Original Article

Enhancement of the dissolution profile of allopurinol by a solid dispersion technique

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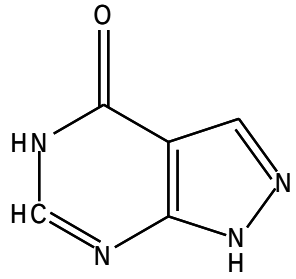
ABSTRACT: The aim of the present study was to improve the solubility, and therefore the dissolution of poorly water-soluble allopurinol. Solid dispersions of allopurinol were prepared with different polymers or carriers such as polyvinylpyrrolidone (PVP K30 and PVP K90), polyethylene glycol (PEG 4000 and PEG 6000), urea and mannitol at two drug : carrier ratios (1:1) and (1:2). Different methods such as melting and solvent evaporation methods were used to improve dissolution characteristics and solubility of allopurinol. The solid dispersions were characterized using a differential scanning calorimeter (DSC) and X-ray diffraction (XRD) while the interactions which took place were identified with fourier transform infrared (FTIR) spectroscopy. Due to formation of hydrogen bonds between allopurinol and urea and mannitol, a transition of allopurinol from the crystalline to amorphous state was achieved. The DSC thermograms of the solid dispersions indicated the potential of heat induced interactions between allopurinol and the carriers used could influence dissolution rate of the drug. The dissolution amount (%) of pure allopurinol was 80% at 45 min. F5, F3, F6, F7, and F1 showed better dissolution percentages of 100, 93, 92.4, 90.6, and 89%, respectively, at 45 min.

Keywords: Allopurinol, solid dispersion, dissolution enhancement, solubility, poorly water soluble

1. Introduction

Allopurinol, chemically known as 1,5-dihydro-4H-pyrazolol (3.4-d) pyrimidin-4-one, is the worldwide mainstay of modern treatment of gout and tumor lysis syndrome. Allopurinol, an isomer of hypoxanthine, and its active metabolite oxipurinol (alloxanthine) act by inhibiting xanthine oxidase, an enzyme which forms uric acid (urate) from xanthine and hypoxanthine. Allopurinol is a polar compound with strong intramolecular hydrogen bonding and limited solubility in both polar and non polar media (*1-3*). Allopurinol is very slightly soluble in water and ethanol. It is practically insoluble in chloroform and ether; and is soluble in dimethylformamide and in dilute solutions of alkali hydroxides (*4-7*).



1,5-dihydro-4H-pyrazolol (3.4-d) pyrimidin-4-one

Solid dispersion techniques have been widely used to improve the dissolution properties and bioavailability of poorly water soluble drugs. Several carrier systems have been used in the preparation of fast release solid dispersions. Polyvinylpyrrolidone (PVP) was used to enhance the dissolution rate of number of drugs such as 5-lipoxygenase inhibitor SB210661 and benidipine HCl (*8*). Dissolution of prednisolone has been enhanced by polyethylene glycol (PEG) fusion dispersions (*9*). Increased dissolution rates and extent of absorption were found in rabbits following administration of the sulphathiazole-urea eutectic mixtures (*10*). In the case of ursodeoxycholic acid the release rate from urea dispersions prepared by the hot melt method was faster than from other carriers studied, including PEG 6000 (*11*).

2. Materials and Methods

2.1. *Materials*

Allopurinol (Allo) powder was kindly provided by Alexandria Company for pharmaceutical industries

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(Alexandria, Egypt). Urea, di-sodium hydrogen phosphate, potassium di-hydrogen ortho phosphate, ethyl alcohol (absolute), and hydrochloric acid were supplied by El-Nasr Pharmaceutical chemicals Co. (Egypt). Mannitol, polyvinylpyrrolidone (PVP) K30 and K90, and PEG 6000 and 4000 were kindly provided by Amoun Company for pharmaceutical industries (Cairo, Egypt).

2.2. *Solubility studies*

An excess amount of allopurinol was added to 10 mL of aqueous solutions containing different concentrations (2.5, 5, 7.5, and 10%, w/v) of urea, mannitol, PEG (6000 and 4000), PVP (K30 and K90) in capped test tubes. The samples were sonicated for 1 h at room temperature. The capped test tubes were shaken at 37ºC for 24 h in a shaking water bath. The suspensions obtained were filtered through a filter paper (double ring, 102), and the filtrate was diluted with distilled water. The diluted solutions were measured spectrophotometrically at a λ_{max} of 250 nm using the same medium as a blank. Each experiment was performed in triplicate. The same technique was used to study the effect of sodium salts of *o*- and *p*-toulic acids on the water solubility of allopurinol (*12*).

2.3. *Preparation of solid dispersions*

Solid dispersions of allopurinol with carriers or polymers (urea, mannitol, PEG 6000 and PEG 4000) at weight ratios of 1:1 and 1:2 were prepared by the melting method (Table 1). After the polymer or carrier was completely melted on a thermostatically controlled hot plate, allopurinol was added and then solidified by pouring on a glass petri dish stored on an ice bath. After cooling the solid, it was kept in a desiccator under vacuum at room temperature for 48 h. The mass was then pulverized with a mortar and pestle and was sieved into defined particle size fractions (200-150 µm) (*1*).

The solvent evaporation method was used to prepare solid dispersions of allopurinol with different polymers (PVP K30 and PVP K90) at weight ratios of 1:1 and 1:2, drug to carrier (Table 1). A solution of allopurinol in absolute ethanol was mixed with a solution of polymer in ethanol. The solvent was subsequently evaporated under a vacuum, using Rota Vapour apparatus at 70ºC and a rotation speed of 100 rpm. The residue was then dried completely in a desiccator for 48 h. The solid mass was then crushed, pulverized, and sieved into defined particle size fractions (200-150 µm) (*1*).

Table 1. Composition of different allopurinol solid dispersions

Codes	Components	Ratios	Methods
PD	Pure drug	-	-
F1	Allo/urea	1:1	Melting
F2	Allo/urea	1:2	Melting
F3	Allo/mannitol	1:1	Melting
F4	Allo/mannitol	1:2	Melting
F5	Allo/PVP K30	1:1	Solvent evaporation
F6	Allo/PVP K30	1:2	Solvent evaporation
F7	Allo/PVP K90	1:1	Solvent evaporation
F8	Allo/PVP K90	1:2	Solvent evaporation
F9	Allo/PEG 4000	1:1	Melting
F10	Allo/PEG 4000	1:2	Melting
F11	Allo/PEG 6000	1:1	Melting
F12	Allo/PEG 6000	1:2	Melting

2.4. *Characterization of solid dispersions*

2.4.1. *Differential scanning calorimetry (DSC) studies*

Approximately 5 mg of samples were weighed and hermetically sealed in the aluminium pans. Samples of drug alone, each excipient alone, physical mixtures of allopurinol with the investigated excipients (1:1, w/w) prepared by simple and perfect mixing and solid dispersion (1:1, w/w) were measured with a Shimadzu Model DSC-50 thermal analyzer (Shimadzu, Kyoto, Japan). The DSC thermograms were obtained over a temperature range of 25-400ºC using a thermal analyzer equipped with an advanced computer software program at a scanning rate of 10ºC/min and a nitrogen gas purge of 40 mL/min. The instrument was calibrated with pure indium as a reference.

2.4.2. *X-ray diffraction (XRD) studies*

X-ray diffraction (XRD) patterns were obtained using CuKα radiation, collimated by a 0.08º divergence slit and a 0.2º receiving slit and scanned at a rate of 2.4º/min over the 2θ range of 5-60º. The diffractometer was a PW 3710 (Philips, Holland).

2.4.3. *Fourier transforms infrared spectroscopy (FTIR)*

Samples of 1-2 mg of drug alone, each excipient alone, physical mixtures of allopurinol with the investigated excipients (1:1, w/w) prepared by simple and perfect mixing and solid dispersion (1:1, w/w) were mixed with KBr (IR grade) compressed into discs in the compression unit under vacuum and were scanned from 4,000-400 cm^{-1} with an empty pellet holder as a reference. The spectrophotometer was a Perkin-Elmer FTS-1710 (Beaconsfield, UK).

2.4.4. *Content uniformity of allopurinol in solid dispersions*

An amount equivalent to 10 mg of allopurinol was weighed from each resultant solid dispersion (with different polymers or carriers) and dispersed in 50 mL phosphate buffer pH 7.4 using a 100 mL volumetric flask and then was stirred for 10 min. The volume obtained was completed to 100 mL with phosphate

buffer pH 7.4 and shaken well. Two mL from the previous solution were taken and were completed to 10 mL with phosphate buffer pH 7.4. The absorbance was measured using a UV spectrophotometer (Model 6405 UV/Vis; Jenway, Ltd., Essex, UK) at 250 nm, using phosphate buffer pH 7.4 as a blank.

2.4.5. *In vitro dissolution of allopurinol from solid dispersions*

The rotating basket dissolution apparatus was used for the determination of dissolution rates of allopurinol solid dispersions. An accurately weighed amount of each solid dispersion equivalent to 100 mg of allopurinol was placed into the basket of the dissolution test apparatus (USP Standards, scientific, DA6D, Bombay-400-069, India). The basket was rotated at 75 rpm in 900 mL of the dissolution medium (0.1 N HCl) and maintained at a constant temperature (37 ± 0.5°C). Aliquots, each of 5 mL, were withdrawn from the dissolution medium at time intervals of 5, 15, 30, 45, 60, 90, and 120 min. The same volume of 0.1 N HCl was used to replace the withdrawn samples. The samples were suitably filtered, diluted, and measured spectrophotometrically at 250 nm. The concentration of the drug was determined from the previously constructed standard calibration curve. Statistical analysis (ANOVA) was performed for all allopurinol solid dispersion formulas with respect to their percent dissolved at 45 min followed by the Tukey-Kramer multiple comparisons test. Also the kinetic parameters for the *in vitro* dissolution of all allopurinol solid dispersion formulas were determined and analyzed in order to explain the mechanism of drug release.

3. Results and Discussion

3.1. *Solubility studies*

The solubility of allopurinol in water at 37ºC was found to be 0.616 mg/mL. Allopurinol has a limited solubility in both polar and non polar media as it is a polar compound with strong intramolecular hydrogen bonding (*1*). Addition of urea and mannitol provided an increase in allopurinol solubility. It is evident that, the increased concentration of urea and mannitol was accompanied by a gradual increase in the solubilized amount of allopurinol. Mannitol as well as urea at a 10% concentration caused more than a two fold increase in allopurinol solubility. Figure 1 shows a linear correlation between the concentrations of urea or mannitol and allopurinol solubility in aqueous solutions of urea or mannitol at 37°C. The aqueous solution of PVP K30 was found to increase the solubility of allopurinol much more than PVP K90. Figure 2 shows a linear correlation between the concentrations of PVP K30 or PVP K90 and allopurinol solubility. Figure 3 shows that the drug solubility increased linearly as PEG

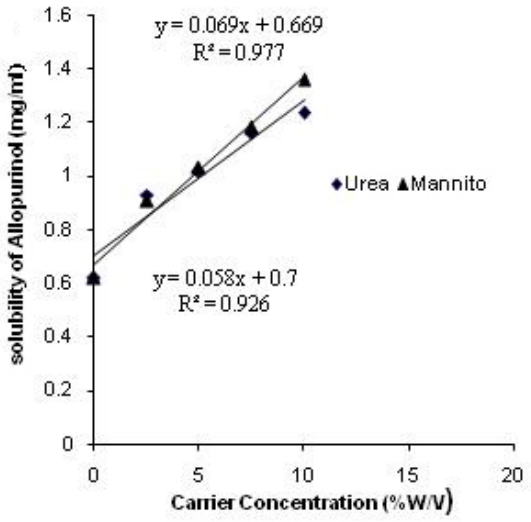

Figure 1. Solubility profiles of allopurinol in aqueous solutions of urea and mannitol at 37ºC.

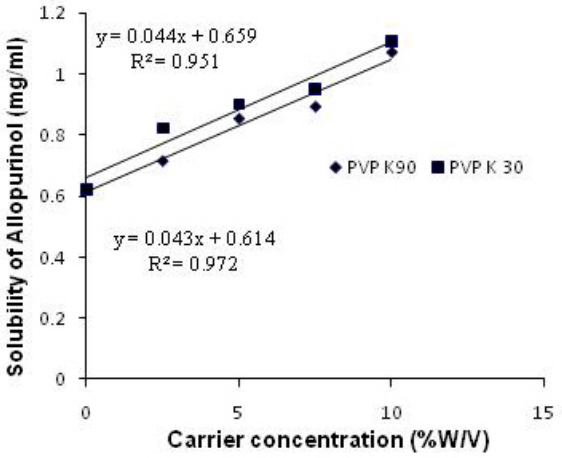

Figure 2. Solubility profiles of allopurinol in aqueous solutions of PVP K90 and K30 at 37ºC.

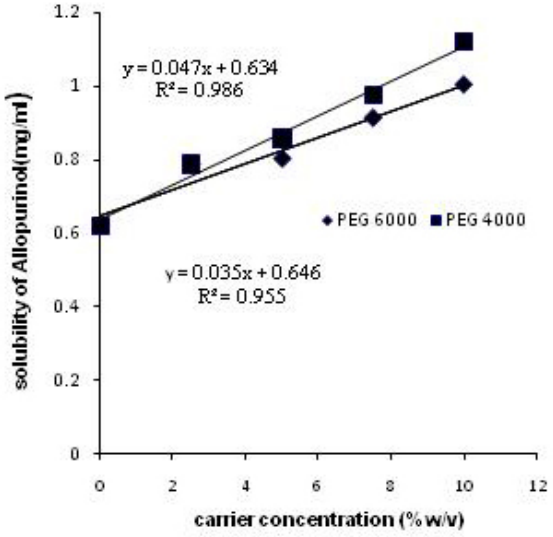

Figure 3. Solubility profiles of allopurinol in aqueous solutions of PEG 6000 and 4000 at 37ºC.

concentration increased. PEG 4000 always showed more solubilizing power than PEG 6000.

3.2. *Characterization of solid dispersions*

3.2.1. *DSC studies*

The DSC thermogram of allopurinol, carriers, their physical mixtures, and the corresponding solid dispersions are shown in Figure 4. The DSC thermogram of allopurinol alone was characterized by a sharp endothermic peak at 386°C corresponding to its melting point. The DSC thermogram of the solid dispersion containing urea shows that allopurinol lost its shape and distinctive appearance, shifted to a lower melting point and appeared as a broad peak around 250-300°C. It was noticed that there was a change in the characteristic endothermic peaks and the melting points of both allopurinol and urea before and after solid dispersion formation. Also there was a decrease in the melting enthalpy of both allopurinol and urea before and after solid dispersion formation. The more amorphous the product, the lower is the ΔH value (*13*). It was also suggested that a very small crystalline portion of allopurinol existed in the solid dispersion melted at a lower melting point than of intact allopurinol. The previous results were concluded when studying the DSC of ofloxacin-urea solid dispersions (*11*). The DSC thermogram of solid dispersions containing mannitol shows that allopurinol lost its shape and distinctive appearance, shifted to a lower melting point than that of intact allopurinol and appears as a shallow broad peak around 328.3°C with a corresponding enthalpy change. As discussed before with urea there was a decrease in the melting point of allopurinol accompanied by a change in the appearance of the endotherm with a corresponding decrease in the ΔH of both mannitol and allopurinol, which suggest a decrease in the crystalline state. The DSC thermogram of both physical mixtures and solid dispersions containing PVP K30, K90, and PEG 4000 showed the sharp endothermic peak of allopurinol nearly at the same position indicating the absence of strong interactions between the components. The increase in the dissolution rate was thus attributed to an increase in the available surface area of the drug due to improved wettability provided by the polymers used. The DSC thermogram of the solid dispersion containing PEG 6000 showed a broad endothermic peak of allopurinol at 373.8 and 381.8°C, respectively. The melting point of allopurinol in PEG solid dispersions showed a shift to lower values from that of pure drug which revealed a crystalline change.

3.2.2. *XRD studies*

The XRD of allopurinol, carriers, their physical mixtures and the corresponding solid dispersion is presented in Figure 5. The X-ray diffraction pattern for pure powdered allopurinol alone showed a major sharp peak of 28° at a diffraction angle of 2θ and an intensity of 6,450 (Counts). A comparison X-ray diffraction pattern of allopurinol and its solid dispersion with urea and mannitol showed a significant reduction in the crystalline state of allopurinol in the solid dispersion. This could be attributed to the retardation of allopurinol crystallization by the carrier (*11*). This also indicates that the drug may be converted to an amorphous form. X-ray diffraction data indicates an interaction between allopurinol and PVP and a much reduced crystallinity extent. The X-ray diffraction study of PEG showed that PEG 6000 is more efficient in the reduction of the crystalline state of allopurinol than PEG 4000 which is comparable to the result of PEG 6000 solid dispersions of nifedipine (*13*). These results indicate that

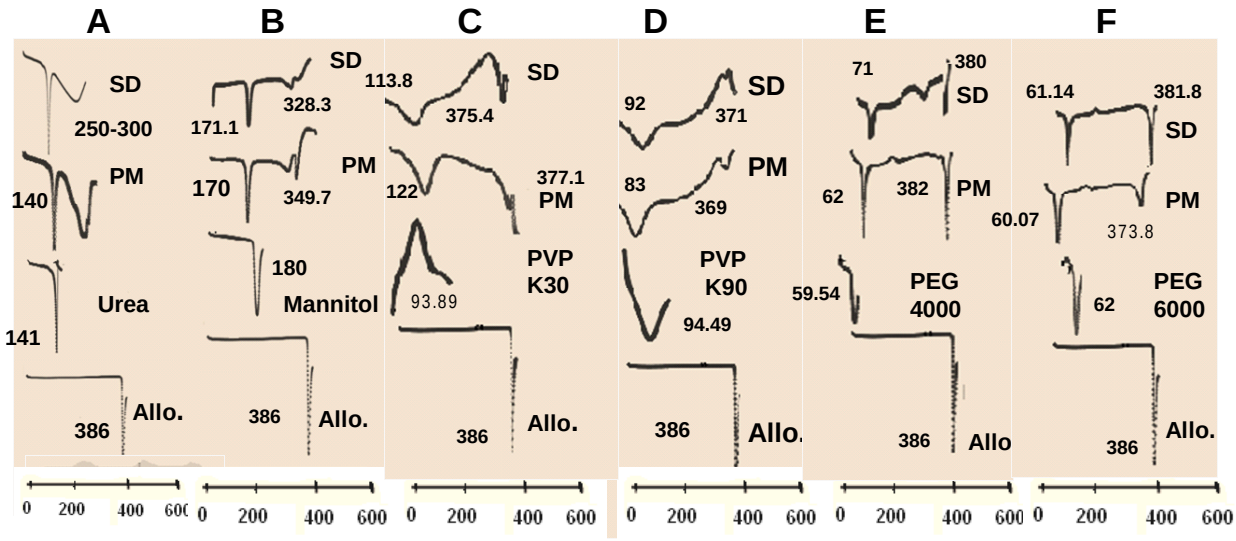

Figure 4. DSC thermograms of allopurinol and various carriers, the physical mixtures, and the corresponding solid dispersions. A, allopurinol and urea; **B**, allopurinol and mannitol; **C**, allopurinol and PVP K30; **D**, PVP K90; **E**, allopurinol and PEG 4000; **F**, allopurinol and PEG 6000. Abbreviations: SD, solid dispersion; PM, physical mixture; Allo, allopurinol.

the polymer should have a suitable molecular length and concentration. This enables formation of a polymer net on the crystal surface or among the drug molecules which results in optimum orientation of proton donating and receiving groups and a strong interaction between drug and polymer (*14-16*).

3.2.3. *FTIR spectroscopy*

Figure 6 shows FTIR spectra for allopurinol in physical mixtures and solid dispersions with different carriers. The FTIR spectrum of pure allopurinol is characterized by absorption bands at 3,167 cm^{-1} at high frequency, most probably attributed to the N-H stretching band of the secondary amine group, and at 3,034 cm^{-1} denoting a C-H stretching vibration of the pyrimidine ring. At low frequencies there is a band at 1,693 cm^{-1} indicating a C=O stretching vibration of the keto form of the 4-hydroxy tautomer. Also the bands at (1,581-1,469.96) cm^{-1} are attributed predominantly to C-N stretching and C-C ring stretching, respectively. Bands at 1,234.55-698.29 cm^{-1} denote CH in plane deformation. The FTIR spectrum of physical mixtures of allopurinol with both urea and mannitol indicates the absence of any interaction between allopurinol and urea or mannitol upon mixing. While the FTIR spectrum of solid dispersions of allopurinol with urea or mannitol indicates the probability of hydrogen bonding between allopurinol and urea or mannitol in the solid dispersion. The FTIR spectrum of physical mixtures and solid dispersions of allopurinol with PVP K30, PVP K90 and PEG 4000 indicates the absence of any interaction

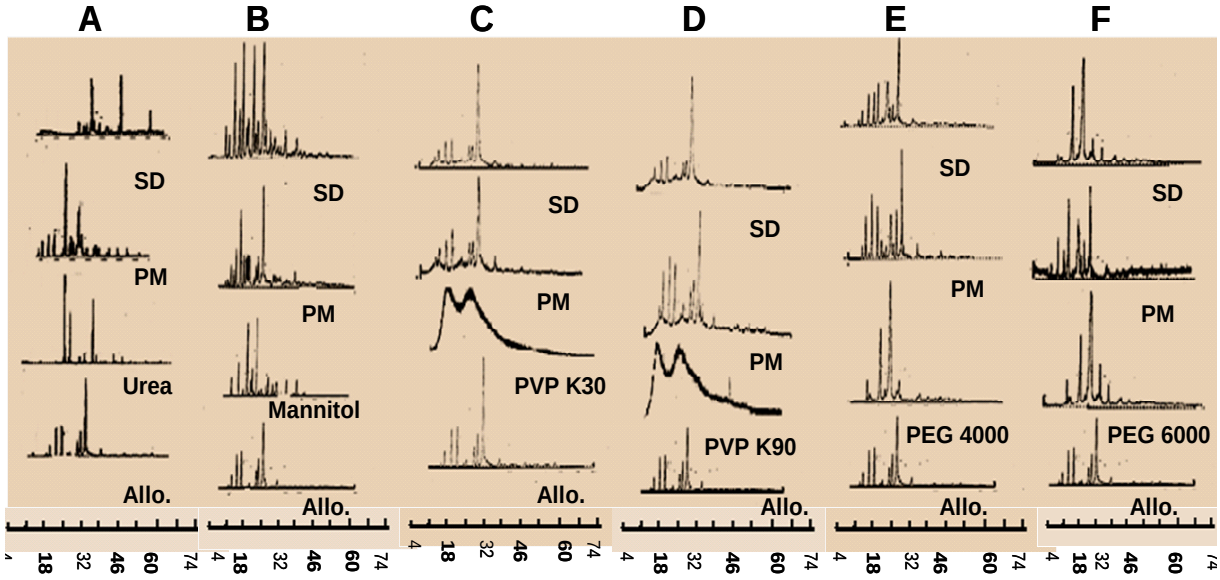

Figure 5. XRD of allopurinol and various carriers, the physical mixtures, and the corresponding solid dispersions. A, allopurinol and urea; **B**, allopurinol and mannitol; **C**, allopurinol and PVP K30; **D**, PVP K90; E, allopurinol and PEG 4000; **F**, allopurinol and PEG 6000. Abbreviations: SD, solid dispersion; PM, physical mixture; Allo, allopurinol.

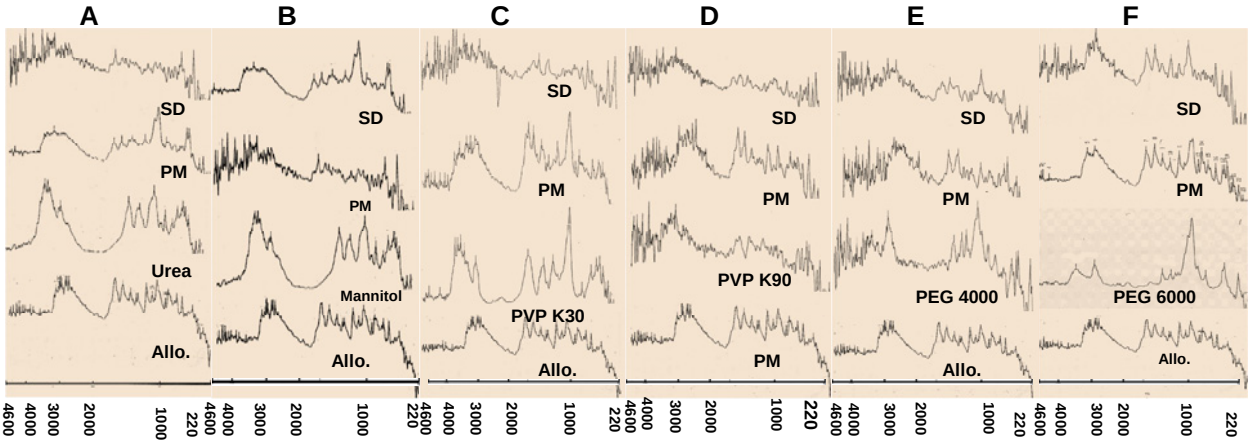

Figure 6. FTIR spectrum of allopurinol and various carriers, the physical mixtures, and the corresponding solid dispersions. A, allopurinol and urea; **B**, allopurinol and mannitol; **C**, allopurinol and PVP K30; **D**, PVP K90; **E**, allopurinol and PEG 4000; **F**, allopurinol and PEG 6000. Abbreviations: SD, solid dispersion; PM, physical mixture; Allo, allopurinol.

between allopurinol and PVP K30, PVP K90 or PEG 4000. Addition of such polymers to pure allopurinol resulted in no shift of any of these characteristic bands, indicating no chemical interaction between the drug and the polymers used. Also the FTIR spectrum of physical mixtures of allopurinol with PEG 6000 indicates the absence of any interaction of allopurinol with PEG 6000 upon mixing. While the FTIR spectrum of the solid dispersion indicates the hydrogen bonding interaction between the lone pair of the amino group of allopurinol and the hydrogen atom OH group of PEG 6000. The same result was obtained by studying the IR spectra of diazepam and temazepam-solid dispersions (*17*).

It was clear that all characteristic bands of allopurinol and its solid dispersions with PVP and PEG appeared nearly in the same regions and at the same ranges and no new bands appeared although the shape of the functional group regions in the spectra of the drug and the polymer used was not identical with that of pure drug alone. This might be indicative of the absence of interactions between allopurinol and the polymers used.

3.3. *Content uniformity of allopurinol in solid dispersions*

The content of allopurinol in each solid dispersion formula was found to be between 97.41 and 105%. The production yield of allopurinol in each solid dispersion formula was found to be between 97.2 and 99.8%.

3.4. *In vitro dissolution of allopurinol from solid dispersions*

Dissolution profiles of the pure drug and drug-carrier binary systems are represented in Figure 7. As is apparent, the solid dispersion technique improved the dissolution rate of allopurinol. The percentages of drug dissolved at 45 min were 100, 93, 92.4, 90.6, and 89 for F5, F3, F6, F7, and F1, respectively. This enhancement can be attributed to the greater hydrophilic character of the systems due to the presence of the carrier, which can reduce interfacial tension between a poorly water-soluble drug and dissolution medium (*18*). The enhancement of the solubility of allopurinol with carriers or polymers used may be attributed to the wetting effect of the highly water soluble carrier or polymer in intimate contact with it. They solubilized allopurinol by breaking up water clusters surrounding the non polar molecule, increasing the entropy of the system and producing a driving force for the solubilization. These results are in agreement with a result by Lian-Kaun *et al*. (*19*). Also the improvement in the dissolution rate may be due to the enhancement of the physical amorphism of the drug (*20*), and this enhancement also might be attributed to the increase in the wettability and solubility of the drug (*21*).

The kinetic data showed that the *in vitro* release of allopurinol followed different kinetic orders, and no definite kinetic order could express the drug release from different types of solid dispersion formulations (Table 2). One way analysis of variance (ANOVA) of allopurinol solid dispersions was performed with respect to their % released at 45 min followed by the Tukey-Kramer multiple comparisons test (Table 3).

4. Conclusion

Based on the current study, improvement in the

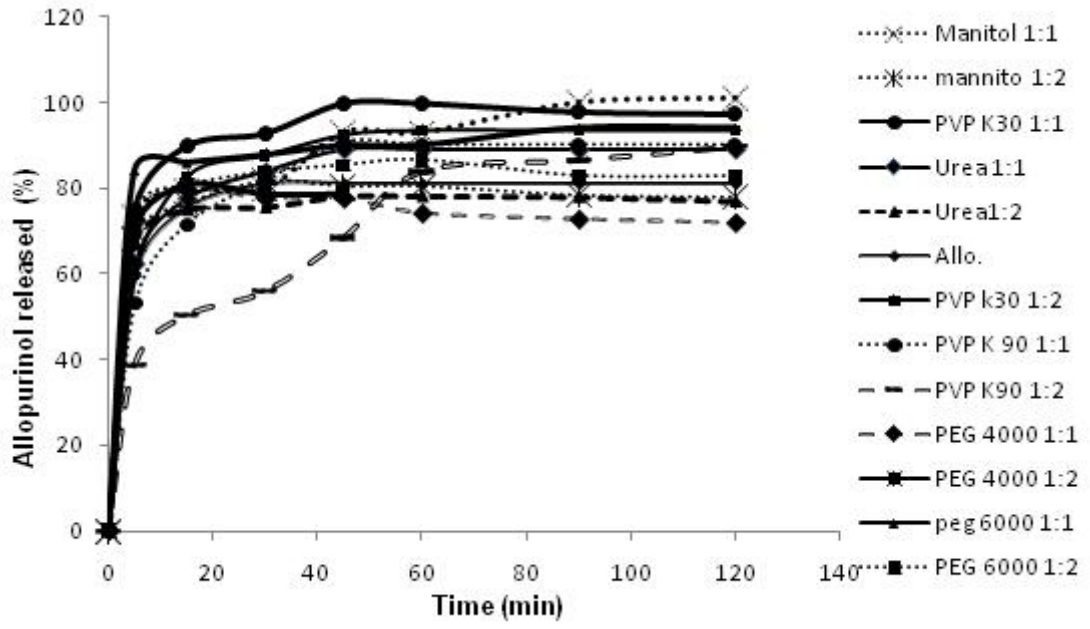

Figure 7. Percentages of drug released from solid dispersions in different ratios compared to pure drug.

Table 2. Kinetic treatments for the *in vitro* release of allopurinol solid dispersions and allopurinol powder

Formula	Correlation coefficient (*r*)					
	Zero-order	First-order	Second-order	Diffusion-order	Hixcon-Crowell	Baker-Lonsd
F1	0.935365	-0.98277	0.995379	0.974801	0.970108	0.977056
F2	0.871449	-0.89258	0.912432	0.923465	0.885616	0.891134
F3	0.955624	-0.87047	0.772401	0.964457	0.955677	0.97143
F4	0.971244	-0.98702	0.996771	0.992855	0.982369	0.985437
F5	0.926467	-0.88244	0.810008	0.962533	0.953079	0.969205
F6	0.847931	-0.94871	0.990815	0.916509	0.918958	0.927665
F7	0.917021	-0.95681	0.94742	0.966857	0.949169	0.955438
F8	0.931216	-0.96605	0.977153	0.971166	0.956931	0.961161
F9	0.935365	-0.98277	0.995379	0.974801	0.970108	0.977056
F10	0.675845	-0.64575	0.611197	0.759726	0.656281	0.650014
F11	0.921085	-0.95216	0.976206	0.9701	0.942469	0.945657
F12	0.921085	-0.95216	0.976206	0.9701	0.942469	0.945657
Allo. 100	0.891272	-0.94153	0.95288	0.942149	0.928143	0.937529

Table 3. Tukey-Kramer multiple comparisons test of allopurinol solid dispersion formulas and pure drug

Formulae	Significance	Formulae	Significance	Formulae	Significance	Formulae	Significance
F1 *vs.* F2	***	F2 *vs.* F9	NS	F4 *vs.* F9	NS	F7 *vs.* F8	***
F1 *vs.* F3	NS	F2 *vs.* F10	NS	F4 *vs.* F10	NS	F7 *vs.* F9	***
F1 *vs.* F4	***	F2 *vs.* F11	***	F4 *vs.* F11	***	F7 *vs.* F10	***
F1 *vs.* F5	***	F2 *vs.* F12	***	F4 *vs.* F12	**	F7 *vs.* F11	NS
F1 *vs.* F6	NS	F2 *vs.* Allo.100	NS	F4 *vs.* Allo.100	NS	F7 *vs.* F12	**
F1 *vs.* F7	NS	F3 *vs.* F4	***	F5 *vs.* F6	***	F7 *vs.* Allo.100	***
F1 *vs.* F8	***	F3 *vs.* F5	***	F5 *vs.* F7	***	F8 *vs.* F9	***
F1 *vs.* F9	***	F3 *vs.* F6	NS	F5 *vs.* F8	***	F8 *vs.* F10	***
F1 *vs.* F10	***	F3 *vs.* F7	NS	F5 *vs.* F9	***	F8 *vs.* F11	***
F1 *vs.* F11	NS	F3 *vs.* F8	***	F5 *vs.* F10	***	F8 *vs.* F12	***
F1 *vs.* F12	NS	F3 *vs.* F9	***	F5 *vs.* F11	***	F8 *vs.* Allo.100	***
F1 *vs.* Allo.100	***	F3 *vs.* F10	***	F5 *vs.* F12	***	F9 *vs.* F10	NS
F2 *vs.* F3	***	F3 *vs.* F11	NS	F5 *vs.* Allo.100	***	F9 *vs.* F11	***
F2 *vs.* F4	NS	F3 *vs.* F12	***	F6 *vs.* F7	NS	F9 *vs.* F12	***
F2 *vs.* F5	***	F3 *vs.* Allo.100	***	F6 *vs.* F8	***	F9 *vs.* Allo.100	NS
F2 *vs.* F6	***	F4 *vs.* F5	***	F6 *vs.* F9	***	F10 *vs.* F11	***
F2 *vs.* F7a	***	F4 *vs.* F6	***	F6 *vs.* F10	***	F10 *vs.* F12	***
F2 *vs.* F8	***	F4 *vs.* F7	***	F6 *vs.* F11	NS	F10 *vs.* Allo.100	NS
		F4 *vs.* F8	***	F6 *vs.* F12	***	F11 *vs.* F12	*
				F6 *vs.* Allo.100	***	F11 *vs.* Allo.100	***
						F12 *vs.* Allo.100	**

*** Significant at $p < 0.001$; ** Significant at $p < 0.01$; * Significant at $p < 0.05$; NS, not significant.

dissolution of the water-insoluble drug allopurinol was achieved through solid dispersion using different carriers, the best of which was PVP K30 in a drug carrier ratio of 1:1, which exhibited complete drug release in 45 min followed by mannitol in a drug carrier ratio of 1:1.

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