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Full Length Original Research Paper

Multi-Approach preparation of solid dispersions for improving dissolution rate of Domperidone Maleate using different ratios of Polymers

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Abstract:

Purpose: The Purpose of the present study was to investigate the possibility of improving the dissolution rate of water insoluble antiemetic drug Domperidone maleate with two different polymers viz. PEG 6000, PVP K25 at different ratios by using various solid dispersion methods.

Methods: Solid dispersions of Domperidone maleate were prepared using different ratios of PEG 6000, PVP K25 as carrier by using solvent evaporation method, fusion method and solvent melt method.

Results: The prepared solid dispersions were characterized for their drug content, in-vitro solubility, in-vitro dissolution studies, FTIR spectroscopy and DSC were performed to identify physiochemical interaction between the drug and carrier and its effect on dissolution behavior. The prepared formulations showed marked improvement in the solubility and dissolution rate of drug which may be due to decrease in crystallinity of drug and additives. Formulation A4 with 1:4:1 of DOM: PEG6000: PVP K25 gave fast dissolution rate 92.56% of drug when compared to other formulations prepared by different methods at different ratios of pure drug and carriers.

Conclusion: The prepared solid dispersion of the Domperidone maleate with PEG and PVP can improve the dissolution rate of the drug (formulation A4 containing 1:4:1). And it can be concluded the solvent evaporation method shows better results compared to fusion method and Solvent Melt method. The solubility and dissolution improvement order is found to be solid evaporation method>Solvent Melt method> fusion method.

Keywords: Domperidone maleate, Solubility, Solid dispersion, evaporation method, fusion method, Solvent Melt method, PEG 6000, PVP K25.

Introduction

The enhancement of oral bioavailability of poor water soluble drugs remains one of the most challenging aspects of drug development. Bioavailability can be defined as rate and extent at which the drug is delivered to the systemic circulation from dosage form and reaches the site of action to produce the desired effect. Hence for drug whose aqueous solubility is less will definitely create bioavailability problem and thereby effecting therapeutic efficiency, once if we are able to increase the aqueous solubility of a drug, the disintegration and dissolution properties can be easily altered, as a result, an increase in bioavailability can be easily achieved [1,2].

According to biopharmaceutical classification system (BCS), Domperidone maleate is classified under class-II (poor solubility and high permeability). It thus provides an excellent safety profile for long-term administration orally in the recommended doses [3].

Domperidone maleate, a dopamine D2 receptor antagonist, is used as a prokinetic and antiemetic agent for the treatment of gastro paresis, nausea and vomiting. Domperidone maleate has low

absorbability after oral administration and undergoes extensive first pass metabolism. The poor aqueous solubility may be one possible reason for its low bioavailability (13-17%) [4, 5].

Many methods are available to improve dissolution rate, solubility characteristics, including salt formation, micronization, complexation, prodrug, addition of solvent or surface active agents and solid dispersions (SD). SD's 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 drug [3].

Solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. Transformation of crystalline drug to amorphous drug upon solid dispersion formulation increases the dissolution rate [3].

Solid dispersion techniques have been used to increase the solubility of a poorly water soluble drug [3]. Solid dispersion is a viable and economic method to enhance bioavailability of poorly water soluble drug and also it overcomes the limitations of previous approaches.

Drug dissolution, absorption, drug bioavailability and clinical effect were observed to be significantly greater than conventional dosage form by preparing solid dispersion mathod. The prepared material used in the preparation of orodispersible tablets and mouth dissolving films etc [4].

The objective of this study is to improve the solubility and dissolution rate of poorly water soluble drug Domperidone maleate by preparing Solid dispersion with PEG 6000 and PVP K25 as carriers. The prepared Solid dispersions were evaluated for solubility and in-vitro dissolution rate studies and absence of any interaction between the drug and polymer was confirmed using FTIR spectral studies and DSC [3].

Bio-pharmaceutics classification system for drugs[3]

Solubility	Permeability	Absorption pattern
High	High	Well absorbed
Low	High	Variable
High	Low	Variable
Low	Low	Poorly absorbed

MATERIALS AND METHODS

Materials

Domperidone maleate a gift sample from the Lupin Pharmaceutical Pvt Ltd, India. PEG 6000 and PVP K 25 were procured from commercial sources. All other chemicals procured were of analytical reagent grade.

Methods

Preformulation study for drug-excipient compatability

The spectrum analysis of pure drug, polymer and physical mixtures of drug and different excipients used for preparation of Solid Dispersions was studied by FTIR. Spectra were recorded by preparing drug potassium bromide (KBr) discs using a Shimadzu Corporation (Koyto, Japan) facility (model - 8400S). The resultant disc was mounted in IR spectrophotometer and the spectrum was recorded from 4000 cm-1 to 500 cm-1 for 12 minutes [4].

Preparation of Solid Dispersions

Solvent Evaporation Method: The physical mixture of the drug and two different water soluble carriers with different concentrations are dissolved in different beakers containing common solvent

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and the resulting clear solution is rapidly heated for evaporating the solvent to get a glassy solid mass (Table 1). Briefly, the water soluble polymer was dissolved in 20% ethanol under stirring, until a clear solution was obtained; Domperidone maleate was then added and stirring was continued for 45 min. The organic solvent was removed by evaporation on a water bath at 60°C. The resultant solid dispersions were stored in desiccators until constant mass was obtained, pulverized and passed through sieve No. 22 [5]. **Fig.1**

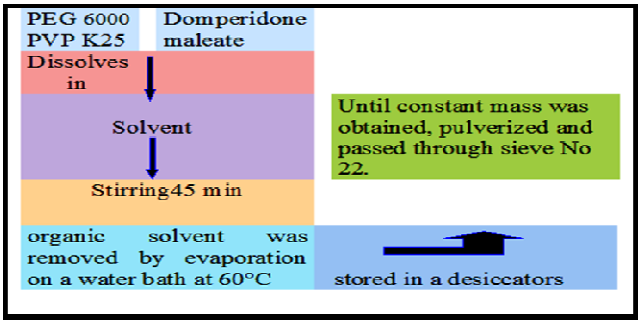

FIG. 1: Flow Chart of Solvent Evaporation Method

Fusion Method: The polymer PEG 6000 and PVP K25were melted at 60°C and then the drug was added, mixed well and cooled in an ice bath to obtain a solid mass (Table 1). The solidified mass was crushed and passed through a sieve No. 22. The resulting solid dispersion was stored in desiccators until used [5] **Fig. 2**.

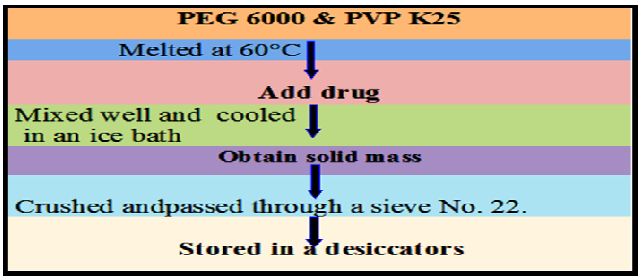

FIG. 2: Flow Chart of Fusion Method

Solvent Melt Method: Solid dispersions of drug with PEG 6000 and PVPK25 were prepared by melt-solvent method (Table 1). In this method, drug was dissolved in methanol and the solution was incorporated into the melt of PEG 6000 and PVPK25at 165°, by pouring into it. It was then kept in an ice bath for sudden cooling. The mass was kept in the desiccators for complete drying. The solidified mass was scrapped, crushed, pulverized and passed through sieve No. 22 [5] **Fig.3**.

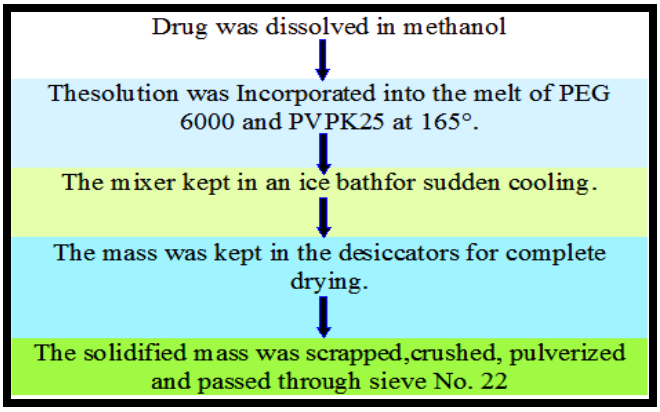

FIG. 3: FLOW CHART OF SOLVENT MELT METHOD

TABLE 1: SOLID DISPERSION FORMULATIONS WITH DIFFERENT CARRIER RATIOS

Ratios (dom.maleate:peg 6000:pvpk25)	Solvent Evaporation	Fusion Method	Solvent Melt Method
1:1:1	A1	B1	C1
1:2:1	A2	B2	C2
1:3:1	A3	B3	C3
1:4:1	A4	B4	C4
1:5:1	A5	B5	C5

Calibration curve for domperidone maleate:

UV Spectrum: Form stock solution in 6.8 phosphate buffer, serial dilutions were done get a concentration of 10µg/ml. UV scan range was taken between the wavelengths 200-400 nm. λ_{max} was observed at 287 nm. Calibration Curve in 6.8 phosphate buffer solutions was plotted with concentrations of 2, 4, 6, 8, and 10µg/ml. Absorbance of these solutions was measured against a blank of 6.8 phosphate buffers at 287 nm **Fig.4**.

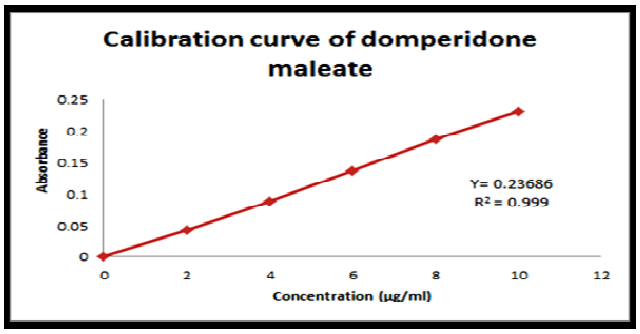

FIG. 4: CALIBRATION CURVE OF DOMPERIDONE MALEATE.

Evaluation tests

Determination of Melting Point

The melting point of Domperidone maleate and formulations was determined by capillary tube method. A small quantity of powder was placed into a capillary tube and the tube was placed in the capillary melting apparatus and the temperature was gradually increased automatically. The temperature at which powder started to melt and the temperature when all the powder gets melted were observed [7].

% Solubility Study

The Solubility of domperidone maleate was carried out by adding an amount of the prepared formulas equivalent to 5 mg of the drug to 10 ml of 6.8 phosphate buffer solutions in conical flask covered with foil and shacked at 37°C for 1 hr. The samples were filtered, properly diluted and analyzed spectrophotometrically at 287 nm to measure the amount of dissolved domperidone maleate [1, 8].

Determination of percent yield

The percent yield of domperidone maleate solid dispersions can be determined by using the following expression [9, 10].

Percent yield = (weight of prepared solid dispersion / weight of drug + carriers) x 100

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 10 mg of domperidone maleate was transferred to a 100 ml volumetric flask containing 20 ml of Dimethylformamide (DMF) and dissolved. The solution was filtered through 0.45µm membrane filter paper. One ml of thissolution was diluted 100 times with same solvent Dimethylformamide (DMF): distilled water (20:80) and the absorbance was measured at 287 nm [11].

Dissolution studies

The dissolution of domperidone maleate from these elected formulas and the corresponding physical mixtures as well as the drug alone were studied using the U.S.P 25 dissolution apparatus II (paddle type). Accurately weighed amounts equivalent to 10 mg of domperidone maleate were dispersed in 500 ml of the dissolution medium (phosphate buffer pH 6.8) at 37±0.5°Cstirred at 100 rpm. At appropriate time intervals, samples (5 ml) were withdrawn over a period of 1 hour and replaced by an equal volume of fresh buffer. The samples were filtered and the drug content was determined spectrophotometrically at 287 nm, all experiments were carried out in triplicate [12]. And the results presented in table no 7.

RESULTS AND DISCUSSION

FT-Infra Red and DSC Studies for Drug-Excipient Compatibility

DSC spectra for Domperidone maleate and all the solid dispersions of different preparation method show that there was no interaction between them

In comparison with pure drug the absorption peak of the FT-IR spectra for Domperidone maleate

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showed no significant shift and no disappearance of characteristic peaks in all the preparations of different methods suggesting that there is no interaction between drug and polymers or no degradation in Domperidone maleate molecule **Fig. 5-6, 7-8**.The differences in transmittance may be due to varied concentration of drug.

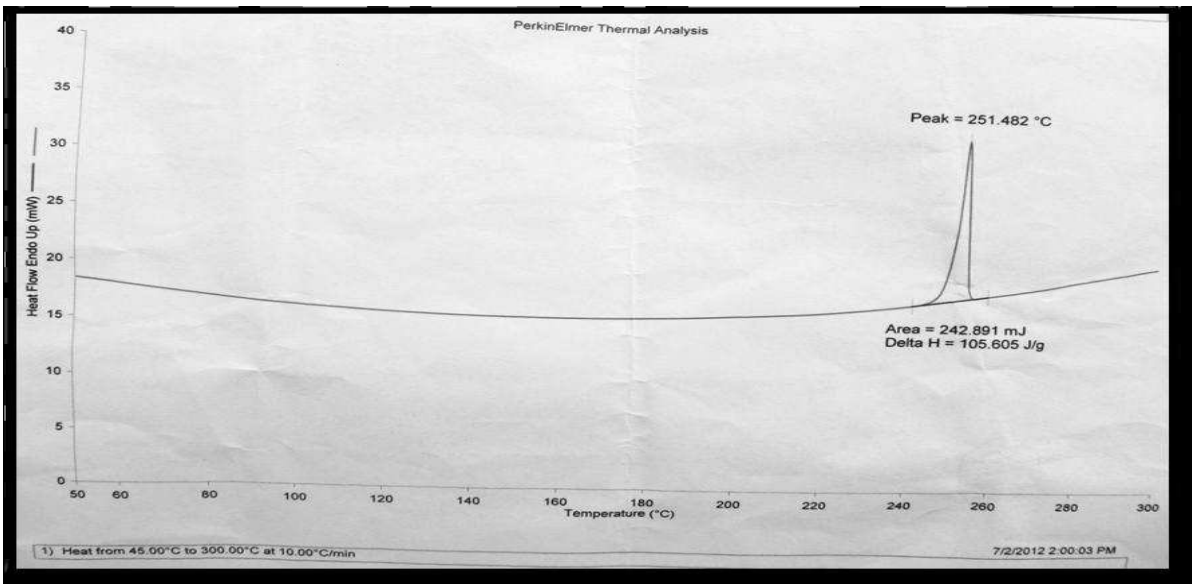

FIG.5: DSC CURVE OF PURE DOMPERIDONE MALEATE

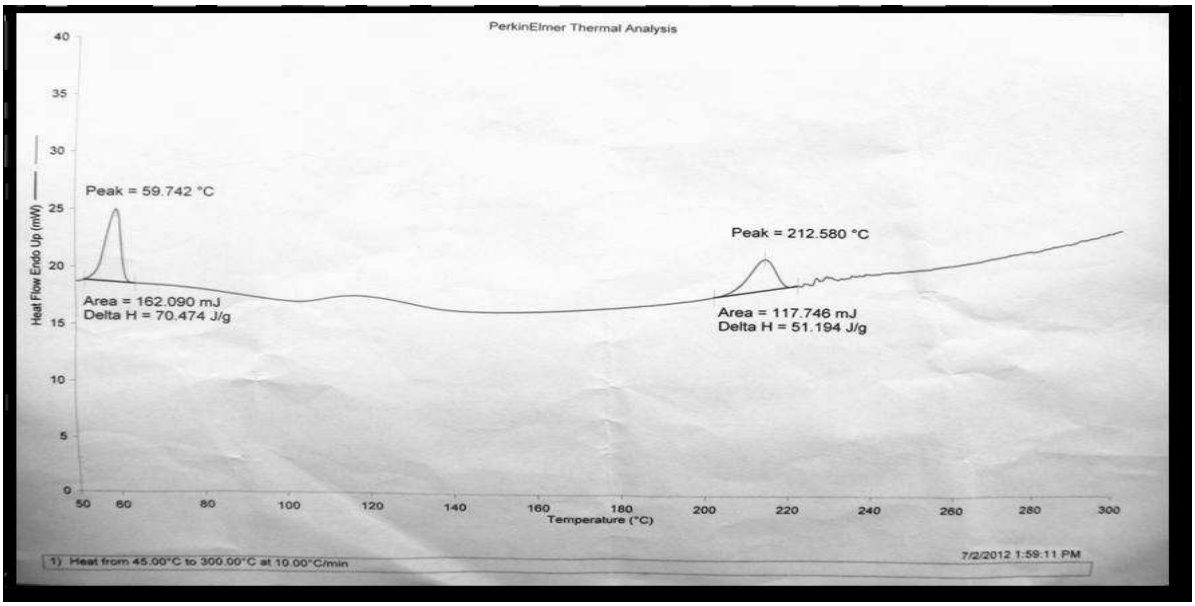

FIG. 6: DSC CURVE OF DOMPERIDONE MALEATE + PEG 6000+ PVP K25 (1:4:1)

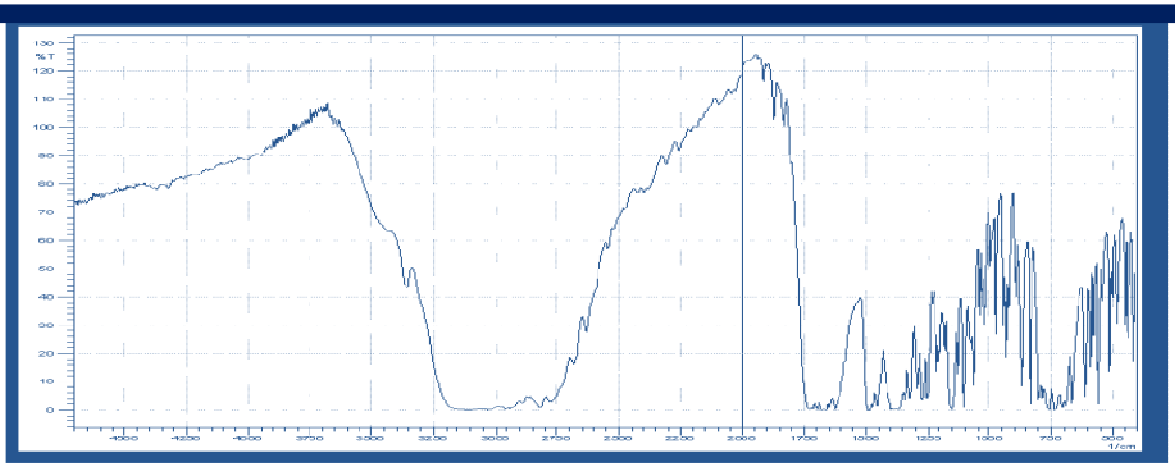

FIG.7: FTIR SPECTRA OF PURE DRUG (DOMPERIDONE)

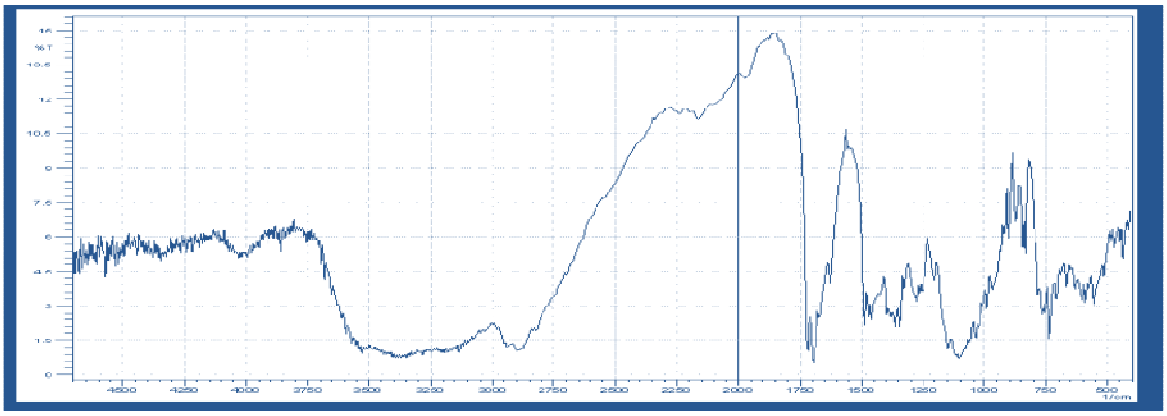

FIG. 8: FTIR SPECTRA OF DOMPERIDONE + PEG 6000 + PVP K25 (1:4:1)

Percentage Yield

The percent yield of Domperidone maleate solid dispersions ranged between 96 to 98%.The results are shown in (Table 2- 4) **Fig.9**

Drug content

The drug content of the solid dispersions was found to be between 95.93 and 98.93% (Table 2-4). **Fig.9**

Determination of Melting Point

Domperidone maleate is a white, crystalline odour less powder. Melting point the drugs was determined by using melting Point determination apparatus, the melting point range was between 240 -242^{0}C.The results of melting points of various solid dispersions are shown in (Table 2- 4), **Fig.9**

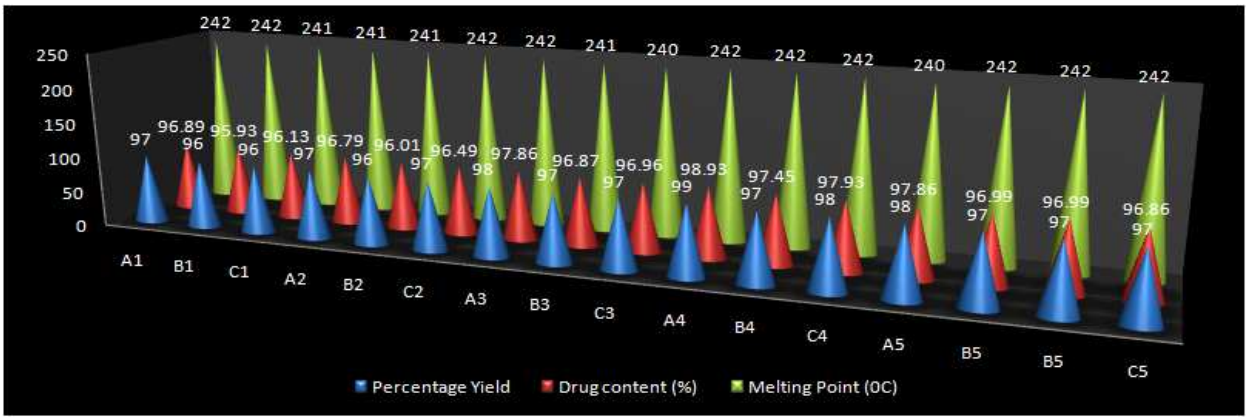

FIG. 9: COMPARISONS OF EVALUATION TESTS

TABLE 2: EVALUATION TESTS OF FORMULATIONS PREPARED BY SOLVENT EVAPORATIONS METHOD

Ratios (dom.maleate:peg6000:pvpk25)	Solvent Evaporation	Percentage Yield	Melting Point (⁰C)	Drug content (%)
1:1:1	A1	97	242	96.89
1:2:1	A2	97	241	96.79
1:3:1	A3	98	242	97.86
1:4:1	A4	99	242	98.93
1:5:1	A5	98	240	97.86

TABLE 3: EVALUATION TESTS OF FORMULATIONS PREPARED BY FUSION METHOD

Ratios (dom.maleate:peg6000:pvpk25)	Fusion Method	Percentage Yield	Melting Point (⁰C)	Drug content
1:1:1	B1	96	242	95.93
1:2:1	B2	96	241	96.01
1:3:1	B3	97	241	96.87
1:4:1	B4	97	242	97.45
1:5:1	B5	97	242	96.99

TABLE 4: EVALUATION TESTS OF FORMULATIONS PREPARED BY SOLVENT MELT METHOD

Ratios (dom.maleate:peg6000:pvpk25)	Solvent Melt Method	Percentage Yield	Melting Point (⁰C)	Drug content
1:1:1	C1	96	241	96.13
1:2:1	C2	97	242	96.49
1:3:1	C3	97	240	96.96
1:4:1	C4	98	242	97.93
1:5:1	C5	97	242	96.86

Solubility studies

The solubility of Domperidone maleate in 6.8 phosphate buffer solutions is 32.52 µg/ml. The results show more solubility of solid dispersions compared to pure drug in 6.8 phosphate buffer solutions that might be due to formation of complexes between drug, PEG 600 and PVPK 25. Formulations prepared by solvent evaporation method A1 to A5show more solubility compared to solid dispersions prepared by other methods. In this formulations A4containingdrug: PEG 6000:PVPK25 at ratio1:4:1shows more solubility. The solubility of formula A4 is 92.91µg/ml. The results are shown in (Table 5) **Fig.10**.

TABLE 5: SOLUBILITY STUDIES

S. No	Formula code	Solubility studies (µg/ml)
1	Pure drug	32.52
2	A1	62.00
3	A2	70.60
4	A3	83.84
5	A4	92.91
6	A5	85.89
7	B1	60.82
8	B2	65.02
9	B3	78.36
10	B4	87.23
11	B5	80.56
12	C1	61.95
13	C2	67.23
14	C3	80.56
15	C4	88.84
16	C5	81.88

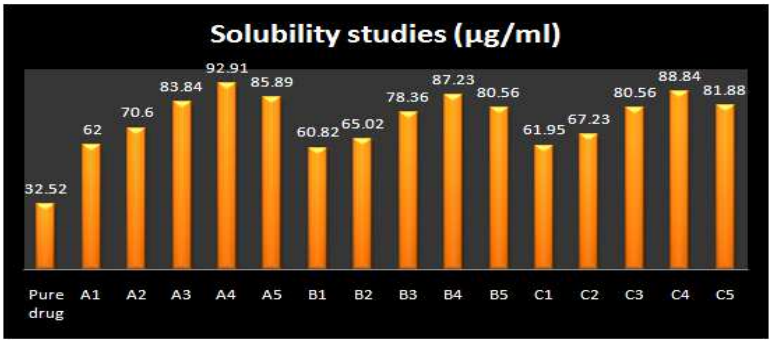

FIG. 10: SOLUBILITY COMPARISON OF ALL FORMULATIONS

Dissolution Studies

From the *In-vitro* study, it can be clearly observed that the dissolution rate of pure drug was low i.e., 30.10% of drug dissolved in 60 min. There was marked increase in the dissolution rate of Domperidone maleate from all the solid dispersions when compared to pure Domperidone maleate itself. Among the three solid dispersion preparation methods, highest dissolution was observed in solid dispersions prepared by the solvent evaporation method. The results are shown in table 6-.The increased dissolution rate may be attributed to the increased drug wet ability, decreased particle size, conversion to amorphous form and solubilization of the drug due to hydrophilic carrier. The formulation (A4) 1:4:1 of DOM: PEG: PVP gives fast dissolution rate 85.77% of drug in pH 6.8 Phosphate media as compared to all other formulations and pure drug in one hour. The order of efficiencies of products based on percentage drug release after 60 minutes is A4> C4> B4> A5> C5> B5> A3> C3> B3> A2> C2> B2> A1> C1> B1> Pure drug. **Fig. 11-14**.

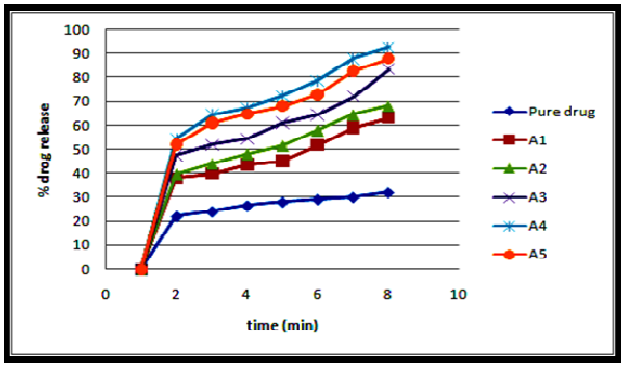

FIG. 11: DISSOLUTION PROFILE OF SOLVENT EVOPARATION MATHOD

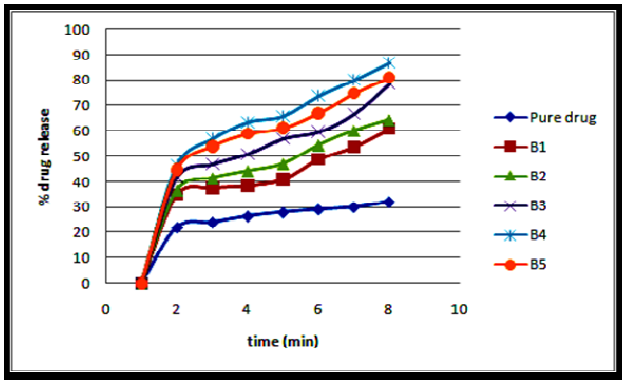

FIG.12: DISSOLUTION PROFILE OF FUSION MATHOD

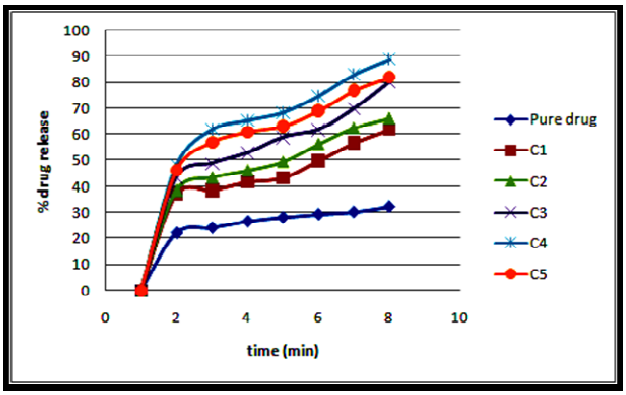

FIG. 13: DISSOLUTION PROFILE OF SOLVENT MELT METHOD

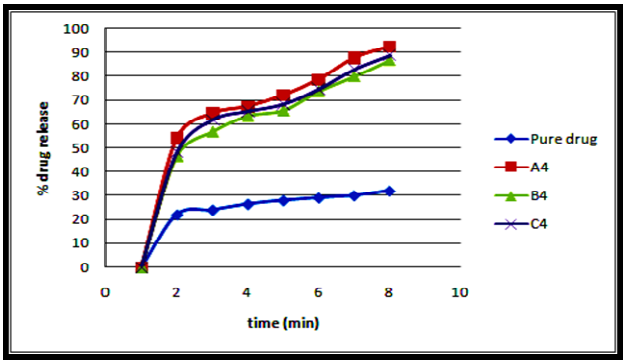

FIG. 14: DISSOLUTION PROFILE OF PURE DRUG, A4, B4, C4

TABLE 6: DISSOLUTION PROFILE OF ALL FORMULATIONS

S. No	Formula code	% of Drug dissolution from different domperidone Formulations							
		0min	5 min	10 min	20 min	30 min	40 min	50 min	60 min
1	Pure drug	0	22.01	24	26.44	27.96	29.1	30	32.01
2	A1	0	38.01	39.89	43.58	45.1	51.72	58.98	62.99
3	A2	0	39.65	43.98	48.13	51.52	58.12	64.63	68.32
4	A3	0	47.55	51.89	54.27	60.96	64.28	71.97	83.26
5	A4	0	54.23	64.56	67.47	72.2	78.84	87.89	92.56
6	A5	0	52.12	60.89	64.74	68.01	72.89	82.78	87.79
7	B1	0	35.90	36.60	38.50	40.97	48.82	53.78	60.79
8	B2	0	36.65	41.48	44.23	47.02	54.46	60.13	64.32
9	B3	0	41.65	46.89	50.97	56.96	59.68	66.67	78.66
10	B4	0	46.63	56.86	63.47	65.82	73.84	80.09	86.86
11	B5	0	44.82	53.97	58.84	61.11	66.89	74.78	80.96
12	C1	0	37	38.6	41.58	43.21	49.82	56.78	61.79
13	C2	0	38.65	43.48	46.13	49.52	56.42	62.63	66.32
14	C3	0	43.52	48.87	52.97	58.96	61.88	69.97	80.26
15	C4	0	48.23	61.86	65.47	68.42	74.84	83.09	88.86
16	C5	0	46.12	56.97	60.74	63.11	68.89	76.78	81.89

Conclusion

Development of Domperidone maleate prepared with PEG 6000 and PVP K25 showed high percentage yield and drug content in solid all dispersions. FT-IR and DSC studies have shown no interaction between the drug, polymer and the solid dispersion preparation. The *in-vitro* dissolution test showed a significant increase in the dissolution rate of solid dispersions as compared with pure Domperidone maleate. It was evident that the solid dispersion (SD) technique had improved the dissolution rate of drug to agreat extent. Solid dispersion of Domperidone maleate using hydrophilic polymeric carriers would improve the aqueous solubility, dissolution rate and thereby enhancing its systemic availability. The solubility and dissolution rates of Domperidone maleate were high in the solid dispersions prepared by solvent evaporation method with ratio of drug: PEG6000: PVP k25 at 1:4:1.Therefore solid dispersion by solvent evaporation method can be an effective way to improve the bioavailability of poor water soluble drugs like Domperidone maleate.

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