Preparation and characterization of domperidone solid dispersions

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Abstract: Domperidone is a highly water insoluble drug exhibiting poor dissolution pattern. The purpose of this work was to increase the dissolution rate of Domperidone by formation of solid dispersion with different water soluble carriers. Binary systems of Domperidone were prepared with polyvinyl pyrrolidone k-30 (PVP), poloxamer 188 (P188) and polyethylene glycol 6000 (PEG 6000) at different weight ratios using the solvent evaporation method, physical mixtures of the same systems were also used. The effect of the method of preparation was also investigated by preparing some selected formulations using melting method. As P188 is known to inhibit CYP3A4 enzyme which is responsible for hepatic metabolism of many drugs including Domperidone, the effect of incorporation of PVP or PEG 6000 as ternary component to P188 solid dispersion on dissolution rate was also investigated. Formulations were characterized by Fourier transform infrared (FTIR) and Differential scanning calorimetry (DSC). Drug content uniformity and dissolution rate were studied. Solid dispersions showed a better dissolution compared to the pure drug and physical mixtures, with PVP showing the highest dissolution efficiency. As indicated from DSC data, Domperidone was in the amorphous form, which confirmed the better dissolution rate of solid dispersions. Some ternary P188 combinations showed a better enhancement in drug dissolution compared to the optimized P188 binary system. This would present a potential of increasing oral bioavailability of Domperidone by increasing its dissolution rate and by inhibiting its pre-systemic metabolism by the presence of P188.

Keywords: Domperidone; solid dispersion; polyvinylpyrrolidone k-30; poloxamer188; polyethylene glycol 6000.

INTRODUCTION

Domperidone is a dopamine antagonist with antiemetic properties and has poor aqueous solubility (0.986 mg/L) (Barone, 1993). Moreover, Domepridone undergoes extensive pre-systemic metabolism (Martindale, 2009). Therefore, a variable and low oral bioavailability (about 13.17%) was reported. Various techniques such as micronization, solubilization, complexation with polymers, change in physical form, use of prodrugs, drug derivatization, and others have been employed in order to improve the dissolution and bioavailability of sparingly water soluble drugs (Garad, 2004; Nokhodchi *et al.,* 2005). Formation of solid dispersion is a widely used technique and has proved to be the most successful, simple and economic in improving the dissolution and bioavailability of poorly soluble drugs (Leuner and Dressman, 2000). Solid dispersions are dosage forms whereby the drug is dispersed in an inert hydrophilic carrier matrix at solid state either by melting, solvent or solvent-melting method (Chiou and Riegelman, 1971; Ford, 1986). Many water-soluble carriers have been utilized in the preparation of solid dispersions, mostly polyethylene glycols (Verheyen *et al.,* 2002; Liu and Desai, 2005), polyvinyl pyrrolidone (Hirasawa *et al.,* 2003; Karavas *et al.,* 2005), lactose (Hirasawa *et al.,* 1998), β-cyclodextrin (Zheng *et al.,* 2005; Salústio *et al.,* 2009), hydroxypropylmethylcellulose (EL maghraby and Alomrani, 2009), poloxamers (Karekar *et al.,* 2009), etc. Previous studies have been carried out to improve the solubility of Domperidone by dispersion with polyvinyl pyrrolidone using kneading method (Venkatesh *et al.,* 2008), Micropelletization technique (Prabakaran and Bajpai, 2006), complexation using β-cyclodextrin and its derivatives (Swami *et al.,* 2010; Ghodkea *et al.,* 2009). All these techniques depended on increasing the dissolution rate of the drug as a tool to increase the oral bioavailability, with no consideration to the hepatic first pass metabolism. Poloxamer188 is a nonionic triblock copolymer composed of two hydrophilic polyoxyethylene chains connected by a hydrophobic polyoxypropylene chain. It has been used by researchers to increase the aqueous solubility of poorly water-soluble drugs (Xie *et al.,* 2009). Moreover, it was shown that poloxamer188 inhibits hepatic CYP3A4 which is the enzyme responsible for metabolism of many drugs, including Domperidone ((Martindale, 2009). Accordingly, the aim of this study was to increase the bioavailability of Domperidone by dual effect, enhancing the dissolution rate of the drug and by reducing its hepatic metabolism. Binary solid dispersion systems of Domperidone were prepared with polyvinyl pyrrolidone k-30 (PVP), poloxamer 188 (P188) and polyethylene glycol 6000 (PEG) at different weight ratios using physical mixing and the solvent evaporation technique. The effect of method of preparation of the solid dispersion on the drug dissolution was studied by using the melting technique of the optimized formula from the solvent evaporation ones. The work was

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extended to study the possible synergistic effect of PVP or PEG when added as a ternary component to the drug : P188 binary system on the drug dissolution rate.

MATERIALS AND METHODS

Materials

Domperidone was obtained as a gift sample from Jamjoom Pharmaceuticals (Jeddah, Saudi Arabia). Polyvinyl pyrrolidone k-30 (PVP k-30), polyethylene glycol 6000 (PEG 6000) and hard gelatin capsules (size 0) were obtained as gift samples from Memphis Co. (Cairo, Egypt). Poloxamer188 (P188) was obtained from Sigma Chemical Co. (St. Louis, MO, USA). Other chemicals and reagents were of analytical grade.

Methods

Preparation of physical mixtures

Physical mixtures containing binary systems were prepared according to the formulas presented in table 1 by mixing Domperidone and the polymers with mortar and pestle according to the geometrical dilution method, followed by sieving (355μm sieve) (Six *et al.,* 2004).

Preparation of solid dispersions

i) Solvent evaporation method

Solid dispersions containing binary and ternary systems were prepared according to the compositions presented in table 1. Briefly, each polymer was dissolved in ethanol under stirring, until a clear solution was obtained, Domperidone was then added and stirring was continued for 45 min. The organic solvent was removed at ambient temperature under reduced pressure. The resultant solid dispersions were stored in a desiccator at room temperature for 24 h before pulverization and sieving (355 μm sieve) (Lingam and Venkateswarlu, 2009).

ii) Melting method

Solid dispersions of Domperidone with either P188 or PEG 6000 at the most appropriate weight ratio (table 1) were further prepared by the melting method. Binary system with PVP was not possible due to the high melting point of the polymer that may affect the drug stability. The polymer was melted at 60°C, and then the drug was added, mixed well and cooled in an ice bath to obtain a solid mass. The solidified mass was crushed and passed through a 355 Table 1m aperture sieve. The resulting solid dispersion was stored in a desiccator until used (Vyas *et al.,* 2009).

Characterization of solid dispersions

Differential scanning calorimetry (DSC)

DSC analysis was performed using DSC (Model DT-60, Shimadzu, Japan). Samples equivalent to about 5.0 mg of the drug were heated in hermetically sealed aluminum pans over a temperature range of 30-200°C at a constant rate of 10°C min^{-1} under a stream of nitrogen.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra were recorded using FTIR spectrophotometer (FTIR-8400S, Shimadzu, Kyoto, Japan). Samples were mixed with potassium bromide (spectroscopic grade) and compressed into disks using hydraulic press before scanning from 4000 to 600 cm^{-1}.

Determination of drug content

Samples of the physical mixtures and solid dispersions (equivalent to 20 mg of the drug) were placed in 25-ml volumetric flasks. Methanol (10 ml) was added, mixed thoroughly and sonicated for 10 min. The volume was made up to the mark with methanol. The solution was suitably diluted with the same solvent and spectrophotometrically (Shimadzu UV-160A Spectrophotometer, Shimadzu, Japan) assayed for drug content at 286 nm ((Swami *et al.,* 2010).

Table 1: The composition of the prepared binary and ternary systems

Formulation	Domperidone	Poloxamer188	PVPk-30	PEG6000
Binary systems:				
B1	1	2	0	0
B2	1	4	0	0
B3	1	6	0	0
B4	1	0	2	0
B5	1	0	4	0
B6	1	0	6	0
B7	1	0	0	2
B8	1	0	0	4
B9	1	0	0	6
Ternary systems:				
T1	1	1	3	0
T2	1	2	2	0
T3	1	3	1	0
T4	1	1	0	3
T5	1	2	0	2
T6	1	3	0	1

Dissolution studies

The dissolution study was performed using USP-II apparatus (Pharma Test SP6-400, Hamburg, Germany), the dissolution medium consisted of 900 ml of distilled water and the temperature was maintained at 37±1°C at 100 rpm. Samples were filled into capsules by placing 20 mg of Domperidone or its equivalent from different formulations and dropped into dissolution medium using sinkers. Samples of 5 ml were withdrawn at 10, 20, 30, 40, 50, 60, 75 and 90 min and replaced with fresh dissolution medium. The samples were filtered through 0.45µm membrane filter and drug concentration was determined spectrophotometrically at 286 nm.

Cumulative percent drug dissolved was determined at each time interval and was plotted against time in min. The dissolution percentage after 10 and 90 min (DP_{10}, DP_{90}) was determined. Additionally, Dissolution efficacy (DE) was calculated from the area under the dissolution curve at time 't' (measured using the trapezoidal rule) and expressed as percentage of the area of the rectangle described by 100% dissolution in the same time (Khan, 1975).

STATISTICAL ANALYSIS

All studies were performed in triplicate and values were expressed as mean ±SEM. The data were analyzed by one-way analysis of variance (ANOVA) and a value of $P<0.05$ was considered as significant.

RESULTS

Characterization of solid dispersions

The solid state characterization of all drug: carrier combinations were studied using Differential Scanning Calorimetry (DSC) and Fourier Transform Infrared Spectroscopy (FTIR).

Differential scanning calorimetry (DSC)

The DSC traces of Domperidone, carriers, binary (B_2, B_6, B_8) and ternary (T_6) systems are shown in figs. 1-3. The melting transition parameters (T_m and fusion enthalpy) are presented in table 2.

Table 2: The melting transition parameters of pure domperidone, carriers, physical mixtures and solid dispersions

Formulation	T_m (ºC)	Enthalpy (J/g)
Pure drug	249.15	112.13
P188	59.12	374.12
B_2 (physical mixture)	56.12	123.12
	248.93	18.78
B_2 (solid dispersion)	54.4	85.27
	246.45	5.97
T_6	54.77	138.24
	241.6	11.26
PVP k-30	99.61	41.4
B_6 (physical mixture)	92.03	257.21
B_6 (solid dispersion)	97.61	257.45
PEG 6000	64.88	619.63

Fig. 1 shows examples of the DSC traces of Domperidone, P 188, B_2 (1:4 drug:carrier ratio) physical mixture, B_2 solid dispersion and T_6 ternary solid dispersion. Pure Domperidone produced a single sharp endothermic peak at 249.15ºC, while pure P188 produced a sharp endothermic peak at 59.12°C (fig. 1). Physical mixing of the drug with P 188 showed a trend of reduced peak sharpness and noticeable reduction in the fusion enthalpy. Formulation of Domperidone as binary co-evaporates with P188 significantly ($P < 0.05$) reduced the T_m of its endothermic peak with marked reduction in the enthalpy compared to that of the pure drug (fig. 1 and table 2). In addition, ternary domperidone dispersion with P188 and PEG 6000 [T_6] produced two endothermic

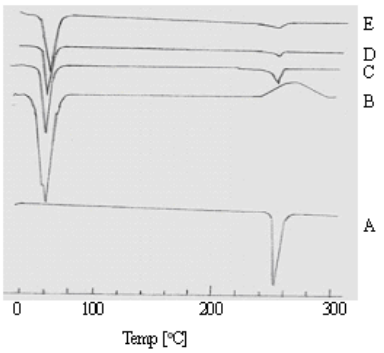

Fig. 1: DSC curves of Domperidone and its different systems with poloxamer188.

A; Domperidone, B; Poloxamer188, C; B_2 physical mixture, D; B_2 binary solid dispersion, E; T_3 ternary solid dispersion.

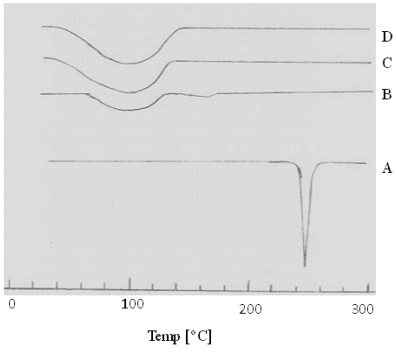

Fig. 2: DSC curves of Domperidone and its different systems with PVP k-30.

A; Domperidone, B; PVP k-30, C; B_6 physical mixture, D; B_6 binary solid dispersion

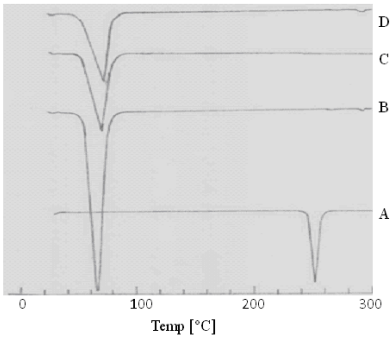

Fig. 3: DSC curves of Domperidone and its different systems with PEG6000.

A; Domperidone, B; PEG6000, C; B_8 physical mixture, D; B_8 binary solid dispersion

peaks corresponding to P188 and the drug with further reduction in Tm when compared to binary solid dispersion.

Fig. 2 shows examples of the DSC traces of Domperidone and PVP alone or as B_6 (1:6 drug:carrier ratio) physical mixture and solid dispersion. Pure PVP produced an endothermic peak at 99.6°C (table 2). The Domperidone/PVP physical mixture and solid dispersion showed disappearance of the sharp endothermic peak of the drug and appearance of one broad endotherm at 92.03 - 97.6°C with increased enthalpy.

Fig. 3 shows examples of the DSC traces of Domperidone and PEG 6000 alone or as binary B_8 (1:4 drug:carrier ration) physical mixture and solid dispersion. Pure PEG 6000 produced a sharp endothermic peak at 64.88°C (table 2). Thermograms of both physical mixture and solid dispersion showed absence of a Domperidone peak but a single endothermic peak corresponding to the fusion of the carrier.

Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of Domperidone alone, carriers and their binary (B_2, B_6, B_8) and ternary (T_6) combinations are shown in Figures 4-6. The FTIR of pure drug was characterized by N-H stretching at 3097 cm^{-1} and C = O stretching at 1714 cm^{-1}, for the presence of –CO-NH group. The spectrum also shows asymmetric C-H stretching at 2952 cm^{-1}, symmetric C-H stretching at 2786.1 cm^{-1}, N-H deformation at 1693 cm^{-1}, C = C at 1604 cm^{-1} and C-N at 1492 cm^{-1}. Pure P188 showed characteristic absorption bands at 3320, 2885 and 1120 cm^{-1} which corresponds to the stretching vibrations of O-H, C-H and C-O groups, respectively (fig. 4).

The FTIR spectrum of pure PVP showed the characteristic absorption bands at 3440, 1656 and 1273 cm^{-1} which corresponds to the stretching vibrations of N-H, ternary amide C = O and C-N, respectively (fig. 5), while pure PEG 6000 showed the characteristic absorption bands at 3313, 2885 and 1107.1 cm^{-1} which corresponds to the stretching vibrations of O-H, $-CH_2$ and C-O groups, respectively (fig. 6). The binary (B_2, B_8) and ternary (T_6) systems containing Domperidone with P188 and/ or PEG 6000 as well as physical mixture of Domperidone with PVP (B_6) showed the characteristic peaks of the drug and the polymers (figs. 4-6). While the FTIR spectrum of Domperidone/PVP (B_6) solid dispersion showed the absence of Domperidone peaks at 3097 cm^{-1} and 1693 cm^{-1} of N-H stretching and deformation, respectively. Furthermore, the peak at 1662 cm^{-1} of C=O in Domperidone was shifted to a lower frequency of 1654 cm^{-1}.

Drug content

Monitoring drug content uniformity in the early stages of formulation or process is an important issue in the pharmaceutical field as it is required for the control of drug quality and sturdiness of the process. The obtained values of drug content were in the range of 96.5 to 102.4 % w/w.

Dissolution studies

The dissolution profiles of pure Domperidone, physical mixtures and solid dispersions are shown in fig. 7. The dissolution percentage at 10 and 90 min (DP_{10}, DP_{90}) and the dissolution efficiency after 90 min (DE%) were calculated and are presented in tables 3-6. The results revealed poor and slow dissolution of pure drug showing a very small dissolution efficiency of 22.5% (fig. 7 and table 3).

Physical mixtures enhanced dissolution rate as compared with the control pure Domperidone. Formulation of the drug in solid dispersions further improved dissolution rate over that of physical mixtures and control. The dissolution extents after 90 min of control, physical mixture with P188 (B_1) and its corresponding solid dispersion were 32.1, 46.9 and 58.2% , respectively (fig. 7A, table 3). In solid dispersion, B_3 (1:6 drug: P188) showed a comparable enhancement in the DE to that of B_2 (1:4 drug: P188), indicating that B_2 is the optimized formula for that particular carrier. Regarding PVP (fig. 7B, table 4), it showed the best enhancement in DE

Table 3: Dissolution percentage (DP) and dissolution efficiency (DE) of domperidone from different systems with poloxamer188

Formulation	DP_{10} ± SEM	DP_{90} ± SEM	DE_{90} (%) ± SEM
Domperidone	13.4 ± 0	32.1 ± 0	22.5 ± 0
Physical mixture:			
B1	23.4 ± 1.0	46.9 ± 1.0	34.3 ± 1.02
B2	33.2 ± 1.0	55.0 ± 2.4	44.1 ± 1.6
B3	21.0 ± 1.8	50.5 ± 1.2	50.5 ± 1.2
Solid dispersion:			
B1	26.2 ± 0.8	58.2 ± 1.4	58.2 ± 1.4
B2	41.3 ± 5.5	75.9 ± 2.2	59.6 ± 2.0
B2 (prepared by melting)	6.4 ± 0.8	53.0 ± 2.0	34.7 ± 1.0
B3	27.6 ± 0.9	71.2 ± 2.4	53.5 ± 1.8

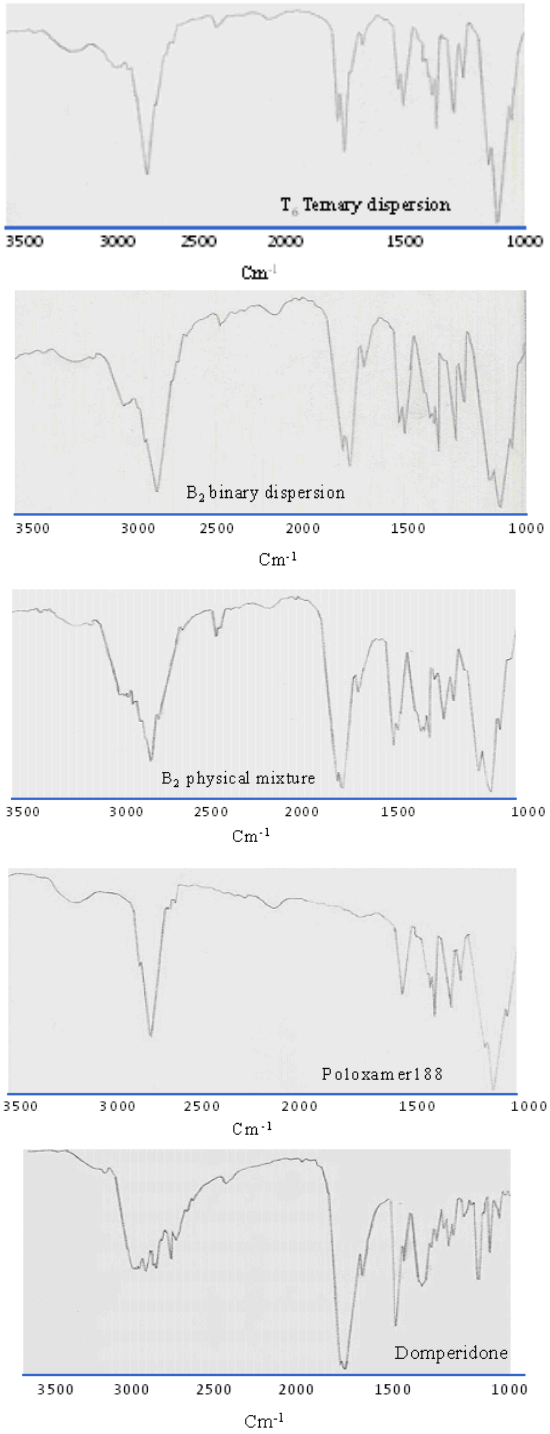

Fig. 4: FITR spectra of Domperidone and its different systems with poloxamer188.

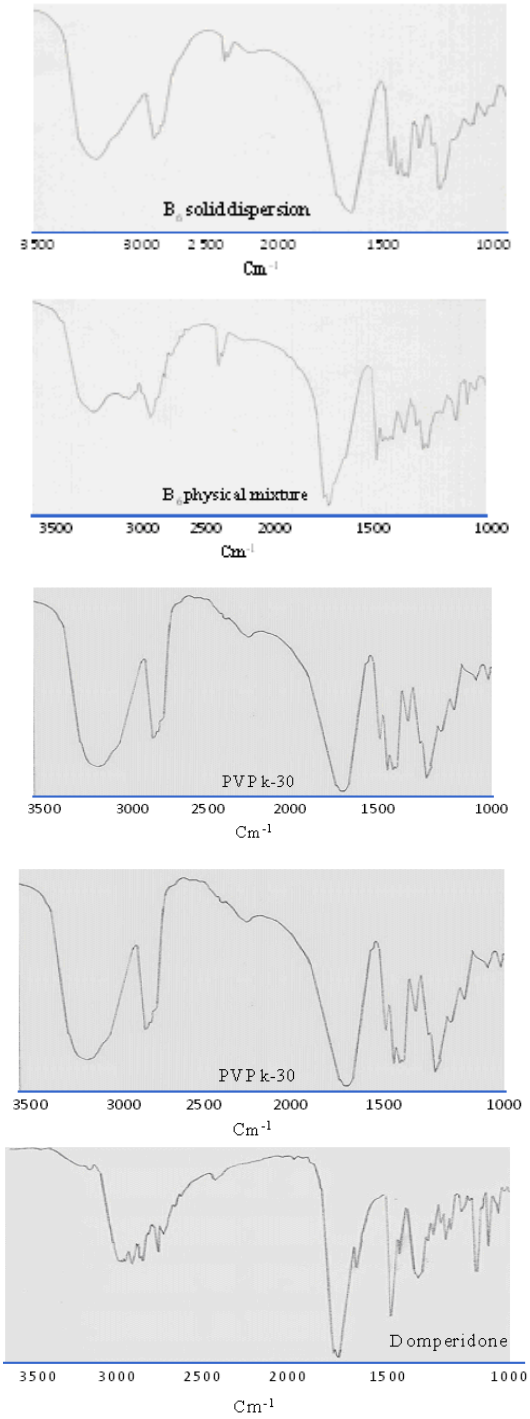

Fig. 5: FITR spectra of Domperidone and its different systems with PVP k-30.

regarding both physical mixtures and solid dispersions, compared to the other two tested carriers. Formulation B_6 (1:6 weight ratio of drug: PVP) showed the best dissolution enhancement where there was almost complete drug release after 20 min with a DE% of 87.9%. PEG 6000 physical mixtures showed a slight, but significant ($P<0.05$), enhancement in DE (fig. 7C and table 5). Formation of solid dispersion using PEG 6000 further improved drug dissolution rate and efficiency but to a lesser extent compared to the other two carriers, with B_8 (1:4 drug: PEG ratio) showing the maximum effect with a DE of about 53%.

Table 4: Dissolution percentage (DP) and dissolution efficiency (DE) of domperidone from different systems with PVP

Formulation	DP_{10} ± SEM	DP_{90} ± SEM	DE_{90} (%) ± SEM
Domperidone	13.4 ± 0	32.1 ± 0	22.5 ± 0
Physical mixture:			
B4	20.9 ± 6.3	75.6 ± 2.03	49.5 ± 3.8
B5	8.5 ± 1.1	100 ± 1.9 (after 50 min)	65.2 ± 2.1
B6	34.2 ± 7.7	100 ± 0.0	82.3 ± 2.4
Solid dispersion:			
B4	15.7 ± 3.04	100 ± 7.8 (after 75 min)	68.4 ± 6.3
B5	10.4 ± 2	100 ± 4.3(after 60 min)	84.9 ± 3.5
B6	27.6 ± 0.9	100 ± 4.7(after 20 min)	87.9 ± 1.9

Table 5: Dissolution percentage (DP) and dissolution efficiency (DE) of domperidone from different systems with PEG6000

Formulation	DP_{10} ± SEM	DP_{90} ± SEM	DE_{90} (%) ± SEM
Domperidone	13.4 ± 0	32.1 ± 0	22.5 ± 0
Physical mixture:			
B7	19.5 ± 0.7	40.9 ± 1.1	32.4 ± 0.9
B8	11.6 ± 2.8	44.1 ± 2.7	29.6 ± 0.9
B9	11.3 ± 4.1	35.3 ± 0.6	26.1 ± 0.9
Solid dispersion:			
B7	11.03 ± 1.1	43.5 ± 2.4	29.3 ± 0.8
B8	37.4 ± 1.2	66.1 ± 2.5	52.7 ± 1.8
B8 (prepared by melting)	20.1 ± 5.3	47.6 ± 1.6	37.5 ± 0.7
B9	29.1 ± 6.2	66.5 ± 3.3	48.4 ± 0.9

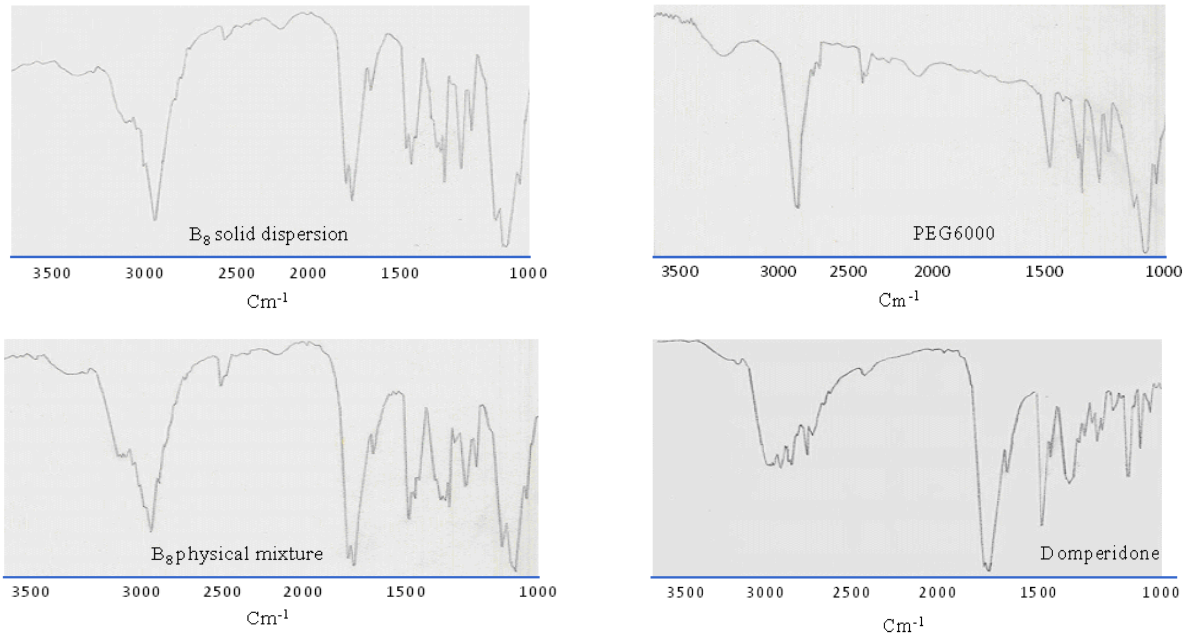

Fig. 6: FITR spectra of Domperidone and its different systems with PEG6000.

To study the effect of preparation technique adopted in preparing the solid dispersion on the drug dissolution, some selected binary systems were prepared by melting technique. Only P188 and PEG 6000 carriers were used due to their low melting point. Binary systems of 1:4 drug: carrier weight ratios (i.e., B_2 and B_8) were used as they showed the best dissolution pattern. From the obtained dissolution parameters (tables 3 and 5) it was clear that solid dispersions prepared by solvent evaporation method were superior to those prepared by fusion regarding drug dissolution efficiencies.

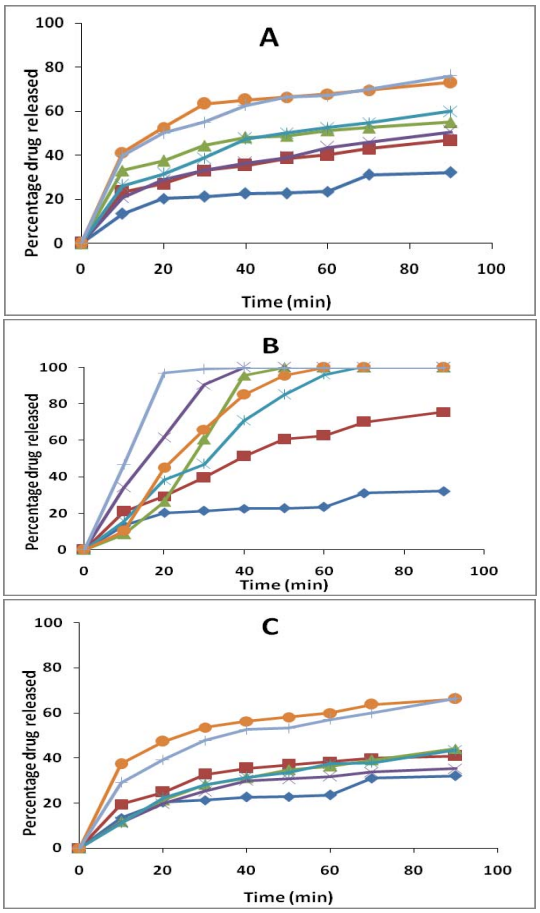

Fig. 7: Percentage drug released versus time of Domperidone from binary physical mixtures (PM) and solid dispersions (SD) using poloxamer188 (A), PVP (B) and PEG 6000 (C) as carrier.
Pure drug (-♦-), physical mixture (-■- 1:2; -▲- 1:4 ; -×- 1:6), solid dispersion (-* - 1:2; - ● -1:4 ; - + - 1:6). Error bars were omitted for clarity.

As mentioned earlier, one of the main aims of this work was to enhance drug bioavailability by increasing drug dissolution and decreasing its pre-systemic enzymatic degradation by the reported inhibiting capability of P188 to hepatic CYP3A4. As B_2 (1:4 drug: P188 ratio) showed the highest dissolution parameters among all tested P188 formulations, it was selected to study the possible synergistic effect of either PVP or PEG 6000 when added as a ternary constituent to B_2 (table 1). The percentage drug released versus time plots for the ternary solid dispersions together with the B_2 and pure drug are presented in fig. 8.

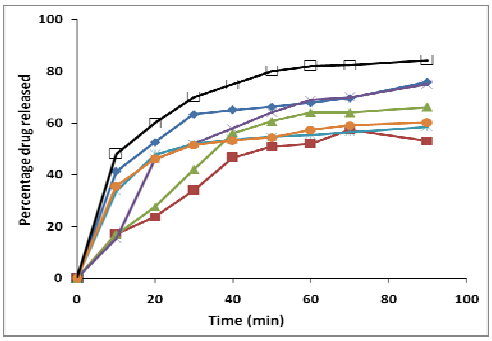

Fig. 8: Dissolution profile of Domperidone from binary B2 system, ternary solid dispersion formulations and pure drug.
(-♦- B_2 ; - ■ - T_1, -▲ - T_2; -×- T_3 ; -*- T_4 ; -● - T_5 ; -□- T_6) . Error bars were omitted for clarity.

All tested ternary solid dispersions, except T_6, failed to further increase the drug dissolution than the corresponding P188 binary system (table 6). Incorporation of Domperidone in ternary solid dispersion with P188 and PEG (T_6) produced a synergistic effect in drug dissolution, where about 84% of drug released after 90 min compared to 76% from the binary P188 solid dispersion (B_2).

DISCUSSION

Differential scanning calorimetry (DSC)

Pure Domperidone produced a single sharp endothermic peak at 249.15ºC indicating its melting point which in good agreement with previous findings on the thermal analysis of Domperidone (Ghodkea *et al.*, 2009). It was unexpected that the physical mixture of drug with P 188 produced a reduction in peak intensities. However, this behavior could be explained on the basis that on heating the physical mixture during DSC measurement, the drug progressively interacts with the molten carrier which melts at lower temperature, with the possible formation of eutectic mixture. Similar explanation was reported (EL Maghraby *et al.*, 2009). Binary co-evaporates of drug with P188 showed increased drug amorphousness as illustrated by marked reduction in T_m and enthalpy of

Table 6: Dissolution percentage (DP) and dissolution efficiency (DE) of domperidone from different ternary systems compared with domperidone alone.

Formulation		DP_{10} ± SEM	DP_{90} ± SEM	DE_{90} (%) ± SEM
Domperidone		13.4 ± 0	32.1 ± 0	22.5 ± 0
Drug : poloxamer : PVP	T1	17.2 ± 0.4	61.4 ± 1.7	42.4 ± 1.8
	T2	17.0 ± 1.9	71.4 ± 3.3	49.7 ± 1.6
	T3	15.4 ± 2.7	77.4 ± 2.3	58.7 ± 1.3
Drug : poloxamer : PEG	T4	33.7 ± 6.8	58.6 ± 1.0	48.9 ± 2.0
	T5	35.7 ± 2.2	60.3 ± 2.5	49.7 ± 2.1
	T6	27.9 ± 4.6	84.3 ± 3.7	66.2 ± 3.6

endothermic peak and this may be due to eutectic formation with P188. Domperidone ternary dispersion with P188 and PEG6000 showed further reduction in T_m compared to domperidone and P188, which was ascribed to eutectic formation. As might be expected, ternary dispersion using PEG 6000 further increased drug amorphousness due to the augmented effect of the two hydrophilic polymers in reducing drug crystalline state.

Pure PVP produced an endothermic peak at 99.6°C (table 2) corresponding to dehydration (Balata *et al.,* 2010). DSC results of Domperidone: PVP binary systems could be attributed to the dispersion of the drug in the molecular state in its carrier matrix. Similar suggestions were recorded by Muralidhar *et al.* (2010).

Pure PEG 6000 produced a sharp endothermic peak at 64.88°C (table 2) corresponding to its melting (Patel and Suthar, 2009). Disappearance of drug peak in the physical mixture could be explained by dispersion of the drug in the molten carrier during DSC measurement. For solid dispersion, the complete absence of Domperidone peak would indicate that the drug may be present in the amorphous state or as a solid solution inside the PEG 6000 matrix. This result was in agreement with that reported by Yamashita *et al.* (2003).

Fourier Transform Infrared Spectroscopy (FTIR)

Results of FTIR studies suggested the absence of any interaction between the drug and P188 or PEG 6000 in binary (B_2, B_8) and ternary (T_6) systems as well as physical mixture with PVP (B_6). On the other hand, there was a probability of hydrogen bonding between Domperidone and PVP in the solid dispersion (B_6).

Drug Content

The obtained results of drug content indicating homogenous distribution of the drug in the prepared physical mixtures and solid dispersion formulations. This indicates the control of drug quality and sturdiness of the process.

Dissolution studies

Dissolution enhancement by physical mixing with different carriers as compared to pure drug can be explained by increased solubility and surface area of the drug that comes in contact with the dissolution medium as the carrier dissolves. This might be due to the surface tension lowering effect of the polymers, resulting in the enhanced wettability of the hydrophobic drug having crystalline surface (Liu *et al.,* 2006). Several mechanisms may be possible for further improvement in drug release rate from the solid dispersion formulations with water soluble polymers. This can be attributed to the reduced crystallinity and particle size, the presence of drug in the form of eutectic mixture or solid solution in water soluble polymer in the molecular state, increased wettability and prevention of aggregation of drug by carriers (Muralidhar *et al.,* 2011; Sharma and Jain, 2010). Increased drug amorphous state was confirmed by the DSC results. It was evident that as the proportion of PVP in solid dispersion increases, the dissolution rate of Domperidone increases. Similar results were reported by Venkatesh *et al.* (2008).

The overall results of the binary solid dispersions showed the superiority of PVP regarding the improved drug dissolution rate and dissolution efficiency. The effect of both P188 and PEG on drug dissolution was comparable. A similar finding was reported where PVP was better than PEG6000 in enhancing the solubility of poorly water soluble drug (Venkateswarlu, 2009). These results were in agreement with Lingam and Venkateswarlu, 2009, who found that the dissolution of celecoxib was enhanced considerably from PVP solid dispersions compared to dissolution of PEG 6000 solid dispersions and plain drug.

The synergistic combination of P188 and PEG (T_6) that had a positive effect on drug dissolution may be explained on the basis that the incorporation of the two water soluble carriers may help to increase amorphousness of the drug, as confirmed by the DSC data. This would suggest that the use of ternary drug:P188:PEG at 1:3:1 weight ratio would present a potential of increasing the oral bioavailability of the poorly water soluble Domperidone by enhancing its dissolution rate as well as by inhibiting its pre-systemic metabolism by the stated inhibiting effect of P188 on liver enzymes.

CONCLUSION

Based on the current study, improvement in the dissolution of the water-insoluble drug Domperidone was achieved through solid dispersion using different carriers, the best of which was PVP K30 in a drug carrier ratio of 1:6, which exhibited complete drug release in 20 min followed by poloxamr188 in a drug carrier ratio of 1:4 and finally PEG6000 in a drug carrier ratio of 1:4. Ternary drug: P188: PEG at 1:3:1 weight ratio would present a potential of increasing the oral bioavailability of Domperidone by enhancing its dissolution rate as well as by inhibiting its pre-systemic metabolism.

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