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Solid Carriers for Improved Solubility of Glipizide in Osmotically Controlled Oral Drug Delivery System

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The purpose of this study was to increase the solubility of glipizide (gli) by solid dispersions SDs technique with polyvinylpyrrolidone (PVP) in aqueous media. The gli–PVP solid dispersion systems was prepared by physical mixing or spray drying method, and characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) analysis, Fourier transformation-infrared spectroscopy (FT-IR) and scanning electron microscopy (SEM). The elementary osmotic pumps (EOPs) were prepared with gli–PVP complex and the effect of the PVP percentages on the enhancing of gli dissolution rate was studied. The influences of various parameters e.g., drug- PVP ratio, level of solubility modifier, coating weight gain and diameter of drug releasing orifice on drug release profiles were also investigated. The solubility and dissolution rates of gli were significantly increased by solid dispersion using spray dried method as well as their physical mixture. The obtained results indicated that gli–PVP solid dispersion system has suitable solubility behavior in EOP tablets.

Keywords solid dispersions; glipizide; polyvinylpyrrolidone (PVP); osmotic pump; differential scanning calorimetery (DSC); X-ray diffraction analysis (XRD)

INTRODUCTION

Oral osmotic controlled drug delivery systems are available in various designs to deliver the drug in controlled manner from dosage forms. Compared with other controlled release systems e.g., matrix or reservoir system, the advantage of osmotic tablets is on the mechanism of drug release. In matrix based system the principal mechanism for drug release is based on drug diffusion through polymer matrix and the release media. Unlike matrix systems, reservoir systems have a drug core coated with a rate-controlling membrane to control the release. In both matrix and reservoir systems, drug diffusion can be altered by the pH of medium, the presence of food and body's physiological factors. Whereas osmotic system utilize the principles of osmotic pressure for the delivery of drugs and drug release from osmotic systems is independent of pH and other physiological parameters. This makes the osmotic drug delivery systems one of the most interesting and widely applicable controlled release dosage forms.

Osmotic tablets offer many advantages such as zero-order delivery rate, improving patient compliance, a high degree of in vitro-in vivo correlation (ivivc) and simple operation.

The elementary osmotic pump (EOP) was introduced by Theeuwes in the 1970s (Theeuwes, 1975). The EOP tablets consist of an osmotic core (contains drug with or without an osmogent) which is coated with a semi-permeable membrane and has a small orifice as a delivery port through which a solution or suspension of the drug will be released over time.

The EOPs after coming in contact with the aqueous fluids imbibe water at a rate determined by the fluid permeability of membrane and osmotic pressure of core formulation (Theeuwes, 1975; Theeuwes et al., 1972). The rate of drug release from osmotic pump is dependent on the solubility of drug and the

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osmotic pressure of the core; hence, these systems are suitable for delivery of drugs with moderate water solubility. Poor water-soluble drugs are considered as inappropriate candidates for EOP systems because of their inadequate solubility in small volume of water imbibed into systems (McClelland et al., 1991). To overcome this problem, other types of osmotic pumps for poor water-soluble drugs have been designed (Kharmnna, 1991; Swanson et al., 1987). Push-pull osmotic tablets were developed in the 1980s to operate as a delivery of water-insoluble drugs successfully (Kuczynski et al., 1997; Theeuwes, 1978); however, this system has some disadvantages, firstly laser drilling technology should be employed to drill the orifice next to the drug compartment (Geerke, 1997). Secondly, lag time of drug release from osmotic pumps after coming in contact with the aqueous media is long (Herbig et al., 1995). In contrast to push-pull osmotic system, EOP tablets are prepared with a simple technology without any lag time for drug release but its disadvantage is the need for drug solubility enhancement to improve the dissolution rate of Poor water-soluble drugs (Thombre et al., 1999; Thombre et al., 1999; Verma et al., 2000; Verma et al., 2002).

Various techniques have been used to improve the solubility and dissolution rate of poor water-soluble drugs such as glipizide (Verma et al., 2002). Amongst them, the solid dispersion technique and the complexation with hydrophilic polymer such as povidone and cyclodextrin are most frequently used techniques (Chiou et al., 1969; Chiou et al., 1971; Okimoto et al., 1998; Okimoto et al., 1999; Simonelli et al., 1994; Yagi et al., 1996). PVP has been widely employed in the solid dispersion technique to enhance solubility by its ability to interact with certain drug molecules such as griseofulvin and probucol (Chiou et al., 1969; Chiou et al., 1971; Simonelli et al., 1994; Vadnere, 2002; Yagi et al., 1996).

This polymer is freely soluble in water and available in various molecular weights, ranging from 10000 to 700000 Da. The main objective of this work was investigating the possibility of improving the solubility and dissolution rate of gli by solid dispersion technique using PVP in EOP tablets. Glipizide is poor water-soluble and weak acid with a pK of 5.9 with a pH-dependent solubility (Raymond et al., 1986). Solid dispersions (SDs) of gli with PVP were prepared by spray drying method and the physicochemical properties of the SDs were characterized by Differential Scanning Calorimetry (DSC), Fourier Transmission-Infra Red (FT-IR), X-Ray Diffraction (XRD) and Scanning Electron Microscopy (SEM) as well as solubility studies were carried out. Then, EOPs were prepared using gli–PVP SDs. The factors responsible for controlling drug release through the osmotic pump were evaluated by release studies.

MATERIALS AND METHOD

Materials

Glipizide was purchased from Fermion (Finland). Polyvinylpyrrolidone (PVP) was obtained from BASF (Germany) and lactose from DMV (The Netherlands). Eudragits® RS and RL were purchased from Degussa (Germany) and hydroxypropyl methylcellulose (HPMC) from Shin-Etsu (Japan). Pregelatinized starch was obtained from Colorcon (UK). Triethyl citrate, sodium lauryl sulfate, acetone, Mg stearate, PEG 6000, meglumine were purchased from Merck (Germany). Except for those used in HPLC analysis with HPLC grade, all the other chemicals were of analytical grade.

Phase Solubility Studies

Solubility studies were carried out according to the method described by Higuchi and Connors (Higuchi et al., 1965). Accurately weighed sample of gli in quantities exceeding its aqueous solubility, was taken into vials to which were added 15 mL of distilled water containing various concentration of PVP (0–2%). The suspension was shaken at room temperature for 48 hr to reach equilibrium and then filtered through a 0.45 μm membrane filter for HPLC assay. All samples were analyzed using a high performance liquid chromatography (HPLC) system consisted of a Waters solvent delivery pump, a Novapak® C18 column (5 micron, Waters co.) attached to a UV detector. Mobile phase was composed of 50:50 methanol and phosphate buffer pH = 6. The flow rate was 1 mL/min and the detection wave length was set at 276 nm. Each sample was determined in triplicate

Incorporation of Glipizide

Physical Mixtures (PM)

Physical mixtures were obtained by homogeneous blending of previously sieved and weighed gli and PVP in tumble mixer for 15 min. (PM_1, PM_2, and PM_3 are various physical mixtures based on the basic amount shown in Table 1).

Solid Dispersions (SDs) by Spray Drying

Solid dispersions of gli in PVP K90 were prepared in three different ratios (1:4, 1:5, 1:6 w/w) by spray-drying method. Gli and PVP K90 were dissolved in minimum amount of ethanol and methylene chloride (1% w/v).

TABLE 1
Basic Tablet Formulation and Varying Range of all Ingredients

Ingredients	Basic Amount (mg)	Varying Range (mg)
Glipizide[1]	10	10
PVP K90 [2]	50	40–60
Lactose	234	234
Sodium lauryl sulfate (SLS)	10	10
Meglumine	8	4–12
Pregelatinized starch	80	70–90
Mg stearate	8	8

[1,2]Gli and PVP K90 were mixed as PMs (PM_1, PM_2, PM_3) and as SDs (SD_1 , SD_2, SD_3) with other excipients.

The resulting mixture was stirred and spray-dried in a Uniglatt Fluid Bed dryer system (Glatt, Germany) under the following conditions: inlet temperature: 80°C, outlet temperature: 40°C, atomizing air pressure: 2.0 bar, air flow rate: 20m^3/hr, flow rate of the solution: 20mL/min and the nozzle orifice size: 1.3 mm. Yield of the spray drying processes for SD_1, SD_2, SD_3 were 73.8%, 78.6 %, 69.8 %, respectively.

Differential Scanning Calorimetery Analysis

The thermal analyses were carried out with a Shimadzu DSC 60 (Japan). All accurately weighed samples were placed in sealed aluminum pans and heated at a rate of 10°C /min in 30–250°C temperature range under a nitrogen flow of 20mL/min.

X-ray Powder Diffractometry

The powder X-ray diffraction patterns were collected with a Philips x'pert–pro (The Netherlands) (cu kα radiation) 2θ angle from 0° to 50° at a scan rate of 0.04°min.

Fourier Transform Infra-Red Spectroscopy (FT-IR)

Fourier transform infrared (FT-IR) spectra were recorded on samples prepared in KBr disks (2 mg sample in 200 mg KBr) using Perkin Elmer (Spectrum 1000) Spectrophotometer. The scanning range was 450–2000 cm^{-1} with a resolution of 4 cm^{-1}.

Scanning Electron Microscopy (SEM)

Photographs of the particles were taken using scanning electron microscope Cam scan MV 2300 (UK). The samples were coated with a thin layer of gold, before scanning.

Preparing Osmotic Tablets

Preparing the Tablet Core

Tablet cores of gli were prepared by wet granulation. The basic composition of tablet core and all the excipients are listed in Table 1. All the excipients (except gli and PVP) were mixed and passed through a sieve with a mesh size of 300 μm. The mixture was granulated with ethanol and the wet mass was passed through a sieve with a mesh size of 1150 μm and dried in an oven at 50°C for 1 hr.

Dried granules were passed through a sieve with a mesh size of 1000 μm and mixed with gli–PVP PMs or SDs for 10 min and then mixed with Mg stearate for 2 min. (All were passed through a sieve with a mesh size of 150 μm).

The mixture was compressed into tablets (theoretically contained 10 mg gli) using automated single-station punching machine (Erweka, Germany). Tablet weight, diameter and hardness were 400 ± 10 mg, 11 mm, 72 ±7.23 N, respectively.

Coating and Drilling of Tablets

Tablets were coated using a coating pan which has spherical stainless steel with 220 mm diameter and rotating speed of 20 rpm. The composition of coating solution used for coating of gli tablets is given in Table 2. The coating has been performed using a spray gun with nozzle diameter of 1.3 mm; spray rate of 5–7 mL/min, spray pressure of 5 bar and the hot air blower was set at 45°C. After coating, the coated tablets were dried at 50°C for 24 hr. All the formulations were drilled by a mechanical drill in the center of each tablet to obtain a uniform orifice with various diameters from 0.3 to 1.0 mm.

Drug Release Analysis

Drug release was determined by evaluating the cumulative amount of drug released from EOP tablets using USP dissolution apparatus type II (paddle method) in 900 mL phosphate buffer (pH 6.8) at 37 ± 0.5°C. The media were agitated at 50 rpm and samples were taken at specified time intervals and analyzed spectrophotometrically at 276 nm for gli content.

RESULTS AND DISCUSSION

Solubility Studies

Phase Solubility of Glipizide (gli) with PVP

The solubility of gli in water and solutions with various pH values is shown in Table 3. It is evident that the pH of solutions has a pronounced effect on the solubility of gli. Figure 1 shows the effect of PVP concentration increasing on the gli solubility in water and buffer solutions with different pH values at 25°C. It is clearly observed that the apparent solubility of gli continually

TABLE 2
Coating Compositions for gli Core Formulations

Ingredients	Amount*
Eudragit® RS	14.3
Eudragit® RL	14.3
HPMC	3.0
Triethylcitrate	2.4
Talc	6.0
Water	60.00

*Composition given in terms of % w/w; total solids in the coating compositions are 40%, average of coating weight for each tablet was 40 mg (10% weight gain).

TABLE 3
Solubility of gli in Water and Buffer Solutions with Different pH Values at 25°C

Medium	Water (pH = 5.7)	Phosphate buffer pH = 7	Phosphate buffer pH = 9
Solubility (μg/ml)	5 ± 0.35*	650 ± 15.41	1380 ± 22.78

*Data are mean ± *SD* (*n* = 3).

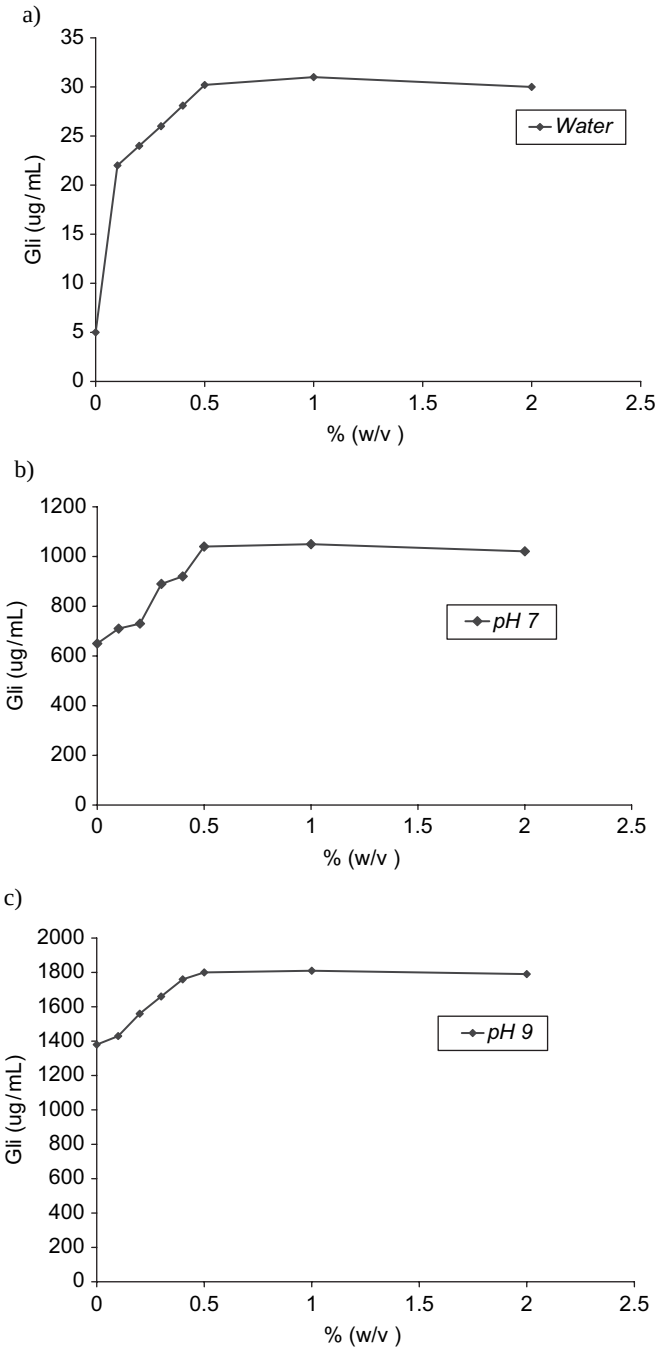


FIGURE 1. Phase solubility diagrams for gli in the presence of PVP K90 in water (Figure 1a), phosphate Buffer pH 7 (Figure 1b) and phosphate buffer pH 9 (Figure 1c) at 25° ± 0.5°C (n = 3).

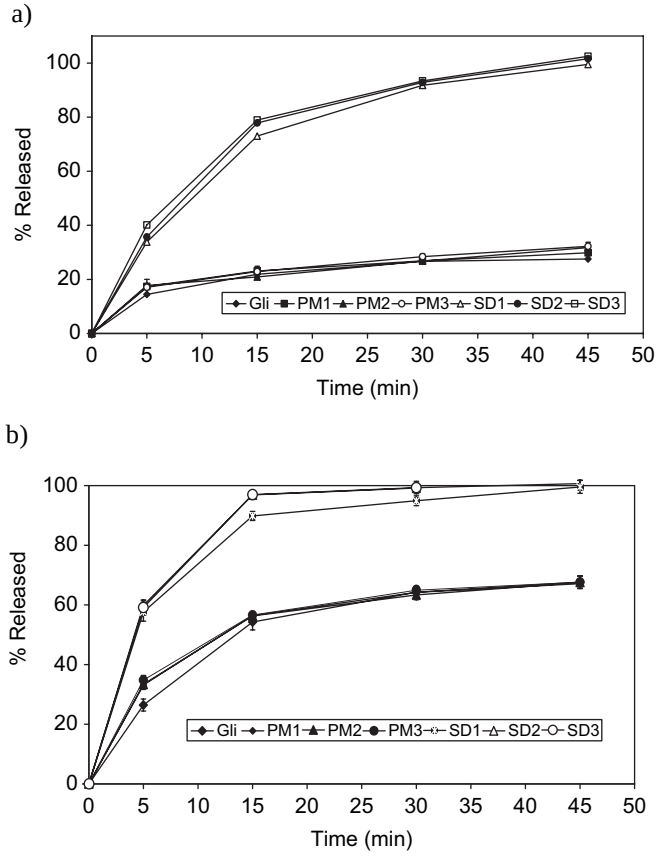


FIGURE 2. Dissolution curves of gli alone and from gli–PVP K90 physical mixtures (PMs) and solid dispersions (SDs) in 0.1 N HCL (a) and phosphate buffer pH 6.8 (b), N = 3, data are presented as mean ± SD.

increased as a function of polymer concentration up to 0.5% w/v of PVP and then remained constant.

Physical Mixtures (PMs) and Solid Dispersions (SDs) Dissolution Studies

Figure 2 illustrates the percentage of drug release versus time for the gli alone and for PMs (PM_1, PM_2, PM_3) and SDs (SD_1, SD_2, SD_3) in a volume of 900 mL in the following two media: 0.1 N HCl simulated gastric fluid (USP) and phosphate buffer solution at pH 6.8 (USP). Gli powder showed poor dissolution in both media with release of 27.2 % ± 3.2 % in 0.1 N HCl and 65.9 ± 2.3 % in phosphates buffer solution at pH 6.8 after 45 min.

PMs resulted in a slight enhancement of drug dissolution which may be attributed to the superficial interaction exists between gli and hydrophilic polymer PVP as a particle carrier. PVP can reduce the interfacial tension between the poor soluble drug and the dissolution medium. Compared with the pure gli and PMs, gli released from SDs exhibited faster dissolution rate in both media. This is due to high surface area obtained by spray drying of solid dispersions.

Physicochemical Properties and Structure of PMs and SDs

Differential Scanning Colorimetery (DSC)

DSC curves of pure materials, solid dispersions and the gli–PVP physical mixtures in the melting temperature range of the drug and dehydration of the carrier are shown in Figure 3.

The DSC curve of gli was typical of a crystalline anhydrous substance with a sharp melting endothermic peak (T onset =

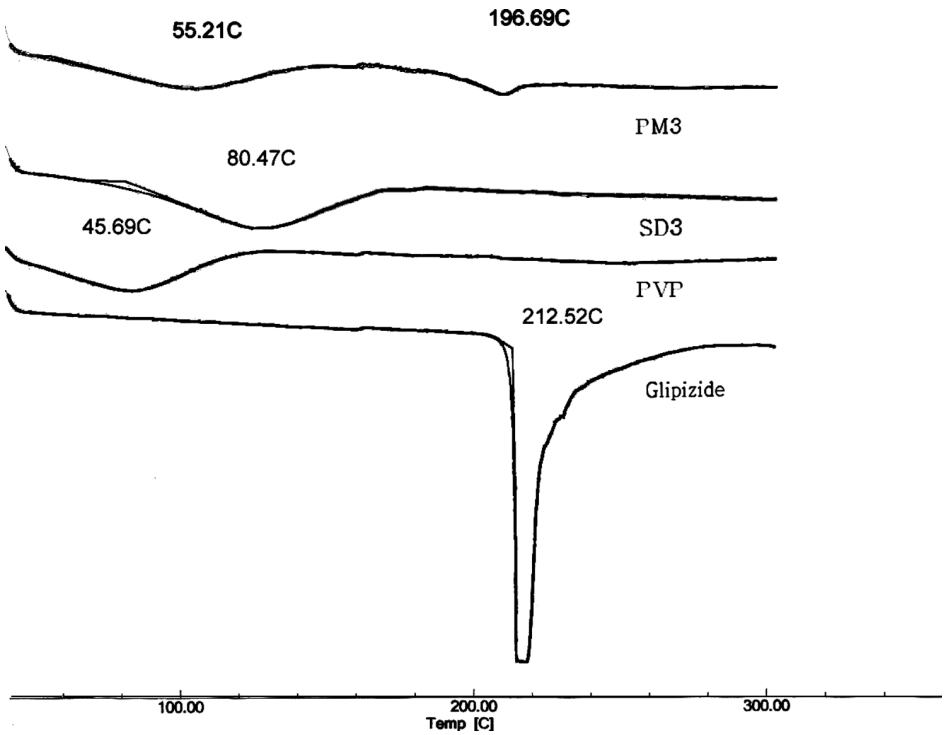


FIGURE 3. Differential scanning calorimetric curves for gli, PVP K90 alone and in physical mixture (PM3) and solid dispersion (SD3).

213.26°C, T peak = 217.66°C). A large endothermal effect associated with water loss was observed in the DSC curve of pure PVP, which had amorphous structure and no melting point was seen in the thermograms. PVP K90 is a hygroscopic polymer and softens at around 150°C with the glass transition temperature (T_g) 185°C (Vadnere, et al., 1998).

The physical mixture showed endothermic peaks of both gli at 196.69°C and PVP at 55.21°C, whereas the solid dispersions only exhibited single endothermic peak at 45.69°C which can be explained on the basis of interaction between the drug and carrier. Total disappearance of gli thermal peak was generally indicated complex formation, drug amorphization or stronger interaction in the solid state between gli and PVP in SDs.

Powder X-ray Diffraction (XRD) Studies

The XRD patterns for the gli, gli–PVP, PMs and the corresponding SDs are presented in Figure 4. In the X-ray differactogram of gli powder, sharp peaks at a diffraction angle of (2θ) are present and it confirms that the drug is in the crystalline form. Typical diffraction peaks of gli in PMs indicating the presence of free crystalline drug were revealed by few broad peaks of low intensity which emerged on the background of PVP as amorphous carrier.

The absence of typical diffraction peaks of gli in SD X-ray diffractogram suggests the formation of gli–PVP binary complex in the solid state and total disappearance of gli crystalline peaks confirmed stronger drug amorphization effect due to the binary complexation.

Fourier Transform Infra-Red (FT-IR) Studies

FT-IR spectra of gli and PVP K90 alone and the corresponding PMs and SDs are shown in Figure 5. The spectrum of gli (Figure 5a) showed the carbonyl stretching at 1649, 1688 cm^{-1} for ureaide ($_{HN}^{}\overset{O}{\underset{}{\overset{\|}{C}}}_{NH}^{}$) and amid group, respectively. Other characteristic bands were found at 1527 cm^{-1} (c=c) and 1159 cm^{-1} stretching of S=O bond in SO_2 moiety. PVP K90 spectra did not show any characteristic band due to its large molecular weight. The presence of characteristic absorption bands of pure drug in PMs Spectra (Figure 5c), though an evident reduction in intensity was observed, confirmed the presence of free crystalline drug the same as DSC and XRD results. In the spectra of SDs (Figure 5d), the absorption band which could be assigned to the carbonyl is changed. The reason for this observation might be interpreted as a consequence of hydrogen bonding between functional groups of gli and carbonyl group of PVP. Therefore, two sharp peaks at 1688 and 1649 cm^{-1} in IR spectrum of gli was shifted to a broad signal at 1640 cm^{-1} of gli-PVP complex. The signals of characteristic bands in PMs were generally stronger than SDs owing to less complexation of drug in the mixtures.

The above results suggest that PMs did not reveal dramatic changes in characteristic peaks of gli which can explain the absence of chemical interactions between gli and PVP as also reported by other investigators (Margarit et al., 2001; Martinez-Oharriz et al., 2002; Mura et al., 2001; Ruan et al., 2005).

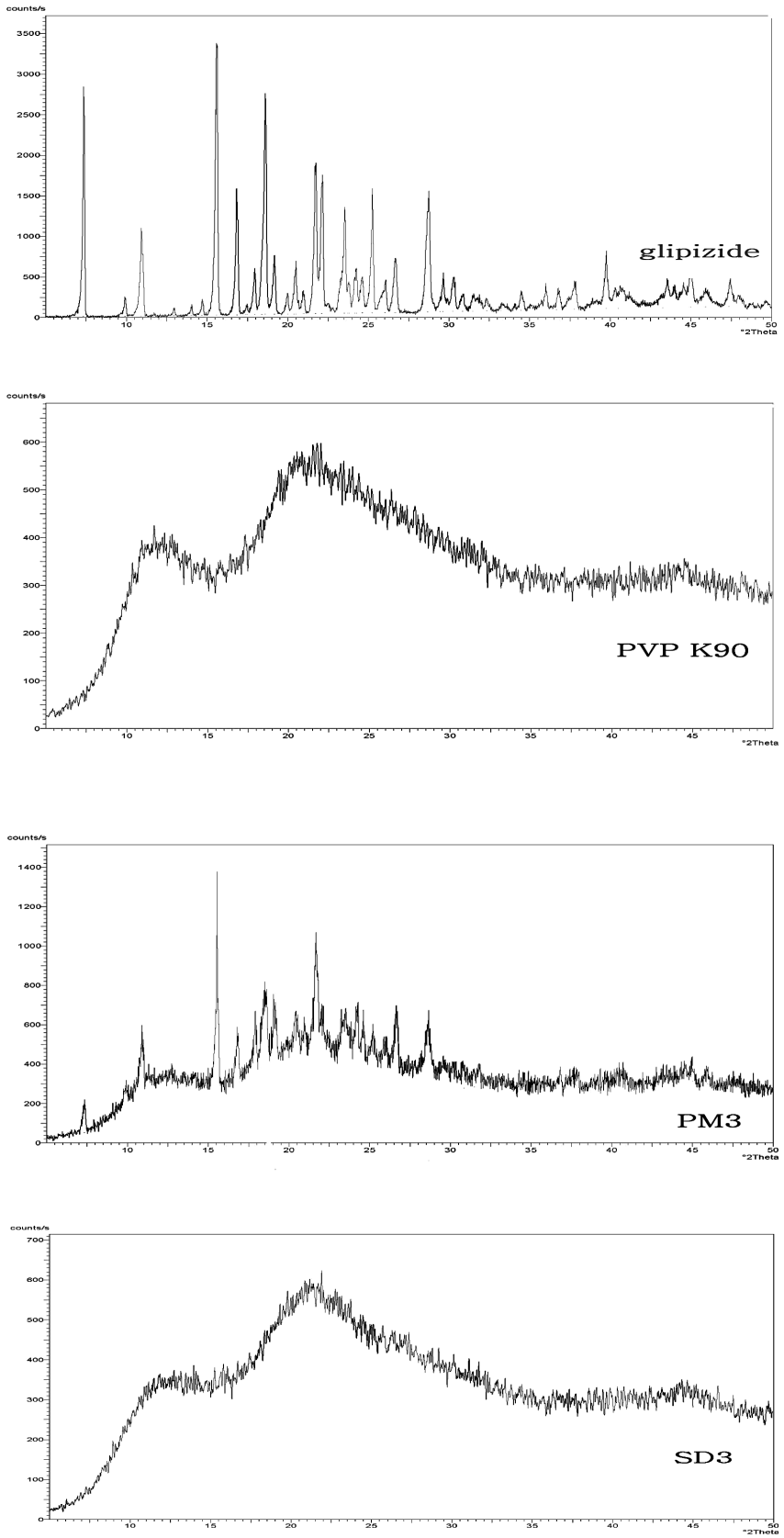


FIGURE 4. X–ray powder diffraction patterns of single components (gli and PVPK90) and physical mixture (PM3) and solid dispersion (SD3).

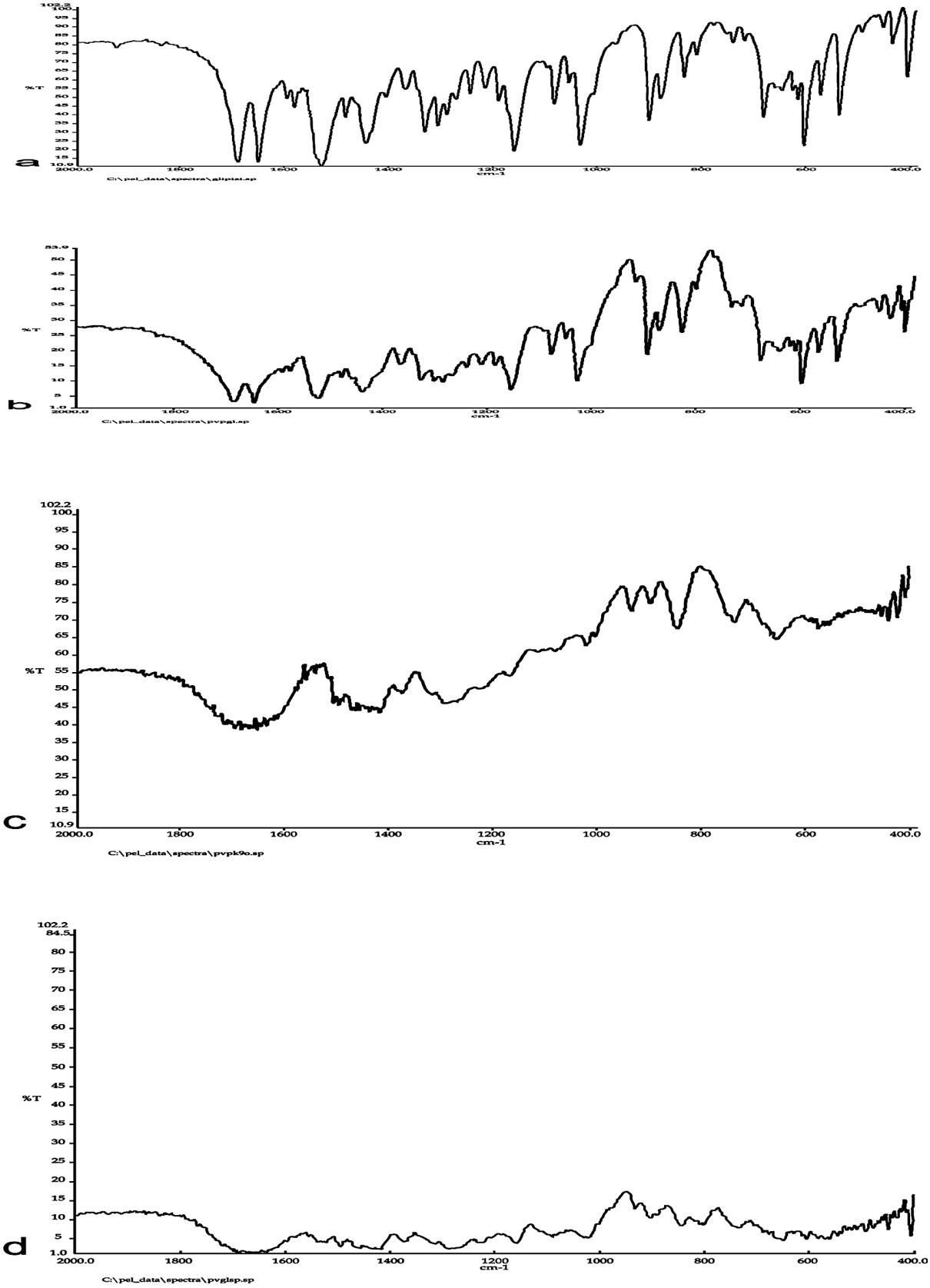


FIGURE 5. FT-IR spectra of pure materials (a) glipizide (b) PVP K90 and (c) PM3 (physical mixture), (d) SD3 (solid dispersion).

Scanning Electron Microscopy (SEM)

SEM photos of gli, PVP K90, PMs and SDs are shown in Figure 6. Gli has appeared as needle-like crystals and PVP K90 has presented amorphous plate-like particles.

In the PMs, the presence of gli crystals which were mixed physically can be detected clearly on the surface of PVP. In the SDs, the original morphology of the gli and PVP disappeared and fibrous structure was present. This major change in shape, size and appearance is an indication of a new single solid phase, thus corroborating the XRD observations. Therefore, the close contact between the hydrophilic polymeric carriers (PVP K90) and gli, the reduced particle size and the high surface area might be responsible for the drug solubility enhancement in SDs.

Influences of Tablet Formulation Variables on Drug Release

To study the effects of tablet formulation variables on release profile, tablets with PMs and SDs were prepared, subsequently coated with the same coating formulation and a 700 μm diameter orifice was drilled on one side of the surface. Tablet cores consist of drug together with hydrophilic polymer (PVP K90) as a carrier for PM and SD systems, other conventional excipients such as osmogent filler (lactose), alkalizing agent as pH modifier (meglumine), wetting agent (SLS) and lubricant (Mg stearate) to form the core compartment.

Effect of gli–PVP Ratio on Drug Release in PM and SD Tablets

The release studies of gli from uncoated core tablets in phosphate buffer (pH 6.8) are shown in Figure 7a for PMs and Figure 7b for SDs. Based on powder solubility results (Figure 2) there was no significant difference in release rate and extent between PM_1, PM_2 and PM_3, but for uncoated tablet cores, the release rate of gli from PM_3 was slower than PM_2 and PM_1. This might be explained by introduction of more binding effect in tablet cores due to increased PVP K90 level and there by slower matrix swelling dissolution rate.

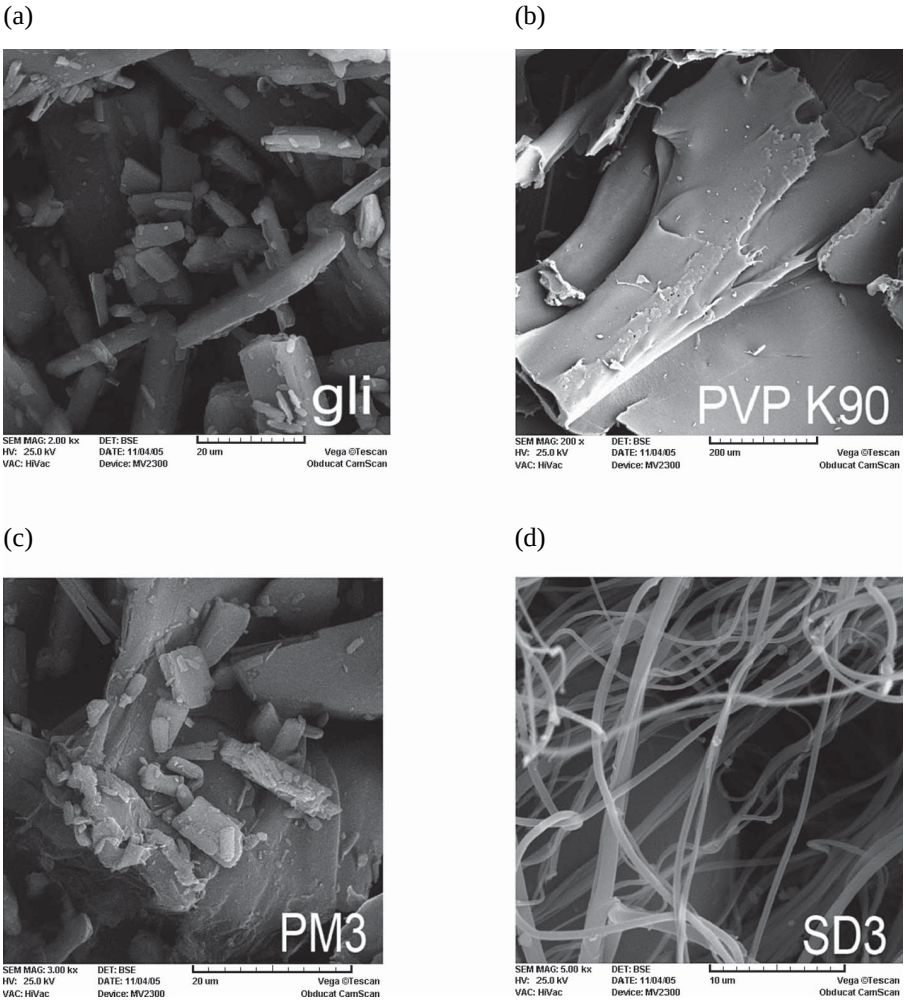


FIGURE 6. SEM micrographs of single components and physical mixture and solid dispersion (a) gli (b) PVP K90 (c) PM3 (d) SD3.

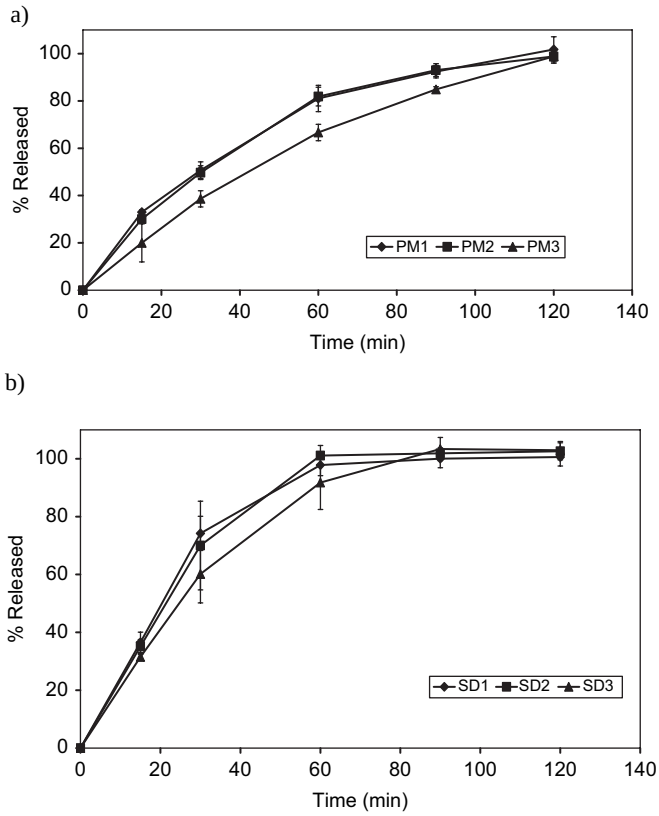


FIGURE 7. Effect of level of PVP on gli release from the tablet cores (7a) physical mixture (PM) (7b) solid dispersion (SD), $N = 6$, data are presented as mean ± *SD*.

The gli SDs uncoated tablets presented better dissolution performance in the rate and extent than corresponding PMs tablets. Several mechanisms have been proposed to account for this enhancement in which decreased crystallinity, increased wettability and reduction of drug particle size were considered to be the predominant factors (Ruan et al., 2005).

In vitro release profiles for PMs and SDs elementary osmotic tablets are depicted graphically in Figures 8a and b, respectively. It is clearly evident from both figures that the amount of PVP has a pronounced influence on extending the release profile. PVP plays the role of hydrophilic carrier and thickening agent which improve dissolution performance in solid dispersions. When EOP tablets are placed in the aqueous media, water penetrates into the core through semi-permeable membrane film by diffusion. The PVP swells and forms a gel in contact with water and a viscous drug suspension is formed in situ within the coated tablets. The viscosity of drug-polymer suspension will be enhanced with increasing amounts of PVP; therefore, stability of suspension increases which inhibits precipitation of drug particles in suspension. The suspension is pumped out through the orifices and consequently, higher release rate could be obtained in the case of higher level of PVP (Figure 8b).

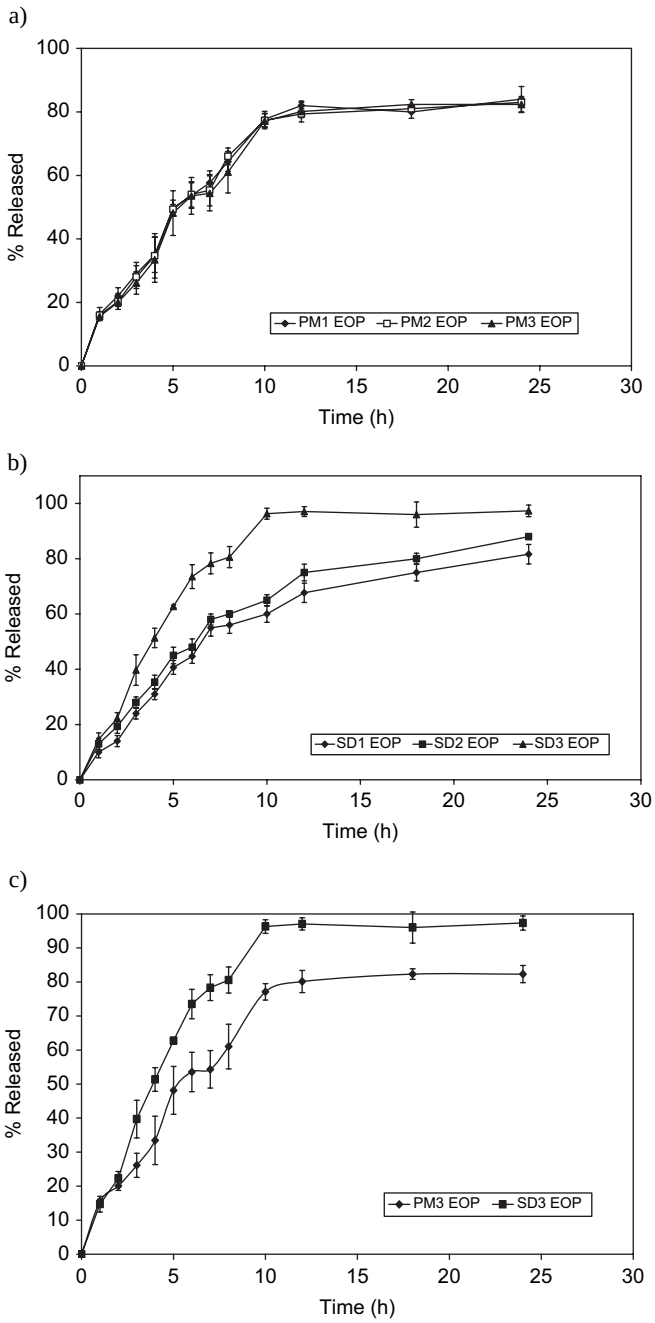


FIGURE 8. Effect of level of PVP on gli release from EOP tablets (8a) physical mixtures (PMs), (8b) solid dispersions (SDs), (8c) comparison of gli release profiles from EOP when the core consists PM3 and SD3, $N = 3$, data are presented as mean ± *SD*.

Figure 8c represents the dissolution profiles for PM_3 and SD_3 EOPs with the same amount of PVP. It is clearly evident that SD EOP tablets are capable of providing higher release rates of gli. The possible reason for this enhancement is due to solubility enhancement by decreasing the particle size and crystallinity as well as increasing the wettability and amorphization of

gli in SDs EOP tablets. Based on the obtained release profiles, SD_3 EOP was considered as the optimal formulation due to linear release of gli to more than 90% within 12 hr.

Effect of pH Microenvironmental Modifier on Drug Release

Gli is a weakly acidic drug and it has been shown that alkalizing agents such as trometamine and sodium carbonate can increase the solubility of gli in EOP tablets (Verma et al., 2000; Verma et al., 2002). To study the effect of level of solubility modifier on drug release, meglumine has been used as a buffering agent. Figure 9 shows the drug release profiles of gli from Meg_1, Meg_2, Meg_3 EOP tablets which contained 1, 2, 3% w/w of meglumine, respectively. It is clearly evident that the concentration of meglumine has a directly profound effect on drug release. As the level of meglumine increases, the microenviromental pH of the core increases above the pK_a of glipizide which results in faster drug release. Similar results have also been obtained by other researchers (Verma et al., 2004; Ouyang et al., 2005).

Influences of Membrane Variables on Drug Release

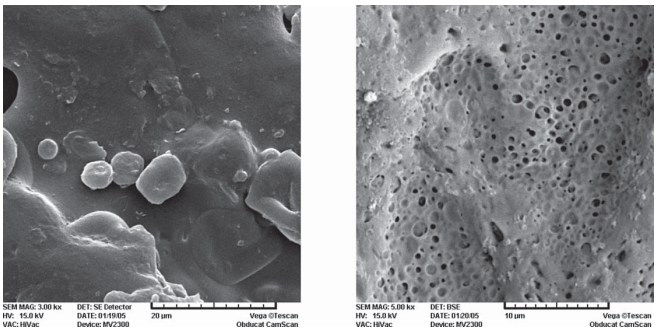
It is important to investigate membrane changes and various parameters such as the type, thickness and amount of pore former which have a profound effect on the drug release from EOP tablets. EOP core compartment is surrounded by a membrane forming polymer, water soluble additives as a pore former and at least one plasticizer capable of improving film-forming properties of the polymer.

The use of acrylic latexes (Eudragit®) as a membrane forming polymer for osmotic systems has been earlier reported in the literature (Jensen et al., 1995). Eudragit® RL and RS are water insoluble, swellable and pH independent film formers. Drug permeability is about two times higher in Eudragit® RL than Eudragit® RS due to the more number of hydrophilic quaternary ammonium groups in Eudragit® RL resulting in faster drug release.

In this study the core tablets were coated with mixtures of Eudragit® RS30D and RL30D which contain HPMC 6 cps as a pore forming agent and triethyl citrate (TEC) as a plasticizer. HPMC and TEC could be leached easily in aqueous media because they are hydrophilic and a porous structure of Eudragit® film remains behind. This increases membrane permeability and drug release rate.

SEMs of membranes obtained before dissolution (Figure 10a) clearly indicates the nonporous uniform and smooth structure of membranes. After dissolution studies, water penetrates into the core tablet through the Eudragit® film by diffusion, HPMC swells and together hydrophilic plasticizer leaches out and forms a porous membrane as could be observed in Figure 10b.

To study the influence of membrane thickness on kinetics of gli release, EOP tablets were coated with different weight of 30, 40, 50 and 80 mg, respectively, using the same coating solution (Figure 11). It was observed that the release rate decreased with increasing total weight gain and membrane thickness. As



(a) Before dissolution studies (b) After dissolution studies

FIGURE 10. SEM micrograph showing the coating membrane structure before (a) and after dissolution studies (b).

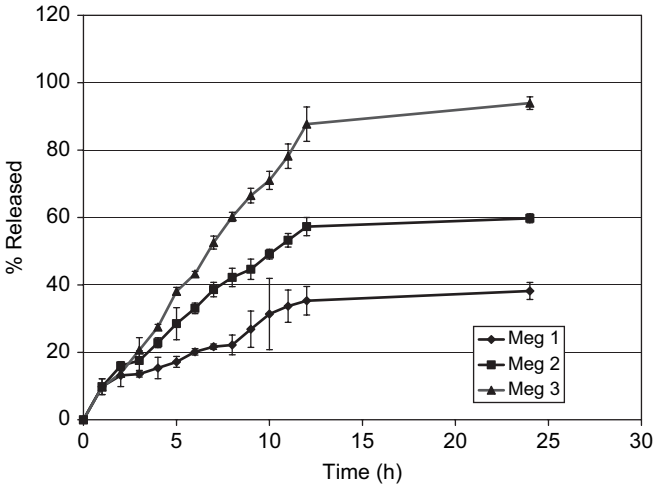


FIGURE 9. Influence of concentration of meglumine on drug release from the EOP tablets, $N = 3$, data are presented as mean ± *SD*.

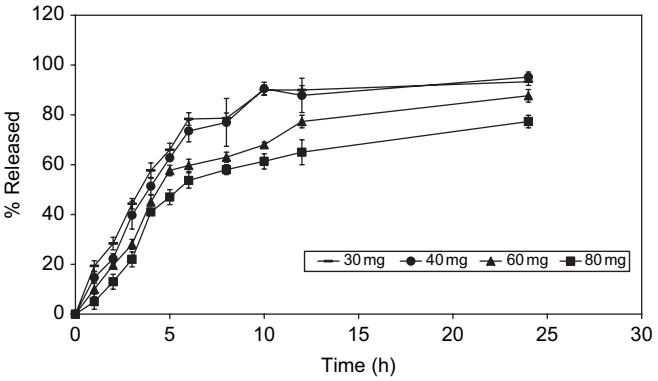


FIGURE 11. Effect of coating weight gain on gli release from the EPO tablets. $N = 3$, data are presented as mean ± *SD*.

the membrane thickness increased, the resistance of the membrane to water diffusion increased and the rate of imbibing water decreased, resulting in lowering the drug release rate.

Figure 12 depicts the release rate, calculated from the zero-order release portions of the release profiles (mainly the first 10 hr), vs. the inverse of membrane thickness or weight. The plots are linear ($r^2 > 0.99$) in various formulations. The linearity of the plots illustrates the dependency of release rate on membrane thickness which can be explained by an osmotic pressure driven release mechanism according to the following equation (Eq. 1; Theeuwes et al., 1983):

$$dm/dt = (AS/h)\sigma\ LP\ \Delta\pi \quad (1)$$

where dm/dt is the zero order release rate of drug, A is the surface area of the film coated membrane, S is the solubility, h is the membrane thickness, σ LP is the hydraulic permeability of the membrane and Δπ is the osmotic pressure difference across the membrane at saturation state.

Effect of Orifice Diameter on Release Rate

The semipermeable membrane of the EOPs contains at least one passageway communicating the contents of the core with the exterior of cores. To study the effect of orifice size, the coated tablets were drilled in the range of 0.3 to 1.0 mm on one side of the surface by mechanical drilling to form a circular orifice. Release rate profiles of gli from these systems with various orifices are compared and shown in Figure 13. It is found that no significant difference exists in the release profiles for various orifice sizes from 0.3 to 1.0 mm ($p > 0.01$). A final orifice diameter of 0.7 mm was chosen as an optimal orifice which did not cause rupture in the membrane during drilling.

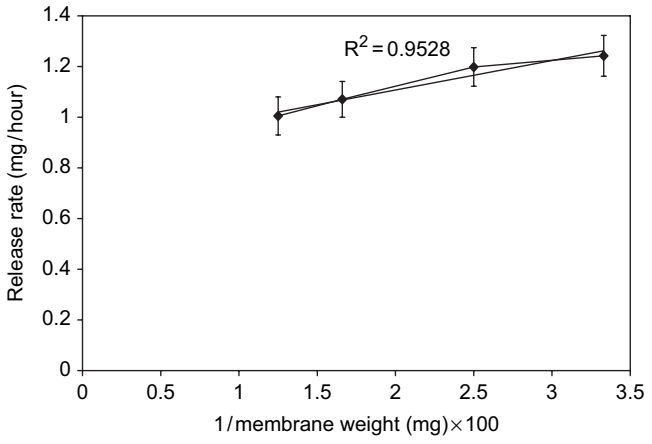


FIGURE 12. Relation between average release rates as a function of coating membrane weight, $N = 3$, data are presented as mean ± *SD*.

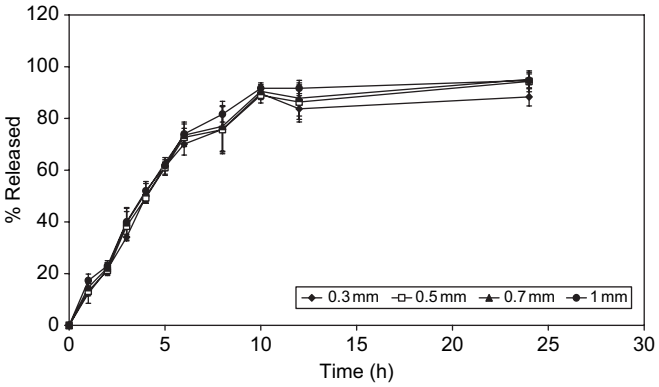


FIGURE 13. Effect of orifice diameter on release rate profiles of gli from EPO tablets, $N = 3$, data are presented as mean ± *SD*.

CONCLUSION

Extended release formulations of gli were developed based on osmotic technology. The solubility studies indicated that the solubility of gli increased significantly at the presence of PVP in comparison with drug alone, specially in high pH. The results of DSC, FT-IR, XRD and SEM, studies confirmed that gli has only physical complexation in PMs and possibly forms amorphization in SDs. The present results suggest that solid dispersion EOP had profoundly positive effect on drug release. Drug releases were directly proportional to the meglumine level but inversely related to the membrane weight and thickness. The release from developed formulations was independent of drug releasing orifice size. Results of SEM studies showed the formation of pores in the membranes after coming into contact with aqueous media. These findings could be very helpful in designing EOPs with solid carriers for improving solubility of poorly water-soluble drugs such as gli in oral osmotically controlled drug delivery system.

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