Polyethylene Glycol Enhances Solubility of Domperidone through Solid Dispersion

Rajender Guleria[1], Vivek Sharma[1*], Ankita Kapoor[1], NS Kaith[2], Ranjit Singh[3]

1. Govt. College of Pharmacy, Rohru Distt. Shimla, Himachal Pradesh-171207, India
2. KVK Rohru-171207 Distt. Shimla, Himachal Pradesh, India
3. School of Pharmaceutical Sciences, Shobhit University, Meerut, (UP) India

ABSTRACT

Domperidone is a water insoluble drug exhibiting poor dissolution pattern. Domperidone is an antiemetic and shows gastroprokinetic properties. It is a weak base and shows poor solubility in alkaline pH. Several methods are being employed to enhance the solubility of domperidone irrespective of its pH dependent solubility. The present protocol aim to design Polyethylene glycol (PEG) based solid dispersions of Domperidone to enhance its solubility. PEG 8000 based solid dispersions containing the drug in different mass ratio i.e. 1:1, 1:3, 1:5 and 1:7 were prepared using fusion method. The prepared solid dispersions were characterized for their drug content, phase solubility studies, Fourier-transform infrared (FTIR) spectroscopy, differential scanning calorimetry (DSC), x-ray diffraction, and in-vitro dissolution studies. All the formulations showed marked improvement in the solubility and dissolution rate of drug which may be due to decrease in crystallinity of drug and additives. It was concluded that prepared solid dispersion of the Domperidone with PEG can improve the solubility and dissolution rate of the drug.

Keywords: Domperidone, PEG, Solid dispersion, Solubility

INTRODUCTION

The therapeutic efficacy of a drug product intended to be administered by the oral route mainly depends on its absorption by the gastrointestinal tract. However, for a drug substance to be absorbed, it needs to be solubilised. Numerous works have been carried out in order to modify the dissolution kinetics of poorly soluble drugs to improve their bioavailability. Among them solid dispersion technology was most widely used.[1, 2] Number of insoluble drugs has shown to improve their dissolution character when converted to solid dispersion.[3]

Domperidone is described chemically as 5-chloro-1-[1-[3-(2, 3-dihydro-2-oxo-1H-benzimidazole-1-yl) propyl] – 4 – piperidinyl] -1, 3 – dihydro - 2H - benzimidazole -2-one.[4] The drug is a benzimidazole derivative with a molecular weight of 426 that acts peripherally by dopamine blockade. It acts as an antiemetic and a prokinetic agent through its effects on the chemoreceptor trigger zone and motor function of the stomach and small intestine. Unlike metoclopramide, it does not cause any adverse neurological symptoms as it has minimal penetration through the blood-brain barrier. It thus provides an excellent safety profile for long-term administration orally in the recommended doses.[5]

When given as immediate release tablet onset of action is half an hour and the drug effect lasts for 4-7h. The elimination half life is 5-7 h. Although, Domperidone is a weak base with good solubility in acidic pH but in alkaline pH, its solubility is significantly reduced.[6] It has poor aqueous solubility (0.986mg/L) and the oral bioavailability of Domperidone has been reported at the range of 13-17%.[5] .The poor aqueous solubility may be one possible reason for its low bioavailability. In order to increase the bioavailability of domperidone, a controlled release dosage form has been prepared to increase the solubility of domperidone in the alkaline medium.[5]

Poorly water-soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased and more reproducible oral bioavailability and subsequently to clinically relevant dose reduction and more reliable therapy. Nowadays, many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, and addition of solvent or surface active agents. Solid dispersion (SDs) is one of these methods, which is most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs.

The concept of SDs was introduced in 1961 by Sekiguchi and Obi[1] in which the drug is dispersed in inert water soluble carrier at solid state. Several water soluble carriers such as mannitol, urea, lactose, citric acid, polyvinyl pyrrolidone (PVP) and polyethylene glycols (PEG) are used as carriers for SDs.[6,7] Physical modifications often aim to increase the surface area, solubility and/or wettability of the powder particles and are therefore focused on particle size reduction or generation of amorphous states.[8]

Present study was designed to study the effect of PEG 8000 as a water soluble carrier on solubility of Domperidone. Effect of drug to carrier ratios on the dissolution of domperidone was also studied. SDs was prepared by fusion method to compare rates of release of drug and extent of solubility. The SDs seems to possess great potential to significantly enhance the solubility and dissolution rate of domperidone.

MATERIAL AND METHODS

Domperidone was received as gift from Arion health care Baddi (Himachal Pradesh, India). PEG 8000 was purchased from Sigma Aldrich, Germany. Double distilled water was used throughout the study and all the other chemicals used were of analytical grade.

Solid Dispersions of Domperidone

Solid dispersions of domperidone at four mass ratios (1:1, 1:3, 1:5 and 1:7) were prepared by the fusion method. PEG 8000 was placed in a porcelain dish and allowed to melt by heating up to 70°C. To the molten mass, an appropriate amount of domperidone was added and stirred constantly until homogenous dispersion was obtained. The mixture was cooled rapidly by placing the porcelain dish in an ice bath for 5 min to solidify with continuously stirring, then powdered in a mortar, sieved through a 100-mesh screen, and stored in a screw-cap vial at room temperature for further use.

Determination of Domperidone Solubility

Solubility determinations were performed in triplicate according to the method of Higuchi and Connors.[6]. In brief, an excess amount of domperidone was taken into a screw-capped glass vial to which 20 mL of aqueous solution containing various concentrations (0-0.3 %w/v) of PEG 8000 was added. The samples were shaken at 25.0 ± 0.5^{o}C for 72 h in a water bath (Rolex, Ambala, India) and filtered through a 0.45μm membrane filter. The filtrate was suitably diluted with distilled water and analyzed spectrophotometrically at the wavelength of 284 nm using a UV-VIS spectrophotometer (Shimadzu UV-1700 Pharmaspec).

Drug Content Estimation

The drug contents in solid dispersion were determined by the UV-spectroscopic method. An accurately weighed quantity of solid dispersion equivalent to 20 mg of domperidone was transferred to a 100 ml volumetric flask containing 20 ml of Dimethylformamide (DMF) and dissolved then make up the volume with distilled water. The solution was filtered through 0.45μm membrane filter paper. One ml of this solution was diluted 10 times with same solvent Dimethylformamide (DMF): distilled water (20:80) and the absorbance was measured at 284 nm.

Dissolution studies

Dissolution studies on domperidone powder as well as the SDs were performed using the U.S. Pharmacopoeia (USP) tablet dissolution test apparatus 2 (6+2 station) Lab India, Mumbai with the paddle rotating at 50 rpm in 900 ml pH 1.2 (0.1N HCl) and pH 6.8 phosphate buffer at $37\pm0.5^\circ$C. SDs equivalent to 20 mg of domperidone were used as samples for the dissolution test. At 10 min intervals, 5 ml samples were withdrawn, filtered through a 0.45μm membrane filter and assayed for domperidone content by measuring the absorbance at 284 nm using UV-Visible spectrophotometer (Shimadzu UV-1700). Fresh medium (5 ml), prewarmed at $37\pm0.5^\circ$C, was added to the dissolution medium after each sampling to maintain a constant volume throughout the test. Dissolution studies were performed in triplicate (n=3).

Fourier-transform infrared (FTIR) spectroscopy

Fourier-transform infrared (FT-IR) spectra were recorded using an FT-IR spectrophotometer (Shimadzu). The samples (domperidone, PEG 8000 and its SDs) were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Differential scanning calorimetry

DSC measurements were performed on a DSC-6100 (Seiko Instruments, Japan) differential scanning calorimeter with a thermal analyzer. Samples (about 1.675 mg of domperidone SDs containing an equivalent amount of the drug) were placed in sealed aluminium pans and heated under nitrogen flow (20 ml/min) at a scanning rate of 10°C min-1 from 25 to 250°C. An empty aluminium pan was used as a reference.

X-ray diffraction

The crystalline state of different samples was evaluated with X-ray powder diffraction. Diffraction patterns were obtained IIC, IIT Roorkee using an XPERT-PRO diffractometer (P

Analytical) with a radius of 240 mm. The Cu Ka radiation (Ka 1.54060Å) was Ni filtered. Diffractograms specification are Step: 0.009^0, Step time – 2 Th/Th locked – Start: 5.000^o End: 119.998^o – 19.25 – Tem 25^oC – Time started 13s -2- Theta 5000° – Theta: 2.500^o –Chi 0.00^o operation smooth 0.150/ Y scale Mul 0.75^o.

RESULTS AND DISCUSSION

Drug Content

Results depicted in Table 1 show that the drug concentration in solid dispersions ranged between 98.3 and 99.8 %.

Table: 1 Percent drug content in solid dispersion of PEG 8000 in mass ratio of 1:1, 1:3, 1:5, 1:7 respectively.

Drug to PEG mass ratio	Formulation code	Drug content (%)
PEG 8000 (1:1)	SD D8_{11}	99.16 ± 1.65
PEG 8000 (1:3)	SD D8_{13}	98.8 3± 2.23
PEG 8000 (1:5)	SD D8_{15}	99.85± 1.96
PEG 8000 (1:7)	SD D8_{17}	98.34 ± 1.38

Solubility and dissolution data analysis

Solubility studies

The phase solubility for the complex formation between domperidone and PEG 8000 was performed by the Higuchi and Connors method [10]. The aqueous solubility of domperidone is increased linearly as a function of carrier concentration. The phase solubility diagram showed A_L type, due to the straight line had a slope less than unity; indicates the formation of complex. The apparent stability constant, K was calculated from the linear plot of the phase solubility diagram according to the equation (1).

$$Ks= \quad Slope/ Intercept (1 - Slope) \qquad (1)$$

Gibbs free energy of transfer of domperidone from pure water to the aqueous solutions of carrier was calculated as in Equation (2):

$$\Delta G_{tr}^{\ 0} = - 2.303RT \log So/ Ss \qquad (2)$$

Where, So/Ss is the ratio of molar solubility of domperidone in aqueous solution of PEG 8000 to that of the same medium without PEG 8000 In solid dispersion of Domperidone with 0.3 w/v PEG 8000 increase in solubility was found to be 10.26 fold as shown in Table 2.

The stability constant, K of domperidone and PEG 8000 complex was found to be 28.63 ml^{-1} mg, which indicates the formation of stable complex for A $_L$ type solid complexes prepared by fusion method. ΔG_{tr}^{0} values were all negative for PEG 8000 at various concentrations indicating the spontaneous nature of the drug solubilization. The values decreased by increasing PEG 8000

concentration, demonstrating that the reaction become more favorable as the concentration of PEG 8000 increased.

Table: 2 Thermodynamic parameters of solubility process of domperidone in aqueous solution of PEG 8000 at 25^{0}c

PEG 8000 (%w/v)	Domperidone (* 10^{-4} mg/ml) at 25^{0}C	ΔG_{tr}^0 (J/Mol)
0	9.86±0.52	0
0.05	23.35±1.10	-2136
0.1	45.6±0.80	-3794
0.15	63.7±0.75	-4623
0.2	78.2±0.60	-5132
0.25	90.37±1.25	-5490
0.3	101.24±1.15	-5768

Dissolution studies

Q10, Q30 and Q60 values (percent drug dissolved within 60 min) are reported in Table 3 and Figure 1. From Table 3, it is evident that the onset of dissolution of pure Domperidone was very slow (62.70% of drug was dissolved within 60 min in pH 1.2 while in pH 6.8 it was 12.42 %). The dissolution rate of Domperidone SDs was considerably enhanced by PEG 8000 within 60 min compared to pure Domperidone. Dissolution was enhanced with SDs as the concentration of PEG increased in pH 1.2 from 48.32 to 78.73 % in SD D8$_{11}$, 48.34 to 88.96 % in SD D8$_{13}$, 52.17 to 94.84% in SD D8$_{15}$ and 51.72 to 92.16% in SD D8$_{17}$. In pH 6.8 it was enhanced from 21.24 to 51.37 % in SD D8$_{11}$, 26.48 to 65.74 % in SD D8$_{13}$, 32.43 to 88.86% in SD D8$_{15}$ and 30.21 to 87.02% in SD D8$_{17}$. Increase in dissolution of Domperidone was approximately similar in SD D8$_{15}$ and SD D8$_{17}$.

(a)   (b)
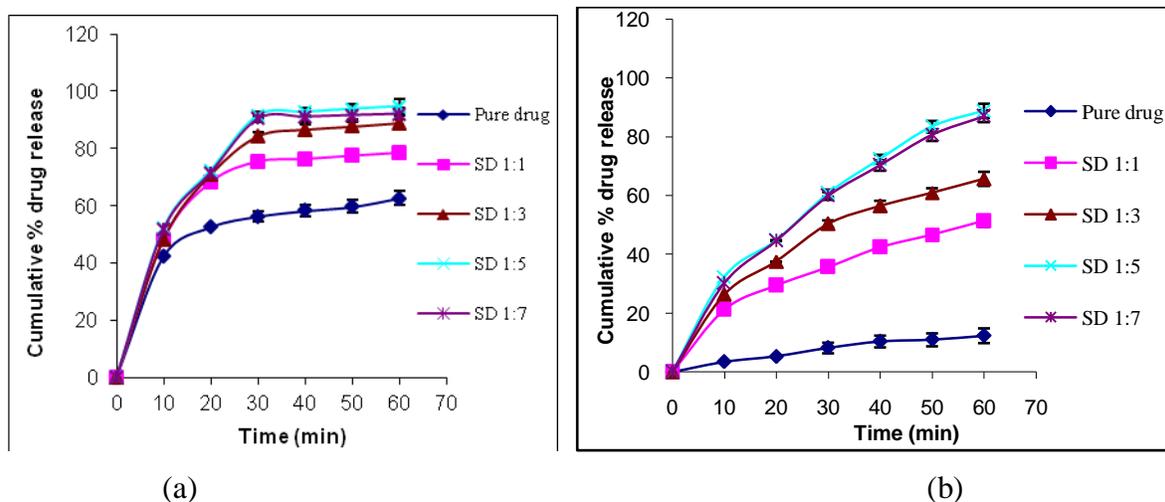
Figure: 1 Percent drug released in (a) 0.1 N HCl (pH 1.2) (b) pH 6.8 from solid dispersion of Domperidone with PEG 8000, vertical bars indicates the standard deviation.

Table: 3 In vitro dissolution of DOM and solid dispersions of DOM in PEG 8000

| Formulation | Dissolution Parameters (n=3) | | | | | |
| | 0.1 N HCl pH 1.2. | | | Phosphate buffer pH 6.8 | | |
	Q_{10}	Q_{30}	Q_{60}	Q_{10}	Q_{30}	Q_{60}
Drug	42.35	56.31	62.70	3.52	8.25	12.42
SD $D8_{11}$	48.32	75.63	78.73	21.24	35.72	51.37
SD $D8_{13}$	48.34	84.34	88.96	26.48	50.43	65.74
SD $D8_{15}$	52.17	91.6	94.84	32.43	60.87	88.86
SD $D8_{17}$	51.72	90.42	92.16	30.21	59.92	87.02

Fourier-transform infrared (FTIR) spectroscopy

FTIR spectroscopy was used to characterize the possible interactions between drug and carrier in the solid state. The FTIR spectra of SDs were compared with the standard spectrum of domperidone and PEG alone (Figure.2 a). NH group which is located at 3360 cm^{-1} from the IR spectra of domperidone shifted to 3430 cm^{-1} in SDs (Table 4). The shift in the peaks associated with the domperidone indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG. This led to the conclusion that the changes seen are a result of intermolecular hydrogen bonding between domperidone and PEG in the solid state.

Table: 4 Stretching vibrations of Domperidone and Solid Dispersion (SDs) of Domperidone with PEG 8000

| Stretching	Pure Domperidone	SDs with PEG 8000
N-H	3360 cm^{-1}	3430 cm^{-1}
C=O	1716 cm^{-1}	1717 cm^{-1}
C-H	2818 cm^{-1}	2852 cm^{-1}

Differential Scanning Calorimetry

The DSC curve of pure domperidone exhibits a single endotherm corresponding to the melting of the drug. The onset of melting was observed at 247.15°C whereas pure PEG 8000 shows a melting endotherm at 60.2°C. Thermograms of SDs (Figure. 2 b) exhibited endothermic peak at 246.9°C. The phase transition profile of the domperidone in the solid dispersion exhibited broad and size reduced peak with a concomitant shift to lower temperature, indicating that domperidone is completely soluble in the liquid phase of the polymer or that the crystalline nature of domperidone is absent. The exothermic peak may be due to crystallization above the glass transition temperature, Tg.
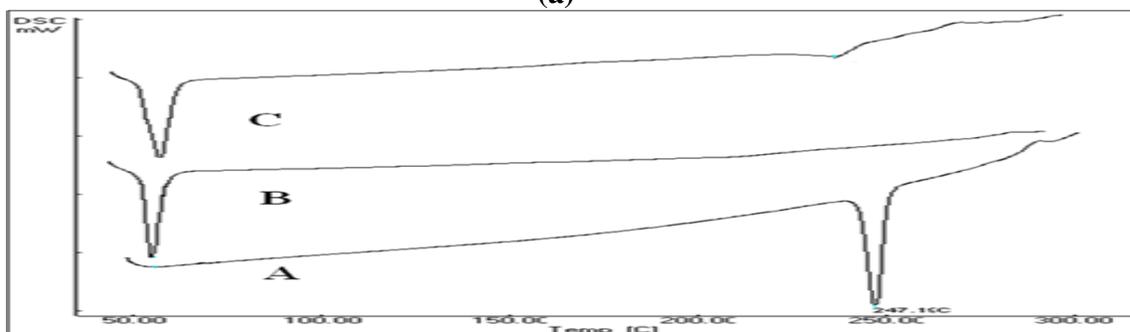
X-Ray Diffraction

The diffraction spectrum of pure domperidone shows that the drug was of crystalline nature as demonstrated by numerous peaks observed at 2θ of 9.39, 11.96, 14.08, 15.09, 15.74, 25.47, 26.23, 27.70, 28.24, 29.24 etc in finger print region. Pure PEG 8000 shows two peaks with the

highest intensity at 2θ and d-spacings of 19.10 and 4.64 Å; 23.24 and 3.8 2Å. Similarly, some changes in domperidone peak position were observed in SDs. The prominent peaks from pure domperidone were clearly seen at the same positions in the SDs, but with decreased intensities. Relative reduction in diffraction intensity (Figure. 2c) of domperidone in PEG solid dispersion at these angles suggests that the size of the crystals was more reduced to a microcrystalline form. Results of this study imply that domperidone is present in microcrystalline form in the SDs.
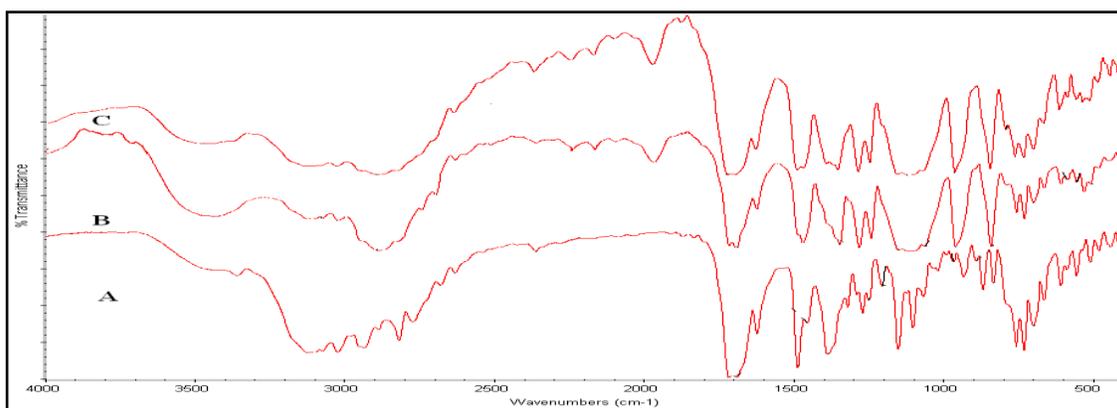
(a)

(b)
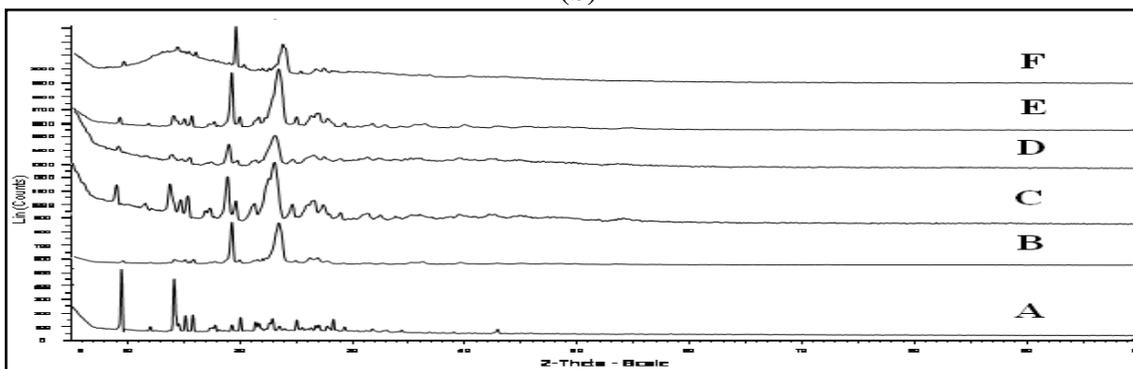
(c)

Figure 2: (a) FTIR spectrograms of A – Domperidone, B-PEG 8000 C-Domperidone-PEG 8000 SD (b) DSC Thermograms of A – Pure domperidone, B-PEG 8000, C-Domperidone-PEG 8000 SD (c) X-ray diffractograms of A-Pure domperidone, B- Pure PEG 8000, C- SD D4$_{11}$, D- SD D4$_{13}$, E- SD D4$_{15}$ and SD D4$_{17}$

In the present study, the phase-solubility results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs.   Increased solubility may be due to improved dissolution of Domperidone particles in aqueous solution of PEG 8000. An indication of the process of transfer of Domperidone from pure water to the aqueous solution of PEG is obtained from the values of Gibbs free energy change. Spontaneous nature of drug solubilisation is indicated by the negative values of Gibbs free energy (⁻Gtr).

The increase in the dissolution kinetics of Domperidone from PEG soluble dispersion might be due to absence of aggregation of drug crystals, the reduction of crystal size, and conversion of the drug from crystalline to amorphous/microcrystalline state. The shift of the peaks of Domperidone (FTIR), in SDs was as a result of physical interaction between Domperidone and PEG 8000. The shift in the peaks associated with the Domperidone indicates an increase in bond strength, possibly due to the stabilizing effect of the hydrogen atoms of PEG interacting with the oxygen atoms of the sulfonyl group. This led to the conclusion that the changes seen are a result of intermolecular hydrogen bonding between Domperidone and PEG in the solid state.

Complexation of drug with suitable carrier alters the solubility and dissolution characteristics due to extremely high aqueous solubility of the carrier. The solubility and dissolution rate improvements are expected due to co-solvency effect and solubilisation effect of carriers in aqueous vehicles. Carrier induced physical modifications as evidenced in the present study is an important tool in designing and formulating immediate and fast release drug delivery systems. The enhancement of dissolution of domperidone from the drug carrier may be due to several factors such as lack of crystallinity, increased wettability and dispersibility. Incorporation of drug with a hydrophilic carrier system offered an increased wetting and reduction in interfacial tension between hydrophobic drug and dissolution medium. Present study like previous ones advocates the utility of solid dispersion technique in enhancement of solubility of poorly soluble drugs.

REFERENCES

1. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture: A comparison of the behavior of eutectic mixture sulfathiazone and that of ordinary sulfathiazole in man. Chem Pharm Bull1961; 9: 866-872.

2. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion system. J Pharm Sci1971; 60: 1281-1302.

3. Madhusudhan B, Rambhav D, Gudsoorkar VR, Shete JS Apte SS. Studies on sulphamethoxazole solid dispersions and their tablets. Indian J Pharm. Sci2002; 64(3): 233-238.

4. Swami G, Koshy MK, Pandey M, Saraf SA. Preparation and characterization of Domperidone- β-cyclodextrin complexes prepared by kneading method. Int J Advances in Pharma Sci 2010; 1: 68-74.

5. Savio C Reddymasu, Irfan Soykan & Richard W McCallum. Domperidone: Review of Pharmacology and Clinical Applications in Gastroenterology. The Am J Gastroenterology2007: 102, 2036–2045.

6. Higuchi T and Connors K. Phase solubility techniques, Advances in Analytical chemistry and instrumentation.*4th ed.,* 1965; 117–123.

7. Vadnere MK. Co precipitates and melts. In: Swarbrick J Boylan J EDS Encyclopaedia of pharmaceutical Technology. 2nd ed. NY. Marcel Dekker Inc. 2002; 641-643.

8. J.E.F. Reynolds, in: 30th ed, Martindale: the Extra Pharmacopoeia, The Pharmaceutical Press, London, 1993,882.