



ISSN No: 0975-7384
CODEN(USA): JCPRC5

J. Chem. Pharm. Res., 2011, 3(6):889-898

Development of Domperidone: Polyethylene Glycol 6000 Fast Dissolving Tablets from Solid Dispersions Using Effervescent Method

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ABSTRACT

Fast dissolving tablets of domperidone solid dispersions were prepared by effervescent method with a view to enhance patient compliance. Domperidone is water insoluble anti emetic drug, with problems of variable bioavailability and bio- inequivalence related to its poor water solubility. The purpose of present investigation to increase the dissolution rate of domperidone by developing domperidone fast dissolving tablets using domperidone solid dispersions, and to determine the influence of amount of superdisintegrant and effervescent materials on tablet disintegration. Differential scanning calorimetry, infrared spectroscopy and scanning electron microscopy were used to characterize the solid state of solid dispersions. Tablets were prepared by conventional direct compression method using Ac-Di-Sol (2-6%) as a superdisintegrant and mixture of sodium bicarbonate (6-18%) and citric acid (3-6%) was used as an effervescent material, along with directly compressible Mannitol to enhance mouth feel. In-vitro dispersion time of the formulation containing Ac-Di-Sol (6%) and mixture of sodium bicarbonate(18%) and citric acid(6%) was found to be 31 seconds and released 88% drug in 5 seconds, whereas marketed tablet released 58% drug in 30 min. Stability study indicated that there were no significant changes in tablet quality was observed.

Keywords: Domperidone, Ac-Di-Sol, Effervescent materials, Scanning electron microscopy, Solid dispersion.

INTRODUCTION

For most of the therapeutic agents oral route still represents the preferred way of administration owing to its several advantages and high patient compliance compare to other routes.

Aqueous solubility is one of the key determinants of new chemical entities as successful drugs; drugs with poor water solubility typically have lower bioavailability. Techniques that have

commonly been used to improve to improve dissolution and bioavailability of poorly water soluble drugs, in general, include micronization, the use of surfactant, and the formation of solid dispersions [1].

Solid dispersion technology is a well known process used to increase the dissolution kinetics and oral absorption of poorly water soluble drugs using water soluble inert carriers [2].

Solid dispersion technique can be applied to increase the dissolution rate by the formation of solid dispersion (SD) with polymeric carrier, such as polyvinyl glycol (PEG) derivatives [3], polyvinyl pyrrolidone (PVP) [4], and hydroxylpropylmethylellulose [5] PEG 6000 has been used as carrier for increasing the dissolution rate of several poorly water soluble drugs, such as prednisone [6], rofecoxib [7], and diclofenac [8].

Domperidone is a widely used antiemetic, poorly water soluble drug, erratically absorbed in stomach and possess several dissolution problem thus it has poor bioavailability (15%).

In the present investigation, an attempt was made to improve the dissolution rate of domperidone by developing domperidone fast dissolving tablets using solid dispersion technique and to determine the influence of amount of superdisintegrant and effervescent materials on tablet disintegration.

EXPERIMENTAL SECTION

Material and method

Domperidone (Madley Pharmaceutical Ltd. Daman, India.), Crosscarmellose sodium (Ac-Di-Sol) (Panacea Biotech, Ltd., Larlu, India). Polyethylene glycol (PEG) 6000, Saccharine-Na, Mannitol, sodium bicarbonate, anhydrous citric acid and magnesium stearate (S.D. Fine chemicals, Mumbai.), and other chemicals and reagent used in the study were obtained commercially and used as received.

Phase solubility study

Solubility requirements for domperidone were carried out by a reported method by Higuchi and Connors [9]. An excess amount of domperidone is placed in to a 25 ml glass flask containing different concentration of PEG 6000 in 20 ml of distill water. All flasks were closed with stopper. The content of the suspension was equilibrated by shaking for 72 hours in a thermostatically control water bath at 37⁰ C. After attainment of the equilibrium, the content of each flask was then filter through a 0.45 μ m filter. The filtrate was diluted and assayed spectrophotometrically for domperidone content at 284 nm. All solubility measurement was performed in triplicate.

Preparation of solid dispersion

Melt method was used to prepare solid dispersions of domperidone with PEG 6000 containing 3 different weight ratio (1:1, 1:3, and 1:5). Domperidone and PEG 6000 were weighed according to these weighed ratios. PEG 6000 was melted at 60⁰C. In this melted PEG 6000, domperidone was added. It was mixed well and flashed cooled on an ice bath and then stored over night in a dessicator. The prepared solid dispersion was then grounded by using a mortar and pestle, sieved through a mesh 40 and stored over a fused calcium chloride in a dessicator for further use [10-11].

Differential Scanning Calorimetry (DSC)

DSC analysis was performed using Netzsch DSC 204, Tokyo, Japan. The sample were heated in a sealed aluminium pans at a rate of 10⁰ C per min in a 30 to 300⁰ C temperature under nitrogen flow of 40 ml/min.

Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectra were obtained on Shimadzu FTIR Model 8400-S spectrometer. The Spectra was recorded as a dispersion of the sample in Potassium Bromide in IR disk (2 mg sample in 200 mg KBr) with the scanning range of 400 to 4000 cm⁻¹ and the resolution was 1 cm⁻¹.

Scanning electron microscopy (SEM)

The morphology of domperidone- PEG 6000 system was investigated by means of ESEM TMP with EDAX (Philips, Holland). Samples were prviously sputter-coated with a gold layer in order to make them conductive. Pictures were taken at an excitation voltage of 30 kv and a magnification of 1500x

Preparation of tablets by effervescent method

Different domperidone fast dissolving tablets were prepared according to the proportion given (Table 1). All the raw material were passed through a screen (40 mesh) prior to mixing. Powdered 1:5 solid dispersion, containing amount equivelent to 10 mg of domperidone, was mixed with the other excipients. Sodium bicarbonate and anhydrous citric acid were preheated at a temperature of 80⁰ to remove absorbed/ residual moister and were thoroughly mixed in a mortar to get a unofrom powder and then mixed with other ingredients. The blend thus obtained was directly compressed on a 10 station mini press tablet machine (CPMD 3-10, Chamunda Pharma Machinery Pvt. Ltd., Ahmedabad, India.) equipped with 9 mm concave punch.

Evaluation of tablet properties

Technological charecterization of tablets including hardness, friability, In-vitro dispersion time, wetting time, weight and drug content is shown in (Table 2)

The hardness of the tablets was measured using a Pfizer hardness tester (Sheetal Scientific Industries, Mumbai, India). The limits for crushing strength of the tablets was kept in range of 3-4 kp.

The friability of the tablets was measured using a Roche Friabilator (Electrolab, Ahmedabad, India). Twenty pre weighed tablets were rotaeted for 4 min at 25 rpm. The tablets were then weighed again, and the percentage of weight loss was calculatedthe limit of the percent friability was kept below 1%.

In-vitro dispersion tiem was determined by placing one tablet in a beaker containing 10 ml of pH 6.8 phosphate buffer at 37⁰ ± 0.5⁰C and the time required for complete dispersion was determined [12].

Drug content was detrmind by weighing randomly selected tablets, pulverizing to a fine powder. The weight equivalent to 10 mg domperidone was weighed and dissolved in 5 ml of methanol in volumetric flask using magnetic stirrer, the volume was adjusted to 100 ml with phosphate buffer (pH 6.8) and the solution was filtered. An aliquot of 1.0 ml of solution were diluted to 10 ml phosphate buffer (pH 6.8) in separate volumetric flask. The content in was determined spectrophotometrically at 284 nm.

Table-1. Composition of domperidone fast dissolving tablets

Ingredients	EP0	EP1	EP2	EP3	EP4	EP5	EP6	EP7	EP8	EP9
SD	60	60	60	60	60	60	60	60	60	60
Sodium bicarbonate	-	12	24	36	12	24	36	12	24	36
Citric acid	-	6	12	18	6	12	18	6	12	18
Ac-Di-Sol	-	4	4	4	8	8	8	12	12	12
Mannitol	133	111	93	75	107	89	71	103	85	67
Saccharine sodium	3	3	3	3	3	3	3	3	3	3
Mint flavor	2	2	2	2	2	2	2	2	2	2
Magnesium stearate	2	2	2	2	2	2	2	2	2	2

In- Vitro Drug Release

Dissolution studies of domperidone from tablets were performed according to the method described in USP XXIV, using USP II apparatus (paddle method). The dissolution test was performed using 900 ml phosphate buffer pH 6.8, at $37^{\circ} \pm 0.5^{\circ} \text{C}$ and 50 rpm. Aliquots (5 ml) was removed from the dissolution medium at specific time intervals and was replenished immediately with same volume of fresh medium, the amount of released domperidone was determined by UV analysis at 284 nm. It was found that PEG 6000 did not interfere with the assay at this wavelength. The results presented are mean values of three determinations.

Stability study for Representative sample (EP9) were carried out at $25 \pm 2^{\circ} \text{C} / 60 \pm 5\% \text{RH}$, and $40 \pm 2^{\circ} \text{C} / 75 \pm 5\% \text{RH}$ for 6 months. The effect on various tablet properties such as disintegration time, Friability and hardness was measured. The data were analyzed by one way analysis of variance (ANOVA). A value of $P < 0.05$ was considered as significant.

RESULT AND DISCUSSION

Phase solubility study

The solubility of domperidone in distilled water is found to be 5.35 $\mu\text{g}/\text{ml}$. The influence of the PEG 6000 upon the solubility of Domperidone is presented in (Figure 1). The increase in the solubility was linear ($r^2 = 0.997$) with respect to the weight fraction of the carrier. At 9% of PEG 6000 the increase in the solubility was ~ 10 fold compare with the pure drug.

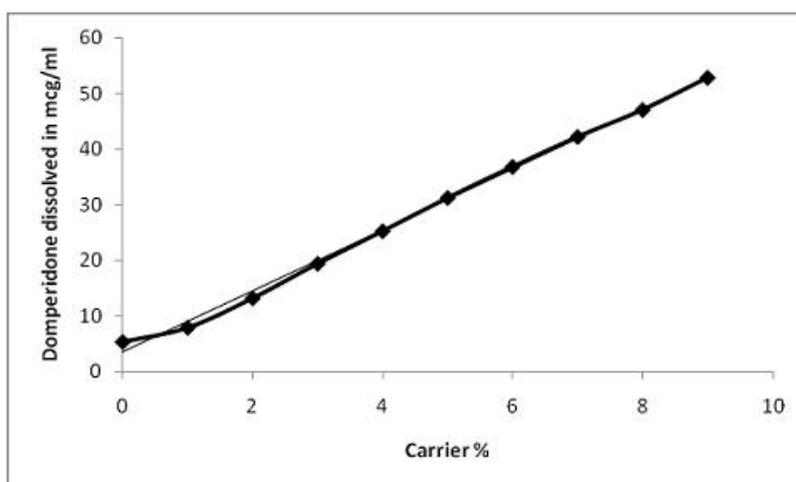


Figure 1-Phase solubility study in distilled water at $37^{\circ} \text{C} \pm 2^{\circ} \text{C}$

The increase in the solubility with increase in PEG 6000 concentration indicates the solvent properties of PEG 6000 for the drug. This feature suggests the A_L - type phase solubility phase

diagram. The increase in the solubility in the presence of PEG 6000 can probably be explained by increased wettability of domperidone. Indeed, PEG 6000 causes a decrease of the interfacial tension between the drug and the dissolution medium.

Solid state studies

The FTIR spectra of domperidone, PEG 6000 and its binary system (1:5) with PEG 6000 are presented in (Figure 2a, 2b and 2c). Pure drug shows sharp characteristic peaks at 2930 cm^{-1} , 1697 cm^{-1} , 1359 cm^{-1} . All the above characteristic peaks appear in the spectra of binary system were independent of the preparation method and there is no significant shift or reduction in intensity of peaks of domperidone was observed.

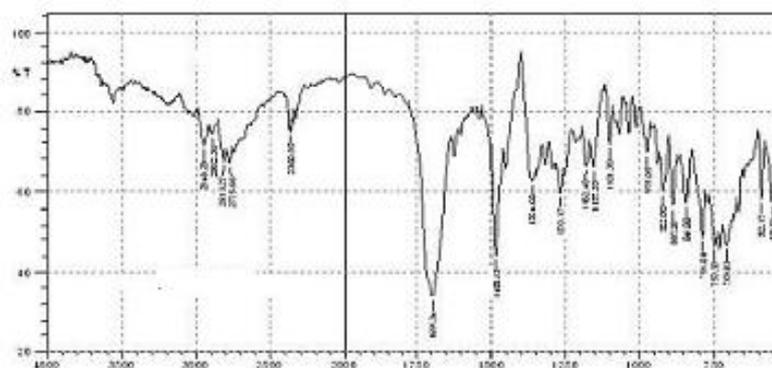


Figure 2a- FTIR spectroscopy of pure domperidone

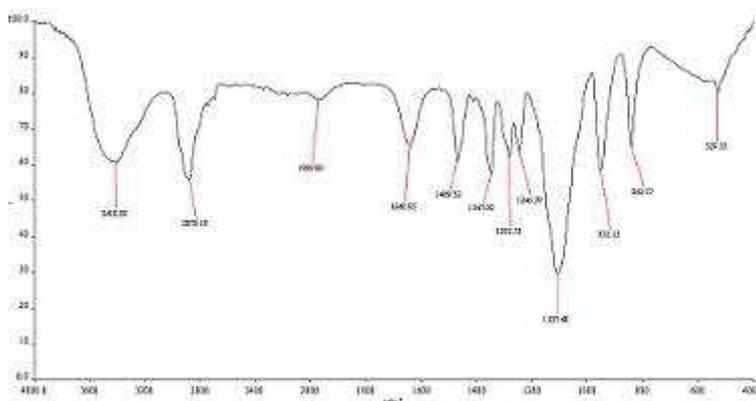


Figure 2b- FTIR spectroscopy of PEG 6000

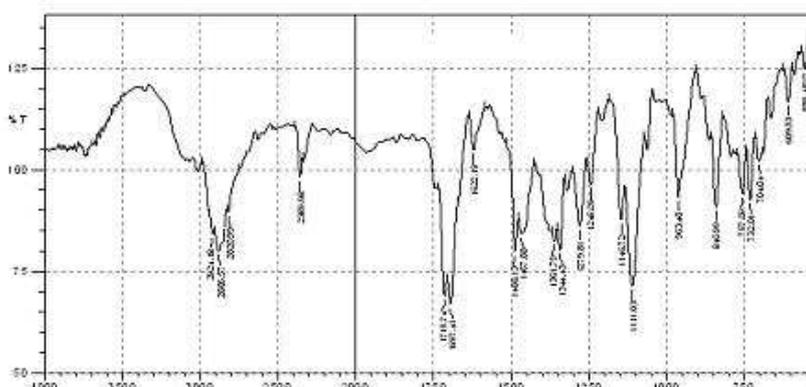


Figure 2c- FTIR spectroscopy of drug/PEG 6000 solid dispersion in ratio of 1:5

Thermal behavior of pure drug, polymer and drug carrier systems are depicted in (Figure 3a, 3b and 3c). Thermal profile of pure drug exhibited a single endothermic effect corresponding to the

melting of domperidone ($T_{\text{fus}} 250.71^{\circ}$, $\Delta H_{\text{fus}} 122.65 \text{ J/g}$) or PEG 6000 ($T_{\text{fus}} 65.14^{\circ}$, $\Delta H_{\text{fus}} 186.5 \text{ J/g}$) respectively. The DSC curve of solid dispersion shown progressive broadening and lowering of drug melting temperature and concomitant reduction of its enthalpy with increasing in carrier content in mixture until total disappearance of drug melting endotherm. This finding could be considered indicative of drug amorphization as a consequence of interaction between components [13]. It also shows the progressive drug dissolution in the melted carrier before achieving its melting carrier, as was previously observed for other the drug-PEG combination [14-15].

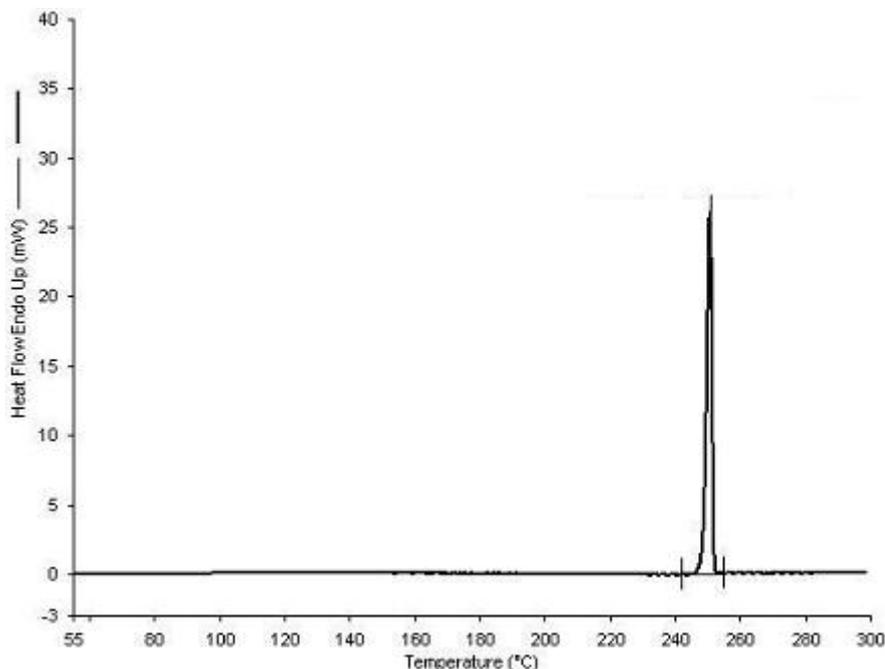


Figure 3a- Differential Scanning Calorimetry of pure domperidone

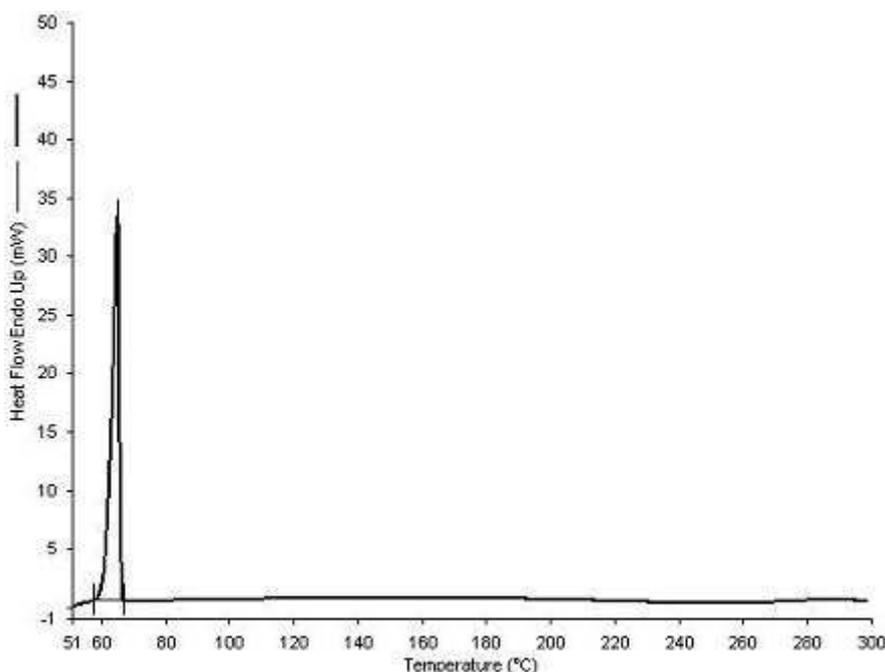


Figure 3b- Differential Scanning Calorimetry of PEG 6000

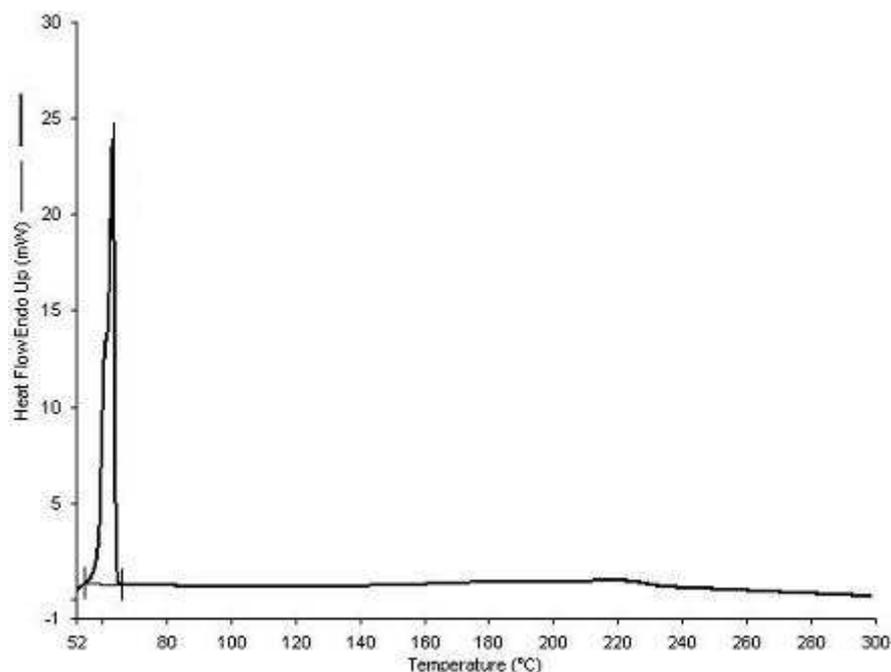


Figure 3c- Differential Scanning Calorimetry of drug/PEG 6000 solid dispersion in ratio of 1:5
(Figure 4a, 4b and 4c) shows SEM images of the pure component and SD system. PEG 6000 (Figure 4b) existed in a crystalline mixture of smooth-surfaced particle with smaller particle, while domperidone (Figure 4a) existed in small irregular particle. On the contrary, SD (1:5) (Figure 4c) consisted of more spherical particles of rather irregular surface. In the case of SD (1:5), at the high polymer ratio, particles presented a surface morphology similar to that of pure PEG 6000. In these monograph, it is impossible to distinguish the presence of domperidone crystals among the PEG particles. The novel arrangement between domperidone and PEG

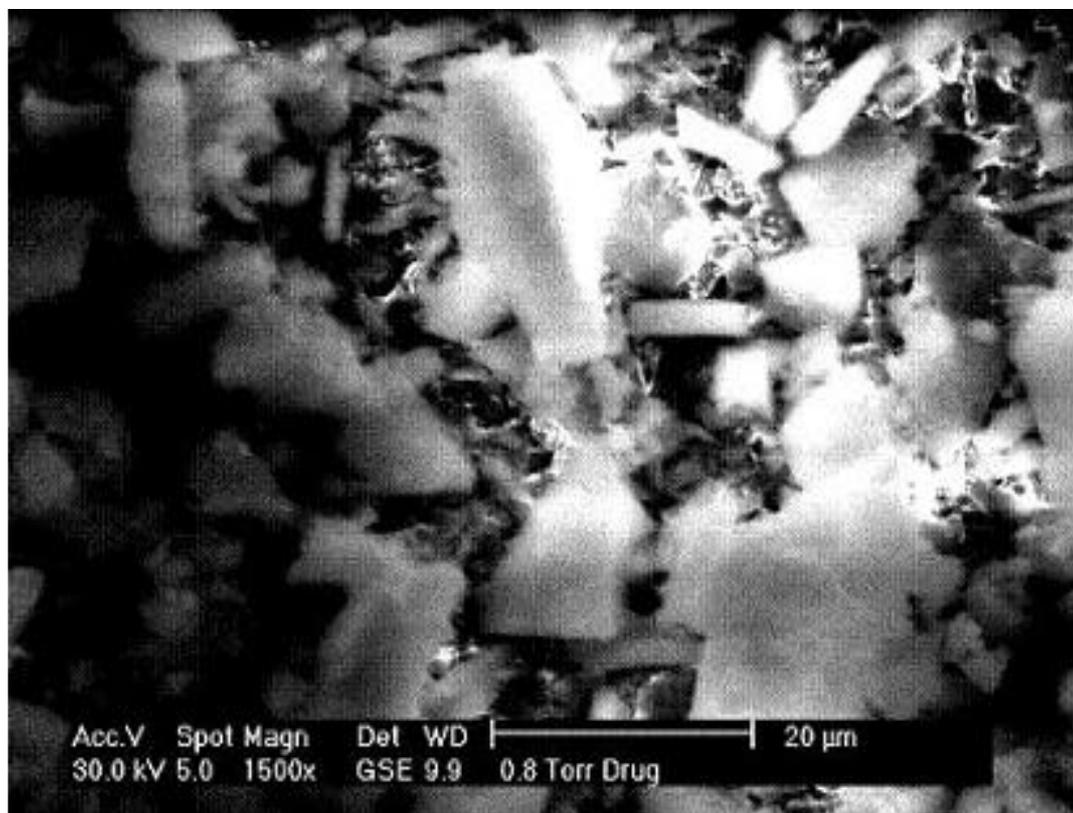


Figure 4a- Scanning Electron Microscopy of pure domperidone



Figure 4b- Scanning Electron Microscopy of PEG 6000

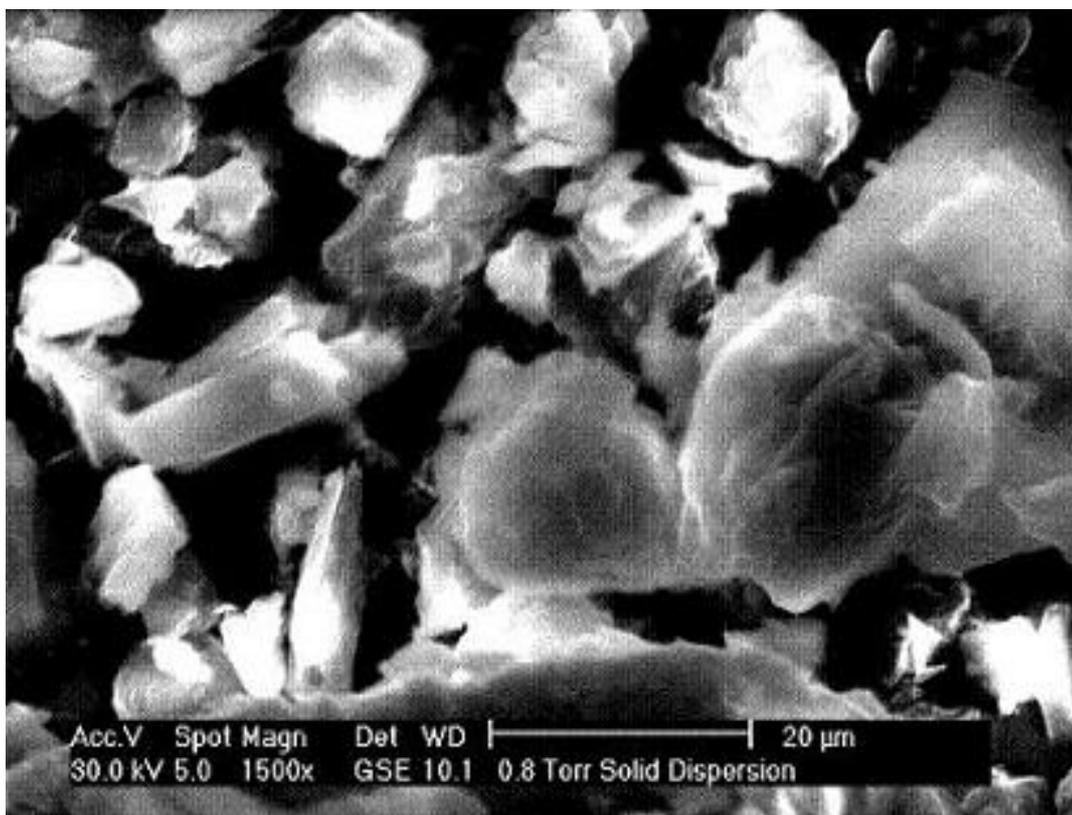


Figure 4c- Scanning Electron Microscopy of drug/PEG 6000 solid dispersion in ratio of 1:5
Particles might be responsible for the enhance drug dissolution rate found for SD system, in comparison with the pure domperidone. To our knowledge, we are the first to attempt to characterize the morphology of domperidone: PEG 6000 system.

Evaluation of tablet properties

The friability, hardness, disintegration time, wetting time, drug content and weight of formulated tablets are described in (Table 2). Hardness of all the formulation was in range of 3.3 -3.5 kg/cm². Friability of all the formulation was below 1% indicates that the tablets had good mechanical resistance. Drug content was found to be in range of 100-103%. The weight variation results revealed that average % deviation of 20 tablets of each formulation was less than $\pm 7.5\%$, which provide good uniformity in all formulations.

In-vitro dispersion time for the fast dissolving tablets, prepared with Ac-Di-Sol (6%) and mixture of sodium bicarbonate (18%) and citric acid (6%) was found to be 31 seconds, while disintegration time of control formulation EP0 was found to be 112 seconds. Ac-Di-Sol is a 'superdisintegrant' of excellent disintegration ability. It swells to a great extent when in contact with water, by a water wicking mechanism; this may be the possible reason for decrease in the disintegration time with Ac-Di-Sol (6%). Results obtained revealed that the In-vitro dispersion time is strongly dependent on the concentration of superdisintegrants and effervescent material. As the concentration of both Ac-Di-Sol and mixture of sodium bicarbonate and citric acid increases, In-vitro dispersion time decreases.

Table-2. Technological characterization of domperidone fast dissolving tablets

Formulation ^a	In-vitro dispersion time (seconds)	Wetting time (seconds)	Hardness (kg/cm ²)	Friability (%)	Drug content (%)	Weight (mg)
EP0	112 (1.8)	108 (1.9)	3.5 (1.0)	0.43 (0.7)	100.4 (1.2)	202 (1.1)
EP1	53 (1.2)	51 (1.2)	3.3 (0.2)	0.51 (0.2)	101.2 (1.0)	200 (2.6)
EP2	50 (0.8)	46 (1.1)	3.3 (0.8)	0.46 (0.5)	100.5 (0.8)	198 (1.5)
EP3	46 (1.1)	42 (1.0)	3.4 (0.6)	0.43 (0.4)	103.2 (0.6)	204 (1.1)
EP4	44 (1.3)	41 (1.4)	3.5 (0.1)	0.53 (1.1)	102.2 (1.0)	201 (1.4)
EP5	42 (1.6)	39 (1.1)	3.4 (0.4)	0.49 (0.9)	101.3 (1.2)	201 (1.6)
EP6	40 (0.6)	36 (1.2)	3.5 (0.5)	0.42 (0.2)	103.2 (2.0)	202 (1.3)
EP7	38 (1.4)	34 (1.3)	3.4 (0.7)	0.54 (0.8)	103.2 (0.4)	202 (1.1)
EP8	35 (1.0)	31 (1.0)	3.5 (0.5)	0.43 (0.7)	102.5 (0.5)	200 (1.0)
EP9	31 (2.7)	28 (1.23)	3.5 (0.6)	0.40 (1.0)	102.4 (0.6)	201 (1.4)

^a mean \pm SD (n=3)

In vitro drug release from all the formulations containing domperidone PEG 6000(1:5) solid dispersion and effervescent material were more than 81% in 5 min. In-vitro drug release profile of formulation EP9 was more than 88% in 5 min compared with marketed tablet 58% in 30 min. (Figure 5), revealed that formulation of tablet using solid dispersion with PEG 6000 increased the dissolution of drug.

The result of stability testing indicate that there is no significant change in disintegration time, friability and hardness at $25 \pm 2^{\circ}$ C/ $60 \pm 5\%$ RH, and $40 \pm 2^{\circ}$ C/ $75 \pm 5\%$ RH was observed.

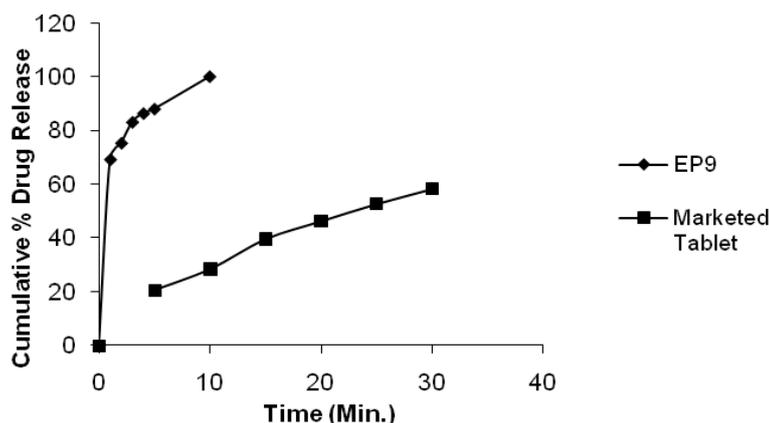


Figure 5- Comparison of In-vitro drug release profile of EP9 and Marketed tablet

CONCLUSION

Fast dissolving tablet of domperidone can be prepared by effervescent method using solid dispersion of drug instead of drug as such. Proper selection of drug/carrier ratio and tablet additives can provide rapid tablet disintegration and release of the drug. The present study showed the suitability of PEG 6000 as a carrier for the preparation of domperidone solid dispersions. As demonstrated by both DSC and SEM, the amorphization of domperidone offered an explanation of better dissolution rate from its solid dispersions. In the present study, use of solid dispersion containing domperidone/PEG 6000 (1:5), Ac-Di-Sol 6% and mixture of sodium bicarbonate(18%) and citric acid(6%) in the tablets disintegrates in 31 seconds, and released 88% drug in 5 min. It's therefore proposed that such tablets could be used in the emergency treatment of emesis.

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