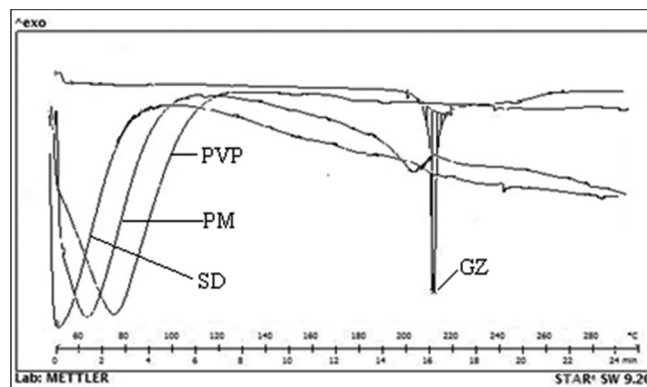
Figure 3: Overlay thermograms of glipizide, polyvinylpyrrolidone, physical mixtures and solid dispersions
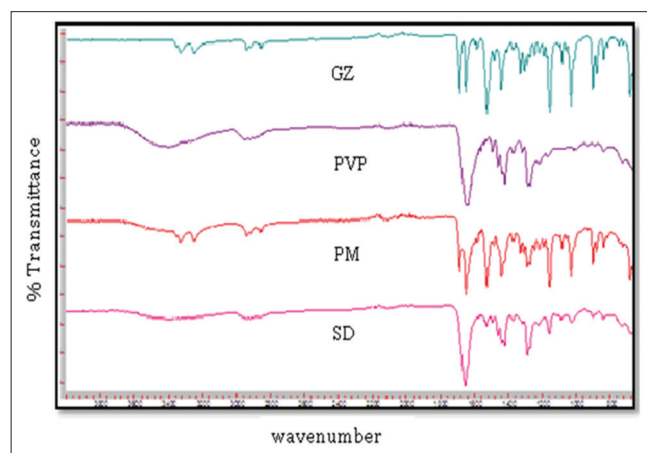
Figure 4: Overlay Fourier transform infra-red spectrums of glipizide, polyvinylpyrrolidone, physical mixtures and solid dispersions

loss was observed in the DSC curve of pure PVP, which had amorphous structure and no melting point was seen in the thermograms.[43]

The PM showed endothermic peaks of both GZ at 200°C and PVP at 65°C, whereas the SDs only exhibited a single endothermic peak at 45°C which can be explained on the basis of complexation between the drug and carrier. Total disappearance of GZ thermal peak indicates complex formation and drug amorphization.

FT-IR spectroscopy

FT-IR spectra of GZ and PVP and the corresponding PMs and SDs were [Figure 4] obtained (Cary 60, Agilent, Germany). The spectrum of GZ showed the carbonyl stretching at 1648, 1687/cm for ureaide (HN-CO-NH) and amide (CO-NH_2) group, respectively. Other characteristic bands were found at 1524/cm (C=C) and 1157/cm stretching of S=O bond in SO_2 moiety.

The spectrum of PVP exhibited important bands at 2950/cm (C–H stretch) and 1647/cm (C=O). A very broadband was also visible at 3443/cm which was due to the presence of water, confirming the appearance of broad endotherm in DSC run due to the presence of water. PMs spectra show the presence of characteristic absorption bands of pure drug with reduced intensity which confirmed the presence of free crystalline drug in PM. The absorption band which could be assigned to the carbonyl is changed in the spectra of SDs. The reason for this observation might be interpreted as a consequence of hydrogen bonding between functional groups of GZ and carbonyl group of PVP.

Therefore, two sharp peaks at 1687 and 1648/cm in IR spectrum of GZ were shifted to a broad signal at 1640/cm of GZ-PVP complex. The signals of characteristic bands in PM were generally stronger than SD owing to less complexation of drug in the mixtures.[44]

Powder XRD

The XRD patterns for the GZ, GZ–PVP, PM and the corresponding SD were obtained [Figure 5]. In X-ray diffractogram of pure GZ, sharp peak which confirms that the drug is in the crystalline form. Typical diffraction peaks of GZ in PMs indicate the presence of free crystalline drug whereas the absence of typical diffraction peaks of GZ in SD XRD suggests the formation of GZ–PVP binary complex in the solid state and total disappearance of GZ crystalline peaks confirmed stronger drug amorphization effect due to the binary complexation.

SEM

SEM micrographs of GZ, PVP, PM, and SD are shown in Figure 6. GZ has appeared as needle-like crystals and PVP has presented amorphous particles. In the PM, the presence of GZ crystals which were mixed physically can be detected clearly. In the SD, the original morphology of the GZ and PVP disappeared and new entity formed. This major change in shape, size, and appearance is an indication of a new single solid phase, which supports the XRD observations. Therefore, the close contact between the hydrophilic polymeric carriers PVP and drug GZ, the reduced particle size and the high surface area might be responsible for the drug solubility enhancement in SDs.

Preparation of core tablets

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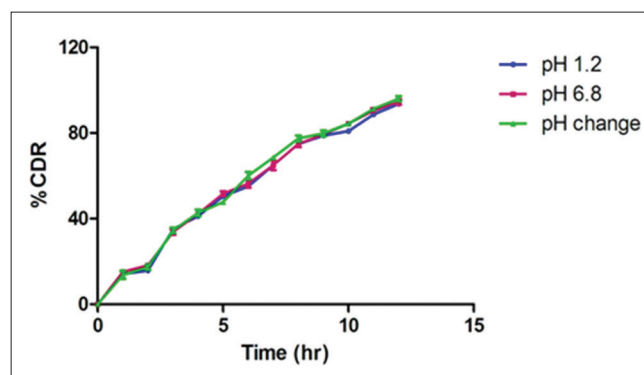
Effect of pH

After studying effect of pH of dissolution medium on GZ release, it was observed that the release profiles of GZ in media of different pH are superimposing [Figure 7]. Hence, it can be concluded that the medium has no influence in
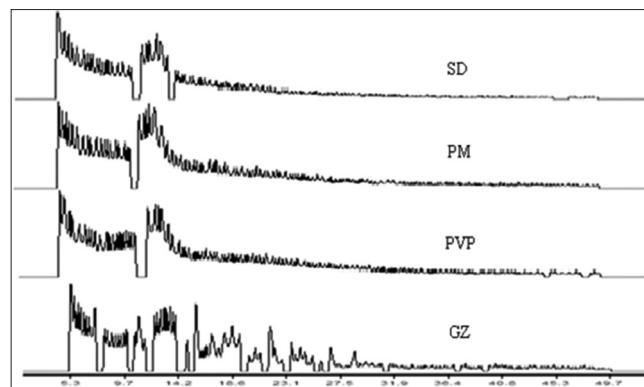
Figure 5: Overlay X-ray diffractograms of glipizide, polyvinylpyrrolidone, physical mixtures and solid dispersions
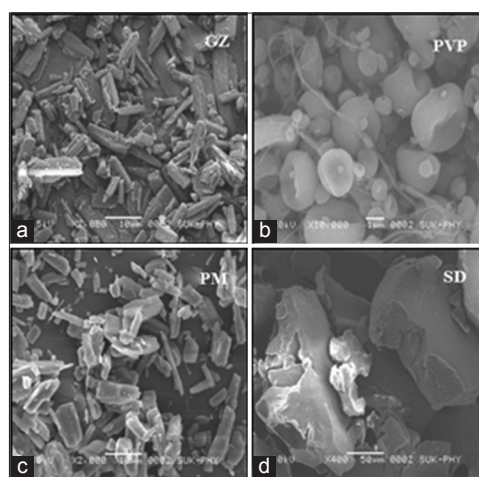
Figure 6: Scanning electron microscopy micrographs of (a) glipizide (b) polyvinylpyrrolidone (c) physical mixtures (d) solid dispersions

Figure 7: Effect of pH on release of glipizide from optimized controlled porosity osmotic pump (A2), (mean ± standard deviation, *n* = 3)

altering the drug release. Hence, it can be predicted that variations in pH of gastrointestinal tract may not affect the drug release.

Effect of agitational intensity

Dissolution study of optimized formulation was carried out at different agitational intensities and it was found that GZ release from the developed formulation is fairly independent of the agitational intensity of the release media and hence, it can be expected that the release from the developed formulation will be independent of the hydrodynamic conditions of the absorption site [Figure 8].

Effect of osmotic pressure

The release study of optimized formulations was carried out in media of different osmotic pressure. The drug release is highly dependent on the osmotic pressure of the release media [Figure 9]. Release of GZ from the formulation decreases as the osmotic pressure of the media increases. The release was inversely related to the osmotic pressure of the release media which confirms that the mechanism of drug release is by the osmotic pressure.

Effect of sodium carbonate on drug release

The core tablets of GZ were formulated using wet granulation technique [Table 1]. Dissolution studies show that the solubility of GZ increases in higher pH media. It is reported that the solubility of GZ in saturated Na_2CO_3 solution was 137.7 ± 0.8 μg/mL, therefore, sodium carbonate was selected as a solubilizer for GZ to modulate the microenvironmental pH within the core during the dissolution process. GZ release from the core tablet without sodium carbonate was incomplete [Figure 10]. Incorporation of sodium carbonate could modulate the solubility of GZ, leading to complete release of GZ from the osmotic systems. From the results obtained, F2 batch was selected and used for coating.
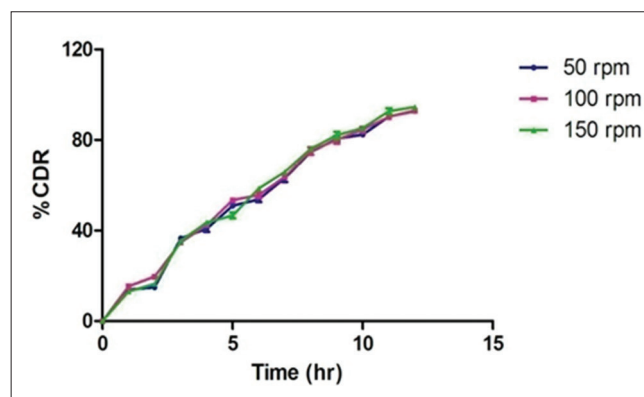
Effect of osmotic pressure (Osmogen)

Level of pore formers

To study the effect of level of pore former, core tablets were coated with coating composition containing 30%, 40% and 50% (w/w) of PVP (A series), and sorbitol (B series) [Table 2]. It was found that the drug release increases as the level of pore former increases. Because as the level of pore former increases, the membrane becomes more porous after coming in contact with the aqueous environment which results in faster drug release.[4] At levels up to 30% and 40% (w/w) of pore former, numbers of pores formed were sufficient to contribute to significant drug release. On the other hand, the release profile from the membrane containing

50% (w/w) of pore former was faster since it became highly porous after coming in contact with water [Figure 11]. Since satisfactory drug release was obtained in the case of formulations containing 40% pore former level (A2 and B2); this concentration was selected for further studies.
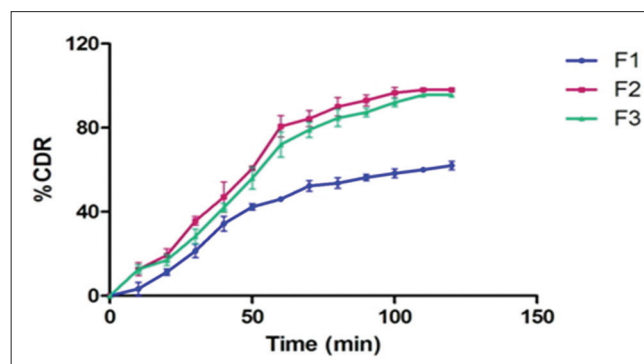
Type of pore formers

To study the effect of type of pore former, core tablets were coated with coating compositions containing different pore formers, viz., PVP 40% and sorbitol 40% w/w of polymer.

Figure 8: Effect of agitational intensity of the release media on release of glipizide from optimized controlled porosity osmotic pump (A2) (mean ± standard deviation, *n* = 3)
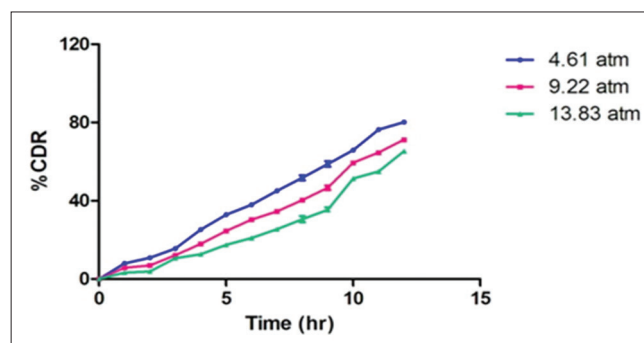
Figure 9: Effect of osmotic pressure of the release media on release of glipizide from optimized controlled porosity osmotic pump (A2) (mean ± standard deviation, *n* = 3)
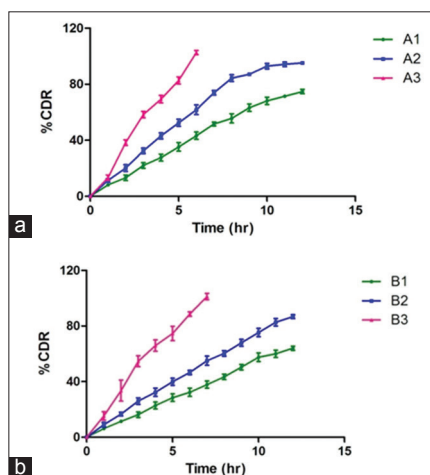

Figure 10: Influence of sodium carbonate on glipizide release profile (mean ± standard deviation, *n* = 3)
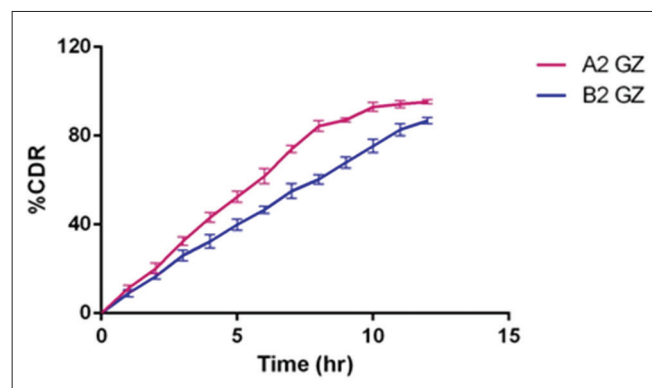
It is evident that [Figure 12] desired drug release can be achieved using different types of pore formers. It has been reported that water-soluble polymers leach out of the coating and produces a porous film with increased permeability or produce hydrated water filled regions within the membrane that allow drug transport across the film.[4] Drug release is higher in the formulation containing PVP as a pore former than with sorbitol. The reason behind this result may be due to the greater aqueous solubility of the PVP and it could be leached out easily and increases the flux rate of fluid.[12] From the results obtained, A2 formulation containing 40% w/w of PVP as pore forming agent was considered as optimized batch and used for further evaluation.

Effect of % coat weight gain

To study the effect of weight gain of the membrane, coating on core tablets were continued for sufficient duration of time (by using A2 batch) so as to get tablets with different weight gain (10%, 12%, and 15%). The release profiles of GZ as function of weight gain of the membrane [Figure 13] were observed that drug release decreases with an
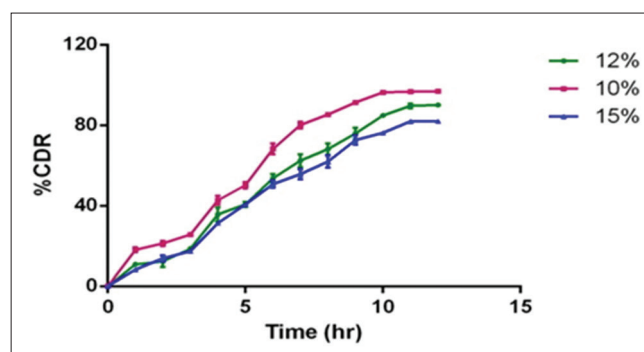
increase in weight gain of the coating membrane and no bursting of tablet was observed during the dissolution in any formulation.

In vitro dissolution

A release profile of optimized formulation was compared with marketed formulation [Figure 14]. From release profile f1 and f2 factors were calculated and it was found 5.9 and 64, respectively. The values of f1 and f2 factors are within limits.[8,9] Therefore, formulated formulation was found to be bioequivalent with marketed formulation.

Drug release kinetics

Dissolution data obtained from formulations were fitted to various mathematical models to describe the kinetics of drug release. The highest value of correlation coefficient was taken as criteria for selecting the most appropriate model. Drug release from osmotic pump fitted well into zero-order kinetics. The compatible fit of the zero order kinetics indicated that the drug release is controlled by a concentration independent release mechanism.[45]


Figure 11: Comparison of *in vitro* release profile of glipizide from controlled porosity osmotic pump of (a) A and (b) B series, (mean ± standard deviation, *n* = 3)

Figure 13: Effect of coat weight gain on release of glipizide from optimized controlled porosity osmotic pump (A2) (mean ± standard deviation, *n* = 3)

Figure 12: *In vitro* release of glipizide from controlled porosity osmotic pump tablet coated with different type of pore former
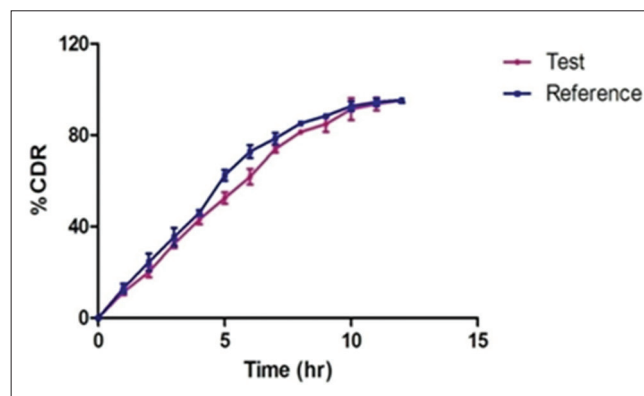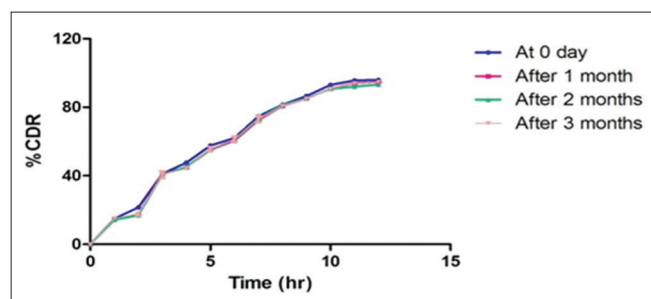

Figure 14: Comparison of release profile of glipizide (GZ) from formulated controlled porosity osmotic pump with marketed formulation of GZ data is presented as mean ± standard deviation, *n* = 3
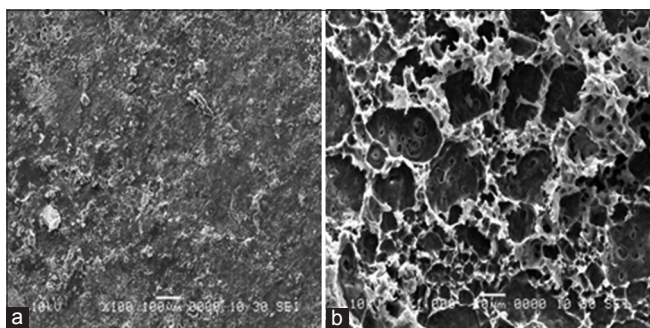
Figure 15: Scanning electron microscopy micrograph of A2 formulation containing 40% w/w of polyvinylpyrrolidone, (a) before dissolution and (b) after dissolution

Figure 16: *In vitro* release of glipizide from optimized controlled porosity osmotic pump (A2) after accelerated stability studies, data is presented as mean ± standard deviation, *n* = 3

SEM

Figure 15a represents before dissolution in which pores are visible as tiny spots and this is possibly due to stress. On the other hand, Figure 15b represents after dissolution in which pores were formed after dissolution and clearly visible and were large in number. The pores were circular.[46] After dissolution, the coating surface becomes more rough on account of leaching of pore former, i.e., PVP.

Finally, it can be concluded that membrane become porous after leaching of pore former from the membrane through which drug release took place. The numbers of pores were directly related to the amount of pore former leached from the membrane.[4] With this results, it can be concluded that the tablets prepared in this investigation were CPOPs tablets.

Accelerated stability study

Optimized formulation A2 was packed in aluminum foil laminated with PVC and stored in ICH certified stability chamber which was maintained at 40°C ± 2°C and 75% ± 5% RH for 3 months.[47,48] Samples were inspected periodically for any change in physical parameters. It was observed that surface was devoid of any change in color or appearance of any kind of spots on it. The formulations were found to be stable in terms of drug content and dissolution. Drug release profile at the end of 3 months is shown in Figure 16.

CONCLUSION

The conclusions arrived in this study indicated that CPOP tablet developed that can deliver MT and GZ simultaneously for 10-12 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 and independent of pH of the environmental medium and the mobility of gastrointestinal tract.

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