



Preparation and characterization of Benzathine Penicillin G solid dispersions using different hydrophilic carriers

Afaf M. Weli^{1*}, Eman Saddar², Jagadeesh G.Hiremath¹, Manickam Balamurugan³

*Corresponding author:

Afaf M. Weli

¹Faculty of Pharmaceutical Sciences, College of Pharmacy and Nursing, University of Nizwa, Birkat Al Mouz 616, Oman.

²Faculty of Pharmacy, Helwan University, Ain Helwan, Cairo, Egypt.

³Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur Campus, Jalan Menara Gading, UCSI Heights, 56000 Kuala Lumpur, Malaysia.

Abstract

Several technical factors related to penicillin G intramuscular injection can affect its bioavailability and hence reduce the efficacy of rheumatic fever prevention program. When small amount of diluent is used, the powder is not completely dissolved and the thick suspension frequently causes obstruction of injection needle. The study aimed to characterize the solid-state properties of solid dispersion systems of benzathine penicillin G (BPG) prepared with hydrophilic carriers by applying solvent evaporation method. The results of spectroscopic studies; Fourier transform-infra red (FTIR), Nuclear Magnetic Spectroscopy (¹HNMR) and Differential Scanning Calorimetry (DSC) revealed no chemical interaction between the drug and carriers. No significant changes in drug crystalline state were observed by X-ray diffraction and Scanning Electron Microscope (SEM) studies, even with using amorphous carriers; polyvinyl pyrrolidone (PVP-K30) and hydroxypropyl methylcellulose (HPMC). All the prepared solid dispersions demonstrated 76-93% yield and % drug content dependent on the polymer type and concentration. The hydrophilic polymers demonstrated potential effect on improving the flowability, wettability and dissolution characters of the drug. The results revealed that it is possible to enhance the dissolution rate of BPG (hydrophobic drug) by increasing the surface area of the drug adsorbed on the surface of hydrophilic polymer by solid dispersion method. Finally, solid dispersion BPG: PEG 4000 at ratio 50:50 gave uniform flowability of the powder (around 30), wettability (12 min) and faster dissolution rates among all the formulations. Thus, it was selected as the best formulation in this study.

Keywords: Benzathine benzylpenicillin G, Solid Dispersion, HPMC, PVP K30, PEG4000, Mannitol.

Introduction

Benzathine penicillin G (BPG) is a semi-synthetic compound derived from natural penicillin through the inclusion of a benzyl ring in the β -lactamic group. The molecular mass is 981.19 Daltons that makes the drug very slightly soluble in water and sparingly soluble in alcohol [1]. The antibacterial activity of BPG is mainly against Gram-positive bacteria (including actinomycetes) and some Gram-negative Cocci, as well as some spirochetes. BPG is widely used in the treatment of numerous infectious diseases, especially those related to obstetric and gynecologic conditions. In general, penicillin is effective in the treatment of localized skin and soft-tissue infections of the nose, throat, lower respiratory tract and genitourinary tract. The solubility of the penicillin in the blood and biological fluids is also rather limited; hence it is applied intramuscularly as a depot therapy in treatments that require low and constant blood levels for a long period of time [2].

Despite the high burden of rheumatic heart disease (RHD) globally, there has never been a sustained and comprehensive international

strategy to control. The global efforts to combat the disease are based on strengthening the secondary prophylaxis strategies. Monthly injections of 1,200,000 UI of BPG (1mg) is considered as the first-line treatment for streptococcal infections [2, 3]. The BPG dosage form available in the pharmaceutical market is the sustained-release intramuscular injection suspension. But its variable physical properties, such as solubility, viscosity and crystal size, deviations on its bioavailability and release profile, pain and lack of patient compliance have meant in treatment failure [4,5].

Many trials were developed to prepare BPG in suitable injectable forms. Use of lidocaine hydrochloride as a diluent for benzathine penicillin significantly reduces the pain of injection without affecting penicillin concentration in body fluids [6]. Santos-Magalhães et.al (2000) carried out formulation of benzathine penicillin G in nano emulsion and nanocapsules dosage forms [7]. Holanda e Silva et.al (2006) demonstrated the ability to incorporate BPG into micellar system, which increases its apparent solubility in water. The incorporated drug is also expected to exhibit improved stability, since the antibiotic enclosed in the hydrophobic core of



micelles is rather shielded from the aqueous external environment [8].

Solid dispersion is an important pharmaceutical technology that has been commonly used to improve dissolution and bioavailability of poorly water-soluble drugs. This technique is based on dispersion of the drug into an inert, hydrophilic polymer matrix and the increase in the rate of drug dissolution is due to the following factors: reduction of the drug particle size to molecular level, solubilizing effect on the drug by the water-soluble carrier and enhancement of the wettability and dispersibility of the drug by the carrier material [9-12]. Other factors such as eutectic formation, increased surface area of the drug due to precipitation in the carrier, formation of true solid solution, precipitation as a metastable crystalline form or a decrease in substance crystallinity may also contribute to increased dissolution [13]. Many carriers such as polyethylene glycol (PEG), polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and mannitol have been reported to improve the solubility and bioavailability of poorly water-soluble drugs [14, 15]. Till now, no formulation of BPG has been developed to keep the drug activity, stability and improve patient compliance. The purpose of this study is to utilize the potentials of the solid dispersion technique for the development of injectable suspension of BPG as a promising means to improve its bioavailability and treatment of rheumatic fever. The physicochemical properties of the prepared solid dispersions with different water-soluble carriers, mannitol, PEG4000, HPMC, and PVP were comprehensively evaluated to select the appropriate carrier. The drug and carriers interaction was evaluated using Fourier transform infrared spectroscopy (FTIR), Nuclear magnetic resonance (NMR), and differential scanning calorimetry (DSC). The prepared formulations were further investigated for crystallinity, drug content, flowability, wettability and *in vitro* dissolution rate studies.

Materials and methods

Materials

Benzathine penicillin G (BPG) was provided by Chemical Industries Development (CID), (Cairo, Egypt). Polyvinyl pyrrolidone (PVP-K30) with a molecular weight of 50,000-55,000 and hydroxypropyl methylcellulose (HPMC) were obtained from National Pharmaceutical Industries Co. (NP Pharm, Russayl, Sultanate of Oman). Polyethylene glycol (PEG 4000) with a molecular weight of 3898 g/mol was obtained from Hoechst Chemikalien (Germany). D (-) Mannitol was purchased from BDH chemical (England). All other materials and reagents were of analytical grade.

Methods

Preparation of Benzathine Penicillin G Solid Dispersions

Benzathine penicillin G solid dispersions were prepared by solvent evaporation method (18), using mannitol, PEG4000, PVP and HPMC at two ratios 50:50 and 70:30. Accurately weighed drug was dissolved in 25 ml of ethanol and dichloromethane mixture at ratio 2:3. The organic solution of the drug was poured into magnetically stirred (IKA Works, (Asia) Sdn. Bhd., Malaysia) aqueous solution of the polymer with least amount of water (3 ml) in porcelain dish. The solvents were allowed to evaporate by constant stirring at room temperature. The dispersions were kept at 40 C (JSR Oven, Made in Korea) for 24 hrs for complete dryness. The resultant solid dispersion was scraped out with a spatula, pulverized in a mortar and pestle and passed through a 150 μ m sieve before packing in an airtight container. The composition of formulations were shown in table -1.

Percentage Practical Yield

Percentage practical yield was calculated in order to determine the efficiency of the method of preparation. Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation.

$$PY (\%) = \frac{\text{Practical Mass (solid dispersion)}}{\text{Theoretical mass (Drug +Carrier)}} \times 100$$

Table I. Percentage yield and drug content of BPG solid dispersions.

Formulations	Drug : polymer ratio 50: 50% w/w		Drug : polymer ratio 70: 30% w/w	
	Yield (%)	Drug content (%)	Yield (%)	Drug content (%)
BPG: PVP	76.8	29.1 \pm 2.5	89.3	45.4 \pm 1.8
BPG: HPMC	80.0	38.5 \pm 2.0	91.3	41.3 \pm 1.5
BPG: PEG 4000	76.7	40.5 \pm 5.5	80.0	50.1 \pm 1.1
BPG: Mannitol	88.7	47.5 \pm 5.0	93.3	39.4 \pm 2.2



Drug Content Analysis

Accurately weighed solid dispersions equivalent to 5 mg of BPG were dissolved in the 10 ml of methanol and filtered by using (0.22 μ m Nylon Millipore, USA). The drug content was directly analyzed at 257 nm by UV spectrophotometer (Perkin Elmer, Lambda Ez 201, USA). The percentage drug content was calculated using the following equation:

$$\% \text{ Drug content} = (\text{weight of drug} / \text{weight of drug loaded solid dispersion}) \times 100$$

FT-IR Spectroscopy (FTIR)

FTIR spectra were recorded on a Perkin-Elmer IR spectrometer (spectrum BX 100, Perkin-Elmer, USA). Samples were prepared in KBr discs (about 10 mg sample for 100 mg of dry KBr). The IR spectra were obtained in the spectral region 450-4000 cm^{-1}

X-ray Diffraction (XRD)

The powder X-ray diffraction (PXRD) patterns of pure ingredients and all solid dispersions were recorded using a wide angle x-rays diffraction (WAXD) experiments. The X-ray diffractometer (Model X'pert Pro, P-Analytical, Netherland) with Cu K radiation at a generator voltage of 45KV and a generator current of 45mA was used. Samples were scanned from $2\theta = 1.5$ at a scanning rate of 2/min.

^1H NMR Spectroscopy

^1H NMR spectrum of pure compound and all solid dispersion samples were recorded in a BRUCKER Avance-400 MHz spectrometer (Biospin AG, Switzerland). Deuterated dimethyl sulfoxide (DMSO) was used as solvent.

Differential Scanning Calorimetry (DSC)

Samples for DSC (3-4 mg) were weighed in the aluminum pans (TA Instruments, Brussels, Belgium) and hermetically sealed. Runs were performed over temperature range 20-250 $^{\circ}\text{C}$, at a constant rate of 5 $^{\circ}\text{C}/\text{min}$ under nitrogen purge (30 ml/min). Octadecane and indium standards were used to calibrate the DSC-7 calorimeter (Perkin-Elmer, Norwalk, CT).

Scanning Electron Microscope (SEM)

Morphological analysis of the drug, polymer and drug-polymer solid dispersions was performed using SEM (JEOL JSM-6510LA, Tokyo, Japan). The films were mounted with a double adhesive carbon tape in order to have good conductivity of the electron beam. The operating conditions were: accelerating voltage 1-10 kV, probe current 45 μA and a different magnification.

Angle of repose

It is the maximum possible angle between the surface of a powder heap and the horizontal plane. It was determined by applying the simple funnel method at fixed height (h). After the cone was formed, the radius (r) of the base was measured. The angle of repose (θ) was calculated using the following equation. $\theta = \tan^{-1}h/r$, where r is the radius of the samples, h is the height of the samples.

Wettability

Sinking method described by Carino and Mollet (17) was used to measure of the effect of hydrophilic carries on improving the drug wetting by the aqueous medium. About 0.3 gm of the powder was distributed as thin layer on the surface of 100 ml distilled water. The time needed for the last traces of powder to sink (sinking time) was determined.

In vitro drug release studies

The dissolution study was carried out using USP XXVII Apparatus I (Hanson Research Dissolution tester, Chatsworth, USA.). The dissolution medium was 900 ml of phosphate buffer solution (PBS) with a pH of 7.4 kept at 37 ± 0.5 $^{\circ}\text{C}$. The drug, solid dispersions were filled in empty hard gelatin capsules and then kept in the basket of dissolution apparatus rotating at 50 rpm. At specified time intervals, samples of 1.0 ml were withdrawn and replaced with fresh medium to provide the necessary sink condition. The samples were diluted with methanol up to 10.0 ml, filtered (0.22 μ m Nylon membrane filter, Millipore, Millex®) and analyzed spectrophotometrically at 257 nm (Perkin Elmer, Lambda Ez 201, USA). Each preparation was tested in triplicate and the mean values were calculated. The cumulative percentage drug release was calculated to establish the drug release profiles of the BPG loaded solid dispersions.

Results

Percentage yield and drug content

The percentage yield of the prepared solid dispersions were in the range of 76.7-93.3% Table 1. The results also showed that percentage drug content values were 29.1, 38.5, 40.5 and 47.5 respectively.

Angle of repose and powder wettability

Angle of repose of solid dispersions prepared with PVP, HPMC and PEG 4000 at different ratios was ranged from 31.67 to 37.46 and mannitol was 42.12 to 45.63 in comparison to pure drug 44 (Table -2). The average wettability of pure BPG was found to be 59 seconds. A minimum wetting time 12.5-22.2 and 8.3-18.5 seconds was recorded for PEG 4000 and mannitol solid dispersions, respectively. Decreasing the polymers concentration (drug: polymer ratio 70:30) increased the wetting time by 10



seconds for both polymers. The HPMC had a little effect on the powder wetting. At ratio 50:50 HPMC showed sinking time (45 seconds) close to pure drug that also increased to reach 68 with decreasing the polymer ratio (70:30 BPG:HPMC) (Table -2). The maximum wetting time was observed for PVP dispersions. The

wetting time of PBG: PVP dispersion (50:50) was 234 seconds and decreased to 172 with decreasing the PVP concentration in the solid dispersion (PBG: PVP (70:30)).

Table 2. Flow and wetting properties of BPG and the formulated solid dispersions

Solid dispersion formulations	Angle of repose		Powder wettability (sec)	
	50:50% w/w	70:30% w/w	50:50% w/w	70:30% w/w
BPG: PVP	31.67±0.47	37.46±1.37	234±8.48	172±12.72
BPG: HPMC	36.50±0.65	35.36±1.00	45±2.82	68±5.65
BPG: PEG 4000	34.06±0.84	33.67±1.28	12.5 ±3.35	22.2 ±4.24
BPG: Mannitol	45.63±1.09	42.12±2.68	8.3 ±0.35	18.5 ±0.71
BPG (pure drug)		44.20±0.91		59 ±1.41

FT -Infrared spectroscopy

To evaluate the chemical compatibility between the drug and hydrophilic polymers, IR analysis was performed. The FT-IR spectra's of BPG, polymers and their solid dispersion formulas were shown in Figure 1A-D. The spectrum of pure BPG exhibited a characteristic band at 3590 cm^{-1} of NH stretching of amide group and three characteristic bands at 1762, 1658 and 1566 cm^{-1} , representing C=O stretching of the lactam, amide and carboxylate groups, respectively. Figure 1A, showed the characteristic absorption peaks of PVP K30 appeared at 3454 and 1654 cm^{-1} , corresponding to stretching vibrations of -OH and the carbonyl groups on the pyrrolidone ring. In the solid dispersion spectra, the characteristic peaks of both BPG and PVP were evidently

observed. The spectrum of HPMC (Figure 1B) showed broad band at 3300-3500 cm^{-1} for -OH stretch and 1100 cm^{-1} for C-O bending. The FT-IR spectra of both the solid dispersions still showed the same bands for BPG and HPMC. Figure 1C, PEG 4000 spectrum showed its imperative peaks at 3425 cm^{-1} , 2890 cm^{-1} and 1109 cm^{-1} for -OH, - CH and C-O-C stretch, respectively. The solid dispersion showed the same bands in agreement with the chemical structures of BPG and PEG4000. Mannitol spectrum (Figure 1D) showed bands of at 3400-3200 cm^{-1} , 1421 cm^{-1} , 1083 cm^{-1} and 1019 cm^{-1} for O-H and CH₂ stretching and C-O bending, respectively. Their solid dispersions also revealed no discrepancies in the position of the characteristic bands of both BPG and mannitol.

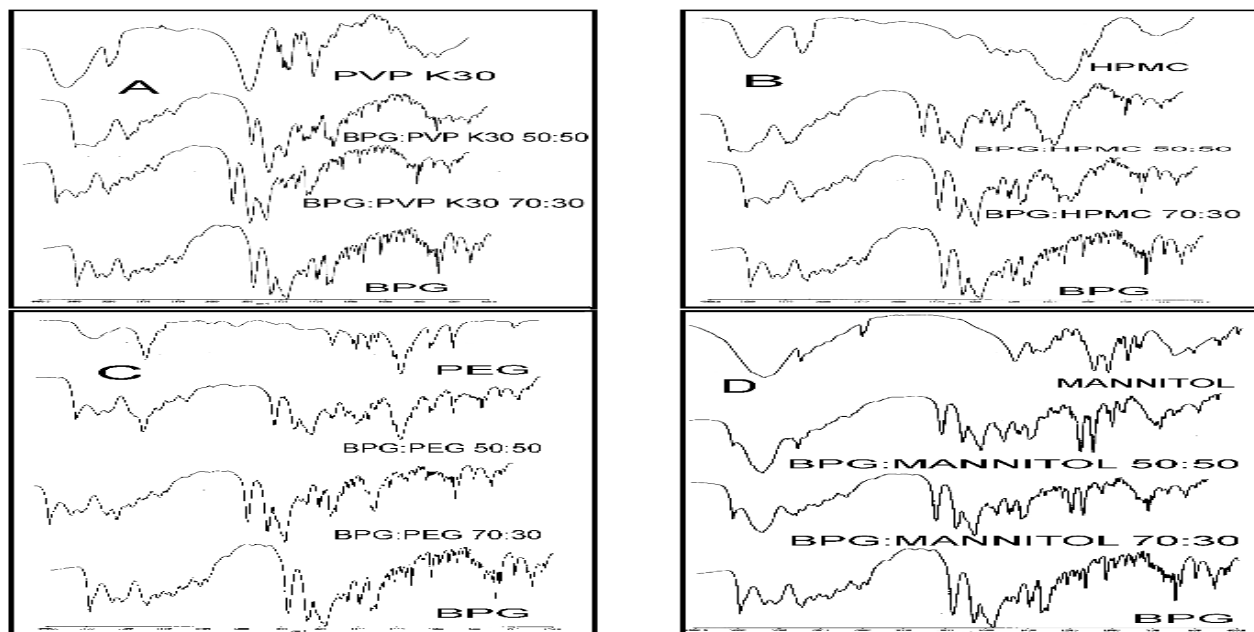


Figure 1. FTIR of pure BPG, two solid dispersions and polymer. (A) PVP K30, (B) HPMC, (C) PEG 4000, (D) mannitol.

X-Ray Diffraction Analysis

The x-ray diffractometry (XRD) spectra of pure compound, polymer and their binary systems were presented in Figure 2A-D. Sharp and intense crystalline peaks of the drug at 2θ of 16, 19, 19.5, 21, 22, 23.5, 26, 29 were observed in diffraction spectra. Thus, a typical crystalline pattern of drug in all solid dispersions, irrespective to the polymer nature was recognized. The results showed that even with using PVP K30 and HPMC in amorphous

state the less characteristics peaks corresponding to the drug (Figure 3A and B) was observed, indicating the presence of drug in an semicrystalline or dissolution state. The X-ray diffraction patterns (Figures 3C and D) also showed less intensity peaks of drug in the solid dispersion formulations revealed may be drug present in the form of semicrystalline or dissolution state or polymeric amorphous state, respectively.

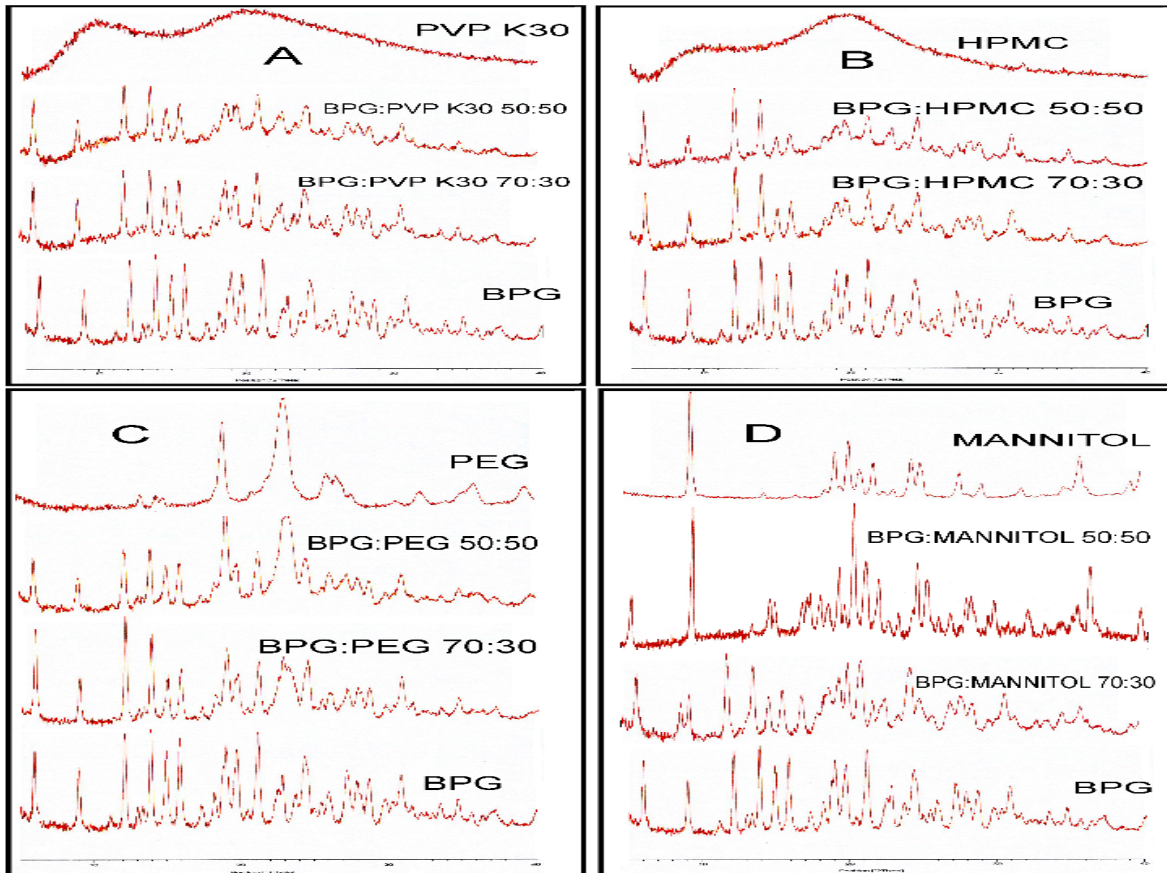


Figure 2. XRD of pure BPG, two solid dispersions and polymer. (A) PVP K30, (B) HPMC, (C) PEG 4000, (D) mannitol.

Differential scanning calorimetry (DSC)

The thermal behaviour of the drug powder, carriers and solid dispersions were presented in Figure 3A-D. The BPG showed an endothermic peak at 124.22 C - 127 °C. Both PVP K30 and HPMC showed no thermograms peaks due to their amorphous state. A sharp endothermic peak was seen at 60.2 C and 165-169 °C corresponding to the melting point of PEG 4000 and mannitol,

respectively. The DSC of drug-polymers solid dispersions showed suppression and broadening in the DSC peaks.



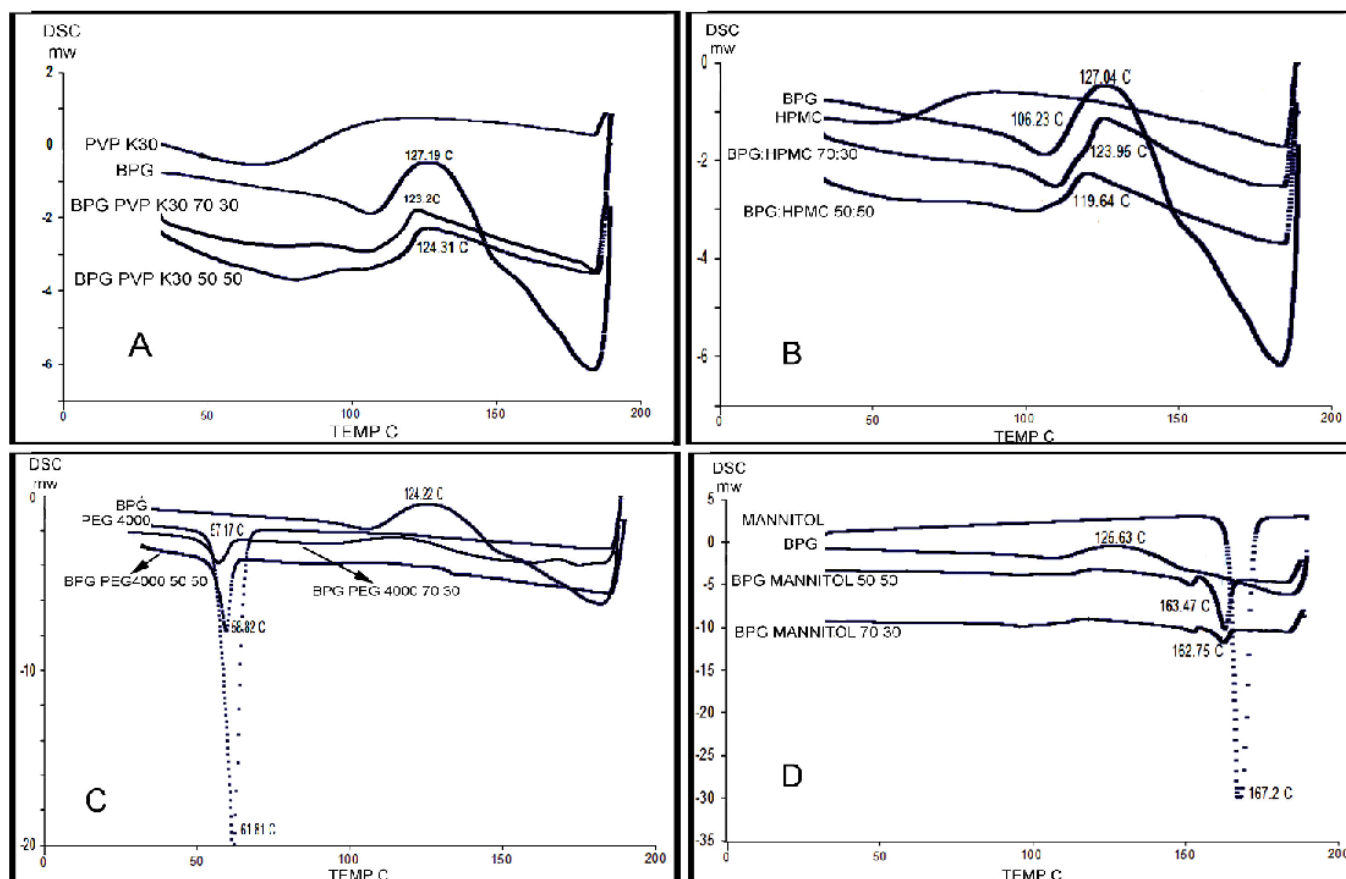


Figure 3. DSC thermograms of BPG, two solid dispersions and polymer (A) PVP K30, (B) HPMC, (C) PEG 4000, (D) mannitol.

Scanning electron microscope (SEM)

Figure 4A-D illustrates the SEM photomicrographs of pure materials and solid dispersions. The BPG exists as aggregates of crystalline particles of irregular size. Figure 4A, shows PVP K30 as amorphous spherical particles. The BPG: PVP solid dispersions appear in the form of tiny aggregates of irregular size pieces. In Figure 4B, HPMC exhibits cylindrical shaped particles similar to fibers in amorphous state. The solid dispersions showed aggregates of irregular particles with porous nature. Figure 4 C and D showed the crystalline state of both PEG 4000 and mannitol that appeared as smooth-surfaced flaks and needle, respectively. The drug-PEG 4000 solid dispersion showed the smallest crystalline particles at drug: polymer ratio 50:50 that showed obvious increase in size with decreasing polymer concentration (70:30). The drug-mannitol solid dispersion showed aggregated crystals with smooth surface and irregular shape.

In vitro dissolution studies

The *in-vitro* release profiles of pure drug and solid dispersions at different ratios were shown in Figure 5 A and B. The dissolution rates of BPG solid dispersions using mannitol, PEG 4000, HPMC and PVP were much higher than the corresponding pure drug that allowed 16% maximum drug release after 60 min. Decreasing polymers concentration showed an obvious decrease in the percentage drug released (Figure 5B). At drug: mannitol ratio 50:50, 57% drug was released during 60 min and decreased to 49% with decreasing the polymer concentration to 30%. HPMC showed 61 and 51% drug release for drug: polymer ratio 50:50 and 70:30, respectively at the end of 60 min. The drug: PEG 4000 at ratio 50:50 showed the greatest release profile (73%) than all other formulations. The effect of decreasing PEG concentration on the drug dissolution was very clear at ratio 70:30, that allowed only 45% drug to be released.

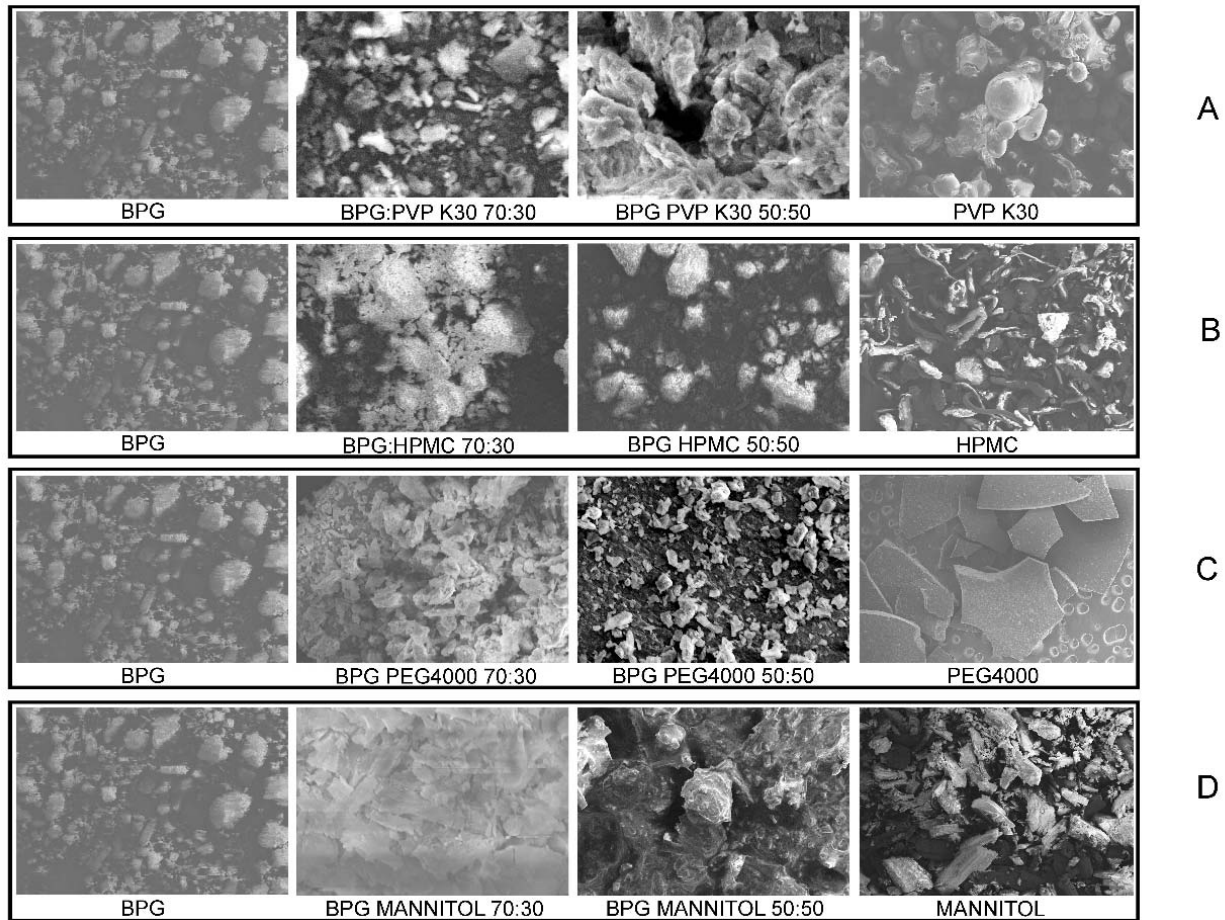


Figure 5. SEM of BPG, two solid dispersions and polymer. (A) PVP K30, (B) HPMC, (C) PEG 4000, (D) mannitol.

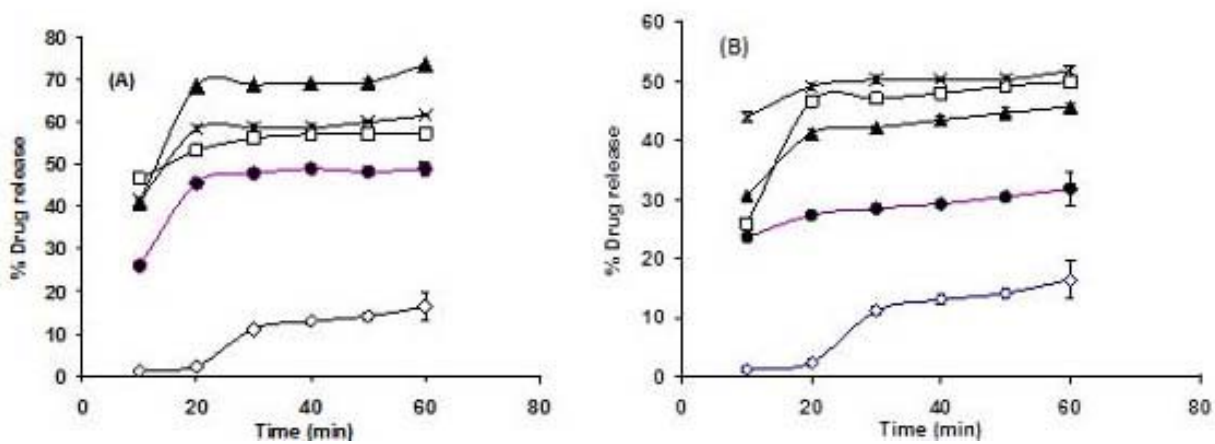


Figure 5. *In vitro* release profiles of solid dispersions (A) 50:50, (B) 70:30. (-) pure drug, (-□-) D: mannitol, (- -) D:PEG 4000, (-X-) D: HPMC, (●) D:PVP.



Discussion

Formulations and evaluation studies

The percentage drug content showed high dependence on the polymer type and concentration. The effect of polymer type was clearly observed at drug: polymer ratio 50:50. Although satisfactory % yield was obtained with decreasing the polymer concentration (drug: polymer ratio 70:30) (Table -1). Such effect was clearly observed with mannitol, PEG 4000 and HPMC. This was probably due to effect of polymer concentration on increasing the viscosity of dispersion medium and hence decreasing the escaping of drug molecules from the polymer solution

FTIR spectroscopy analysis.

FTIR spectroscopy analysis was done to analyze physicochemical interactions between BPG and different hydrophilic carriers in form of solid dispersions. In the solid dispersion spectra, the characteristic bands of both BPG and PVP were evidently observed, and the spectra can be regarded as a simple superimposition of that of drug and the polymer. The same could be noticed for BPG and HPMC solid dispersions. In the case of BPG and PEG4000 solid dispersions, any sign of interaction would be reflected by a transformation in the position of C=O vibration and disappearance of O-H stretching, which has not been observed in this instance indicating a significant absence of interaction between BPG and PEG 4000. Also the FTIR characterized solid dispersions of BPG and mannitol revealed no discrepancies in the position of the characteristic bands of both BPG and mannitol. The spectra of IR analysis revealed no difference in the position of absorption bands, especially with respect to OH, C=O, NH, hence providing the absence of hydrogen bonding interaction in solid state between polymers and BPG.

X-Ray diffraction analysis

In order to investigate both the polymorphic transformation, which would occur during preparation of the solid dispersion, and the possible influence of carriers on phase transformation, X-ray diffraction was performed. The only distinguished difference was the relative reduction in diffraction intensity of BPG in these preparations, suggesting a reduction on crystals size to the microcrystal form [16]. These results were also supported with published data [17] that in developing of a solid dispersion systems containing poorly water soluble drugs, the method of preparation plays an important role in the solubility and crystallinity of the drugs. In preparing of solid dispersion by surface-attached method, the organic solution of drug was poured into the mechanically stirred aqueous solution of the polymer that allowed drug precipitated may be as fine semicrystalline state. The method of preparation showed change in the drug crystallinity may be in the form of semicrystalline state or polymeric amorphous state as

evidenced by low intensity characteristics peaks of drug in formulations. Additionally, the hydrophobic nature of the drug was expected to shift to hydrophilic one, as a result for attachment of the drug into the surface of hydrophilic carrier's molecules.

DSC

DSC technique draws attention to the interaction between the drug and excipients in its formulation. When guest molecules are included in host molecules, their melting, boiling and sublimation points shift to different temperature or disappear (16). The thermograms of the solid dispersions of BPG: PVP K30 and BPG:HPMC showed that the drug peak was suppressed and shifted, suggesting that the drug was able to dissolve in the carrier to form a solid-solid solution, as evidenced by XRD data. For BPG: PEG 4000 solid dispersions, the peak of PEG 4000 at 60.2°C in solid dispersions is slightly shifted to lower temperature and no peak for the drug is observed. This phenomenon could be attributed due to the drug is uniformly distributed in the polymer system as a semicrystalline or amorphous state. The thermal study of the thermograms of the solid dispersions of BPG: mannitol revealed that the peak height is reduced and had become broader in nature indicates that the drug may be present in form of dissolution or semicrystalline state.

SEM

The BPG: PVP solid dispersions appear in the form of tiny aggregates of irregular size pieces whereas; original morphology of both components is disappeared. The HPMC solid dispersions showed aggregates of irregular particles with porous nature. The PEG 4000 and mannitol based formulations showed smooth-surfaced flaks and needle shape particles. The drug-PEG 4000 solid dispersion showed the smallest crystalline particles at drug: polymer ratio 50:50 that showed obvious increase in size with decreasing polymer concentration (70:30). The drug-mannitol solid dispersion showed aggregated crystals with smooth surface and irregular shape.

Angle of repose and powder wettability

The effect of the hydrophilic polymers on the flow behavior of solid dispersion was also reported [18,19]. The two hydrophilic polymers PEG 4000 and mannitol showed obvious effect on improving the wettability of the powder dispersions. Decreasing the wetting time may be considered as one of the reasons for improving the drug release. Consequently, solid dispersions using PEG 4000 and mannitol would be effective in improving the hydrophilic character and wettability of BPG.

Dissolution studies

The dissolution profiles of BPG were found to depend on the carrier used. A rapid initial dissolution rates were observed for all solid dispersions. Increases in dissolution rates were partly



dependent on the ratios of BPG to carrier. The least effective polymer on improving the drug dissolution was PVP that also had retarding effect on the powder wettability. Mannitol allowed fast wetting of the drug powder due to its mechanism of disintegrant that promote capillary action, absorb moisture, swell and enhanced the drug release from the dispersion system. Thus, the experiments showed that hydrophilic polymers can be used to improve the dissolution characteristics of poorly soluble drug in pharmaceutical formulations.

Conclusion

The major problem of BPG is its very low dispersion in aqueous medium and low solubility in biological fluids. From the present study it can be easily demonstrated that hydrophilic polymers mannitol, HPMC and PEG 4000 has potential effect on improving the wettability and dissolution characters of the drug. The results revealed that it is possible to enhance the dissolution rate of BPG

(hydrophobic drug) by increasing the surface area of the drug adsorbed on the surface of hydrophilic polymer by solid dispersion method. The formula of BPG: PEG 4000 at ratio 50:50 yielded best results in terms of % yield, % EE, flowability, wettability and dissolution rate.

Acknowledgements

The authors are very thankful to the Research committee, University of Nizwa for funding this project (A/09-10UoN/25/P&N/IF). The authors would like extend their sincere thanks to Mr. Salim Al-Saidi, Mr. Saif Al-Mannary and Mrs. Suad Al-Burtammani for their help in completing the spectroscopic studies at Sultan Qaboos University. The authors also thank Mr. Abdulrahman Al-Nabhani for his help in obtaining the SEM photographs. Many thanks to Pharmacist Mustafa Zahran Alkamyani in Pharmaceutics laboratory for his help in the release study.

References

- [1]. Miller EL. The penicillins: A review and update. *J Midwifery Women Health*. 2002; 47: 426-434.
- [2]. Gerber MA. So what's wrong with penicillin for strep throat? *Pediatrics*. 2004;113:1816-1819.
- [3]. Kassem AS, Zaher SR, Abou Shleib H, El-Kholy AG, Madkour AA, Kaplan EL. Rheumatic fever prophylaxis using benzathine penicillin G (BPG): two-week versus four week regimens: comparison of two brands of BPG. *Pediatrics*. 1996;97: 992-995.
- [4]. Carapetis JR, Currie BJ, Mathews JD. Cumulative incidence of rheumatic fever in an endemic region: a guide to the susceptibility of the population. *Epidemiol Infect*. 2000;13:239-244.
- [5]. Peloso UC, De Souza JC, Botino MA, Miniti A. Penicillin concentrations in sera and tonsils after intramuscular administration of benzathine penicillin G to children. *Pediatr Infect Dis J*. 2003;22:1075-1078.
- [6]. Amir J, Ginat S, Cohen Y H, Marcus T E, Kehher N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. *Pediatr Infec Dis J*. 1998;17: 890-893.
- [7]. Santos MNS, Pontes A, Pereira VMW, Caetano MNP. Colloidal carriers for benzathine penicillin G: nanoemulsions and nanocapsules. *Int J Pharm* 2000;208:71-80.
- [8]. Holanda E, Silva KG, Xavier J. FH, Farias, IEG, Caldas NJA, Silva AKAS, Nakashima JT. A new insight about pharmaceutical dosage forms for benzathine penicillin G. *Rev Cienc Farm Basica Apl*. 2006;27:21-26.
- [9]. Swarbrick J. *Encyclopedia of Pharmaceutical Technology*. 6th ed. New York: Marcel Dekker, 1990. p. 31-63.
- [10]. Craig, DQM. The mechanism of drug release from solid dispersions in water-soluble polymers. *Int J Pharm*. 2001;231:131-144.
- [11]. Serajuddin ATM. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. *J Pharm Sci*. 1999; 881058-1066.
- [12]. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R. Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm*. 2003; 267, 79-91, 2003.
- [13]. Shivalingam BMR, Kishore RYV, Rao S, Rajesh K, Sunitha N. Formulation and evaluation of aceclofenac solid dispersions for dissolution rate enhancement. *Int J Pharm Sci Drug Res*. 2010;2:146-150.
- [14]. Yamashita K, Nakate T, Okimoto K, Ohike A, Tokunaga Y, Ibuki R, Higaki K, Kimura T. Establishment of new preparation method for solid dispersion formulation of tacrolimus. *Int J Pharm*. 2003;267: 79-91.
- [15]. Teeranachaideekul V, Junyaprasert VB, Souto E B, Muller R H. Development of ascorbyl palmitate nanocrystals applying the nanosuspension technology. *Int J Pharm*. 2007;354: 227-234.
- [16]. Liu X, Lin H, Thenmozhiyal JC, Chan S, Paul HC. Inclusion of acitretin into cyclodextrins: phase solubility, photostability and physicochemical characterization. *J Pharm Sci*. 2003;92: 2449-2457.
- [17]. Rajesh A, Singeeta A, Lamba HS, Bhandari A, Sadeep K. The effect of the preparation of solid dispersion method on the solubility and crystallinity of sulfasalazine. *Int Res J Pharm*. 2011;2:200-206.
- [18]. Singh A, Sharma PK, Meher JG, Malviya R. Evaluation of Enhancement of



solubility of paracetamol dispersion technique using polymer concentration flow properties. Asian J Pharm Clin Res. 2011;4:117-119.

[19]. Raghavendra RNG, Kulkarni U, Setty CM. Comparative Study on Effect of different techniques used in the

formulation of felodipin fast dissolving tablet. Int J Pharm Sci. 2010;2:152-159.

