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Research Article

STUDIES ON ENHANCEMENT OF DISSOLUTION RATE OF DOMPERIDONE BY SURFACE SOLID DISPERSION TECHNOLOGY

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ABSTRACT

The objective of the present investigation was to study the influence of water insoluble carriers like Avicel, pregelatinised starch, crospovidone and Cab-o-sil on enhancement of dissolution rate of domperidone from surface solid dispersions, prepared using solvent evaporation method. The surface solid dispersions on Cab-o-sil with drug to carrier ratio of 1:10 showed highest dissolution rate and dissolution efficiency in comparison to pure drug and physical mixture. X-ray diffractometry, differential scanning colorimetry, Fourier transform infrared spectroscopy and gas chromatography studies were conducted on Cab-o-sil surface solid dispersions. The surface solid dispersions were developed into tablets. These tablets, apart from fulfilling the official and other specifications, exhibited higher dissolution rates and dissolution efficiency in comparison with prepared and marketed tablets.

Keywords: Domperidone, Pregelatinised starch, Avicel PH102, Crospovidone, Cab-o-sil.

INTRODUCTION

The effort to improve dissolution of poorly and practically insoluble drugs remains one of the most challenging tasks in drug development[1]. Several methods have been introduced to increase dissolution rate and thereby oral absorption and bioavailability of such drugs[2]. *Surface solid dispersion* is a technology of dispersing one or more active ingredients on a water insoluble carrier of extremely high surface area, in order to achieve increased dissolution rates and bioavailability of poorly and practically insoluble drugs. When drug is deposited on the carrier by using volatile solvent, then this technique is also termed as *solvent deposition* technique[3]. Surface solid dispersion technique has been extensively used to increase the solubility, dissolution and consequently the bioavailability of many practically insoluble or poorly water soluble drugs such as piroxicam[4], meloxicam[5] and ketoprofen[6]. In-vivo results have substantiated the fact that surface solid dispersion improves the release profile of many drugs resulting in rapid onset of action and bioavailability[7].

The carriers used in the surface solid dispersions are water insoluble porous materials and hydrophilic in nature[8]. Many commonly used tablet excipients like Avicel, Cab-o-sil, crospovidone and pregelatinized starch have been used as carriers for surface solid dispersions[9]. The release of drug from the carrier material depends on hydrophilic nature, particle size, porosity and surface area of the carrier.

Domperidone is an anti-emetic and gastro-prokinetic. It is a D2 antagonist and is used in the treatment of nausea and emesis.

According to biopharmaceutical classification system (BCS), domperidone is classified under class-II (poor solubility and high permeability). Domperidone is practically insoluble in water. This poor solubility may cause poor dissolution and unpredictable bioavailability[10].

The aim of this study was to enhance the dissolution rate of domperidone using silica adsorbates. The carriers used were Avicel, Cab-o-sil, crospovidone and pregelatinized starch. The SSDs were prepared at various drug to carrier ratios by solvent evaporation method. The drug release was run using the No.2 USP dissolution test apparatus at pH 1.2, 3.1, 4.0, 5.8, 6.8, 7.4 and the dissolution rates of SSDs were compared to those of plain drug and marketed tablets.

MATERIALS AND METHODS

Materials: Domperidone, a gift sample from Sri Krishna Pharmaceuticals, Hyderabad. Crospovidone, pregelatinized starch and Avicel pH102 a gift sample from Dr.Reddy's laboratories, Hyderabad. Cab-o-sil a gift sample from AVL Pharmaceuticals, Hyderabad. Sodium starch glycolate and other tablet excipients all are of Pharmacopoeial grades were procured. Methanol AR from SD Fine Chem was used.

Preparation of calibration curve

100mg of drug is taken in 100ml volumetric flask and methanol is added to dissolve the drug. Make up the volume to 100ml with methanol. From this solution 2, 4, 6, 8, 10, 12 mcg/ml concentrations were prepared, and their absorbance is noted at 283nm using systronics UV visible spectrophotometer.

Preparation of surface solid dispersion and physical mixture

The SSDs of domperidone and water insoluble carriers (Avicel, Cab-o-sil, pregelatinised starch and crospovidone) were prepared by solvent evaporation method. The required amount of drug was dissolved in methanol to get a clear solution in a dry mortar. The water insoluble carrier (passed through 120 mesh) was then added to clear drug solution and dispersed. The solvent was removed by continuous trituration until a dry mass was obtained. The mass obtained was further dried at 50^0c for 4 hrs in an oven. The dried product was crushed, pulverized and sifted through mesh 100. In each case SSD in the insoluble carriers were prepared at four different ratios of drug:carrier namely 1:5, 1:10, 1:15, 1:20 respectively. Physical mixtures containing one part of drug and 10 parts of either carrier were prepared by manual shaking in a glass bottle for 30 minutes. The powder mixtures were sifted through 100# sieve and were freshly prepared prior to analysis. Results were conformed on six batches for all carriers.

Dissolution rate study

Dissolution rate of domperidone as such and from various domperidone surface solid dispersions was studied using paddle type dissolution apparatus. The dissolution rate was studied in 900ml of 0.1N HCl (pH 1.2). Domperidone (10 mg) and SSD equivalent to 10 mg of domperidone, a speed of 50 rpm and a temperature of 37 ± 0.1^0C were used in each test. Sample of dissolution medium of 5ml was withdrawn through a filter of 0.45μm at different time intervals, suitably diluted and assayed for domperidone by measuring absorbance at 283 nm by UV-Visible spectrophotometer. An equal volume of fresh dissolution medium was immediately replaced. The dissolution of plain drug, and marketed product (Domstal 10mg) was also carried out. Dissolution experiments were conducted in triplicates.

Preparation and evaluation of tablets with surface solid dispersions

Domperidone tablets of SSD of domperidone-Cab-o-sil (1:10) were prepared by direct compression method (Table 3). SSD was dry mixed thoroughly in a polythene bag with Avicel PH 102 for 15 minutes. The blend was compressed into 200 mg tablets on a rotary tablet punching machine with punch size of 9 mm. Similarly tablets of plain domperidone were also prepared by direct compression as per the formula given in Table 3.

Prepared and marketed tablets were evaluated for different parameters.

FTIR spectroscopy

The FTIR spectra were recordrd by using KBr disc as reference on a FTIR spectrophotometer. The FTIR spectra of domperidone, physical mixture and SSD are shown in Fig 3.

X-Ray Diffraction Studies (XRD)

X- ray powder diffraction patterns of drug and its solid were obtained on a D-5000 Semens X-ray diffractometer, employing Cu K_a radiation (wave length=1.5406A^0). The diffractograms were run at a 2.4^0/min The diffractograms are shown in Fig 4.

Differential Scanning Colorimetry (DSC)

DSC thermograms of domperidone and its solid dispersions in Cab-o-sil were recorded on PerkinElmer Thermal Analyzer. Samples (3-4 mg) were sealed into aluminium pans and scanned at a heating rate of 10.00^{0}C/min over a temperature range of 32.0^{0}C to 350.0^{0}C under a nitrogen gas stream. The DSC thermograms are shown in Fig 5.

Gas chromatography

The determination of methanol was performed by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector employing nitrogen as carrier gas. Headspace GC is used to detect solvent residues. The packed column was BD-624 capillary column. Oven was programmed at 5^0 C/min for 10min, 15^0 C/min upto 250^0 C with a hold time of 7min. The GC determinations of domperidone and its solid dispersions are shown in Fig 6.

RESULTS AND DISCUSSION

Water dispersible carriers like Cab-o-sil, crospovidone, Avicel and Pregelatinised starch were selected for the study. The SSD obtained for all carriers were free flowing powders. All the carriers taken gave rapid and higher dissolution of domperidone when compared to pure drug. Among the carriers tested Cab-o-sil and crospovidone showed higher enhancement in dissolution of domperidone. (Table 1)

The order of increasing dissolution rate observed with various carriers at all ratios studied were; Cab-o-sil > crospovidone > pre gelatinised starch> Avicel PH 102. In each case the dissolution rate was increased as the concentration of carrier was increased from 1:5 to 1:10. However, improvement in the dissolution with 1:15 and 1:20 ratios when compared to 1:10 ratio was marginal. Hence, a drug:carrier ratio of 1:10 ratio is considered optimum.

Domperidone tablets could be prepared by direct compression method employing 1:10 SSD of drug:Cab-o-sil. Similarly tablets containing pure drug were also prepared. All the tablets prepared were of good quality fulfilling the official I.P and GMP requirements of tablets (Table 4). Dissolution characteristics of prepared tablets in comparision with SSD tablets and marketed samples in different media were studied. (Table 2). The dissolution of domperidone from these SSD's followed first order kinetics (Table 5).

Evaluation by FT-IR spectra

Drug and carrier interaction in the SSD prepared were evaluated by FTIR spectra study. The FTIR spectrum of domperidone and its physical mixture and SSD are shown in Fig 3. The FTIR spectrum of domperidone showed its characteristic IR absorption peaks at 1685, 1102 and 481 cm^{-1}.The characteristic peaks for SSD and physical mixture were found at 1693, 1106 and 471 cm^{-1} . These spectrum observations indicated no interaction between domperidone and the carrier used in SSD and physical mixture.

Evaluation of X-Ray Diffraction

The changes in the physical state of drug in the SSD were evaluated by XRD. X ray diffractogram of domperidone and SSD's, which gave highest enhancement in dissolution rate of domperidone, i.e., domperidone: Cab-o-sil were taken. X ray diffractogram of domperidone and SSD's are shown in Fig 4.

Evaluation by Differential Scanning Colorimetry

DSC was used to evaluate drug excipient interaction in surface solid dispersions

prepared. DSC of domperidone and its SSD's prepared were shown in Fig 5.The DSC curve of domperidone showed a single sharp endothermic peak at 255^{0}c corresponding to its melting point. The SSD and physical mixture also show melting point at same temperature indicating no interaction between drug and excipients.

Evaluation for residual solvents

Residual solvent concentration in surface solid dispersion of domperidone prepared using methanol was performed by Gas chromatography. The levels of methanol were below detectable limits. Hence, the solvent deposition method was efficient in removal of solvents from SSD well below permissible levels. Standard chromatogram for residual solvent obtained during the study and the chromatogram obtained after residual analysis are shown in Fig 6.

CONCLUSION

Surface solid dispersion technique was successful in improving the dissolution rate of domperidone. The nature and amount of carrier used played an important role in the enhancement of dissolution rate. This surface solid dispersion could then be incorporated successfully, into a tablet by direct compression method. The SSD tablets also showed enhancement of dissolution rate of drug when compared to marketed product and prepared tablets in different media.

Table 1: Comparison studies of Dissolution profiles of different SSD

S. No.	Excipient	Ratio	% Release in 5 min	% Release in 30 min	DE_{30}
1	Avicel	1:5	24.38	56.21	23.75
		1:10	26.53	59.18	26.99
		1:15	28.33	62.47	28.92
		1:20	31.91	65.42	30.17
2	PGS	1:5	48.41	72.91	42.73
		1:10	50.92	75.89	46.03
		1:15	53.07	77.39	46.62
		1:20	55.58	81.07	47.83
3	CPV	1:5	57.37	80.35	50.65
		1:10	61.31	84.04	53.59
		1:15	63.11	86.61	54.95
		1:20	65.26	90.30	56.03
4	Cab-o-sil	1:5	63.11	90.17	54.61
		1:10	71.00	99.07	62.71
		1:15	74.94	99.85	63.43
		1:20	76.73	99.89	64.71
5	Phy.mixture	1:10	64.90	74.25	56.83
6	Plain drug	-	21.51	51.96	20.9

Table 2: Dissolution data of prepared, marketed and SSD tablets in all media

Media	Formulation	% Release in 5min	% Release in 30min	DE_{30}
1.2 pH	Prepared Tablet	41.24	69.69	39.8
	Marketed product	41.95	94.31	43.8
	SSD Tablet	65.26	94.59	57.97
3.1 pH	Prepared Tablet	34.94	57.30	32.84
	Marketed product	39.10	73.29	37.17
	SSD Tablet	60.00	86.50	52.69
4.0 pH	Prepared Tablet	26.60	56.94	30.14
	Marketed product	37.30	61.58	34.4
	SSD Tablet	56.12	77.04	48.94
5.8 pH	Prepared Tablet	23.07	43.08	22.2
	Marketed product	29.26	49.45	27.3
	SSD Tablet	51.09	70.23	45.14
6.8 pH	Prepared Tablet	15.19	33.21	14.76
	Marketed product	17.89	38.72	19.11
	SSD Tablet	45.71	64.21	40.27
7.4 pH	Prepared Tablet	9.24	31.75	9.73
	Marketed product	13.60	39.08	15.6
	SSD Tablet	32.09	51.67	29.13

Table 3: Preparation of tablets of Surface solid dispersion and plain drug

Ingredients	Amount (mg)/tablet (SSD)	Amount (mg)/tablet (Plain)
Drug + Cab-o-sil	110	10
Avicel PH 102	80	80
Dicalcium phosphate	-	84
Starch	-	20
Sodium starch Glycollate	10	-
Talc	-	4
Magnesium stearate	-	2

Table 4: Evaluation of tablets of Surface solid dispersion and plain drug

S. No.	Evaluation Tests	SSD tablets	plain tablets
1	Disintegration Time	1.25 min	4.15 min
2	Hardness	4.96±0.11 Kg/cm2	5.00±0.14 Kg/cm2
3	Friability	0.499%	0.498%
4	Weight Variation	201.2±1.30	200.1±1.12
5	Assay	99.77± 4.081%	99.97± 4.072%
6	Content uniformity	98.57±2.07	98.57±2.17

Table 5: Different Release Rate Constants of domperidone SSD on Cab-o-sil (1:10)

Media	Parameters	Zero order	First order	Hixson Crowell ($Q^{1/3}$-$Qt^{1/3}$)
0.1N HCl (1.2pH)	K	3.418	-0.031	0.0851
	r^2	0.665	0.812	0.7601
0.01N HCl (3.1pH)	K	3.076	-0.024	0.0704
	r^2	0.656	0.769	0.728
0.001N HCl (4.0pH)	K	2.851	-0.021	0.062
	r^2	0.653	0.747	0.713
5.8pH	K	2.662	-0.0186	0.0561
	r^2	0.665	0.7489	0.7192
6.8pH	K	2.43	-0.016	0.0493
	r^2	0.682	0.757	0.731
7.4pH	K	1.88	-0.0109	0.0351
	r^2	0.734	0.789	0.770

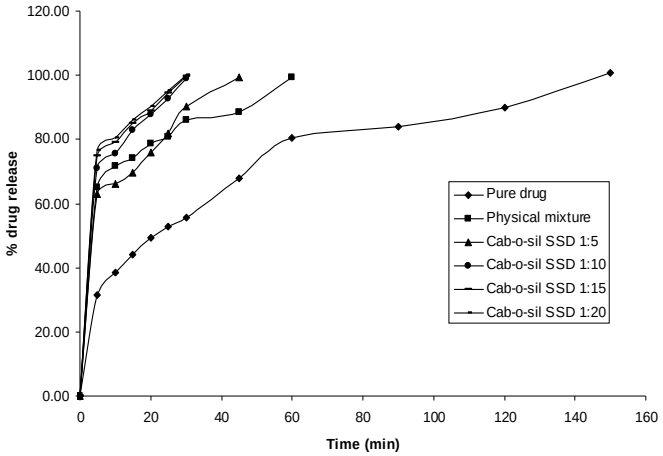


Fig. 1: Dissolution profile of pure drug, physical mixture and various drug to carrier ratios of domperidone on Cab-o-sil

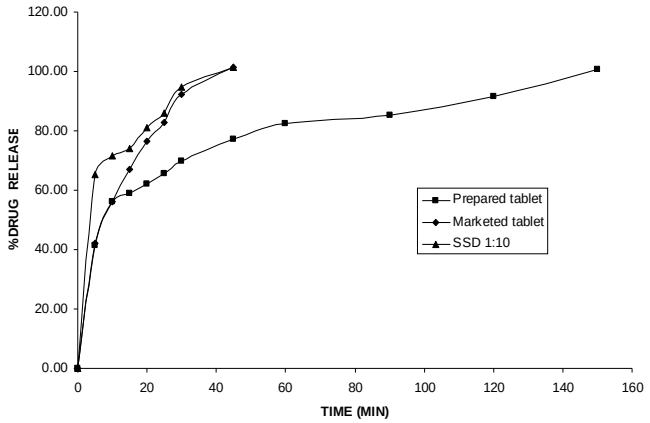


Fig. 2: Dissolution profile of SSD tablets, marketed product and prepared tablet in 0.1N HCl

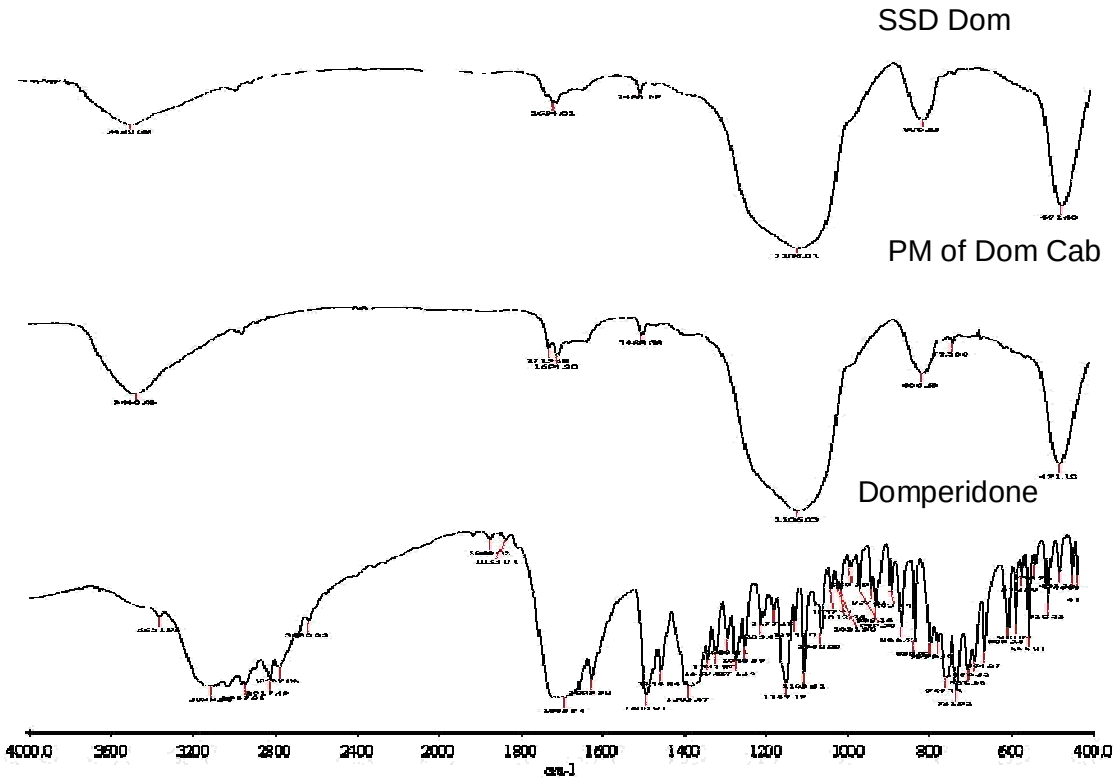


Fig. 3: Characterization of domperidone by FTIR Spectroscopy

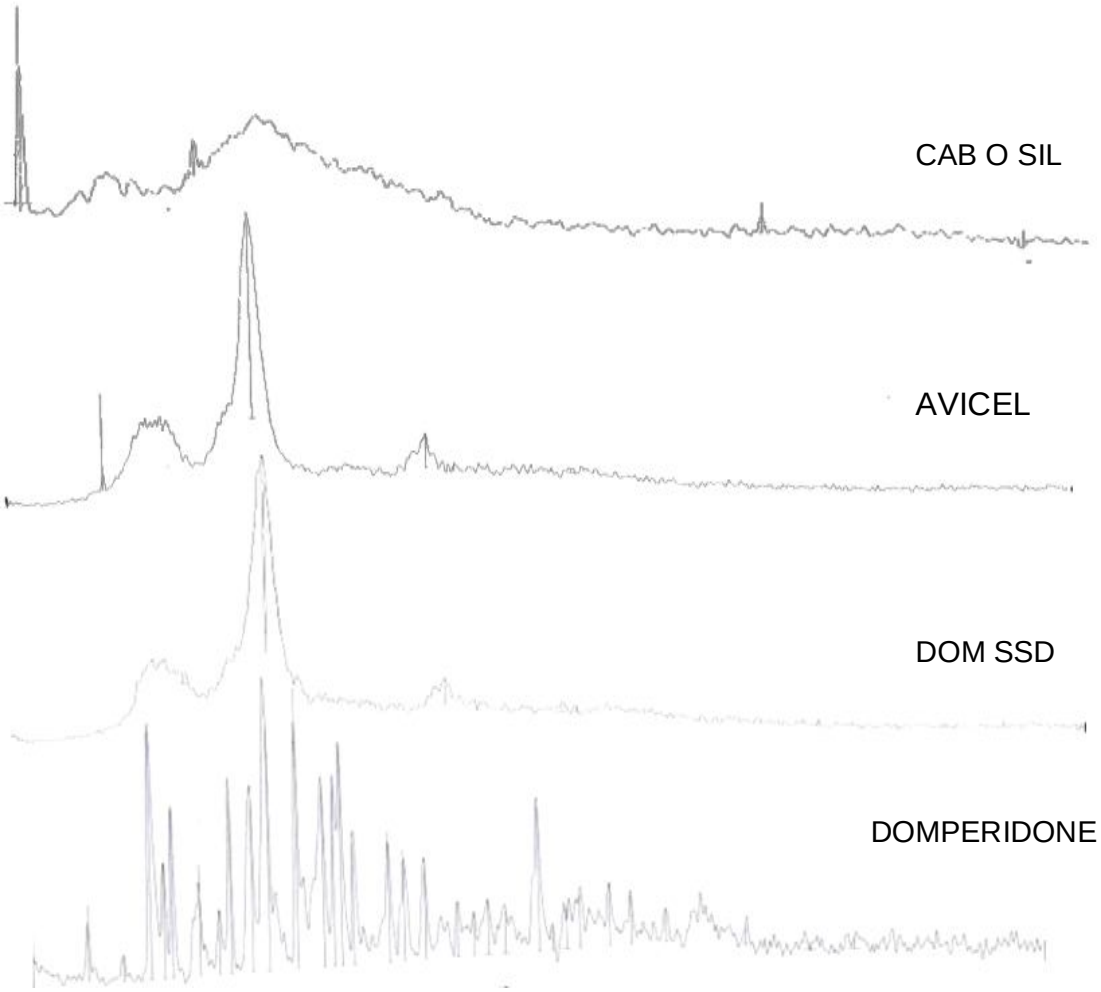


Fig. 4: Characterization of domperidone by XRD

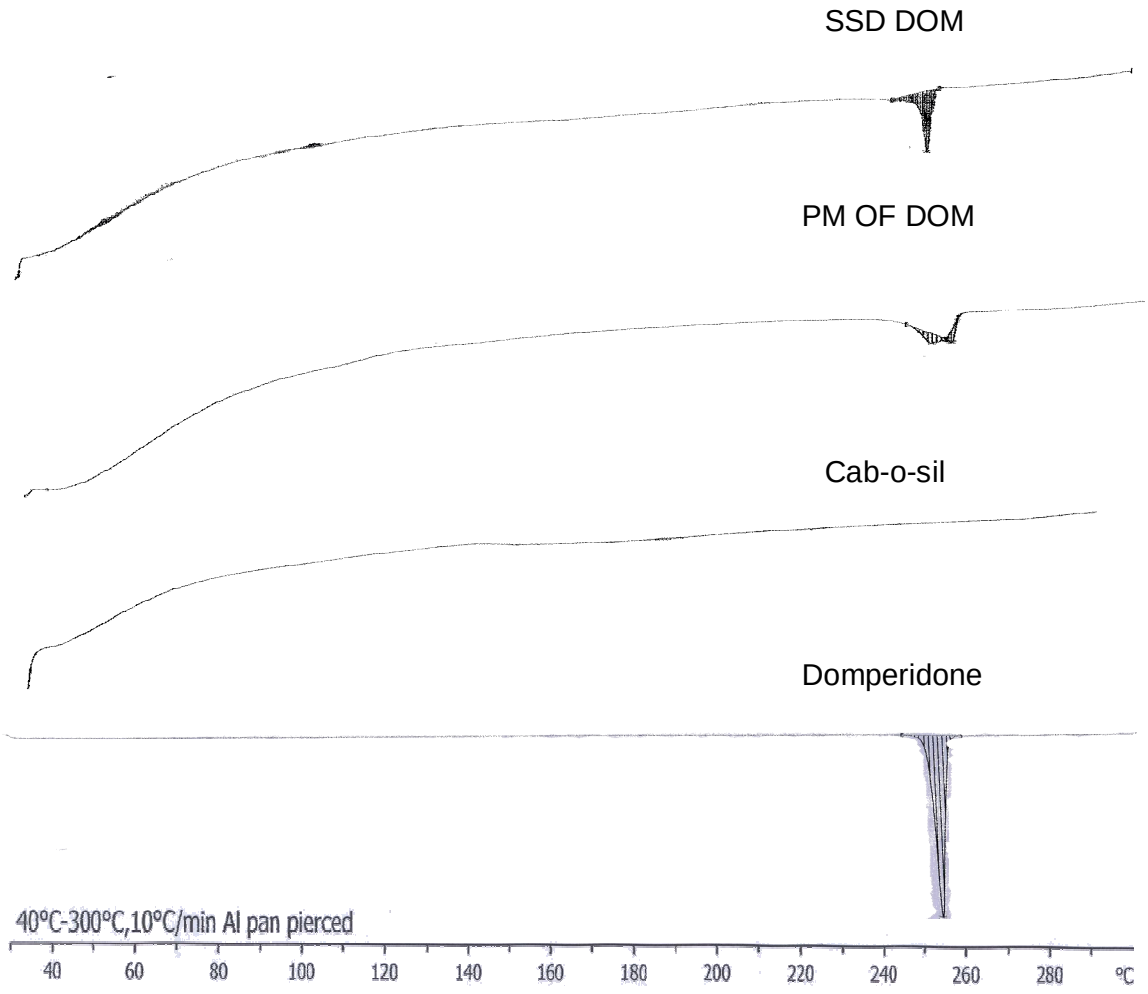


Fig. 5: Characterization of domperidone by DSC

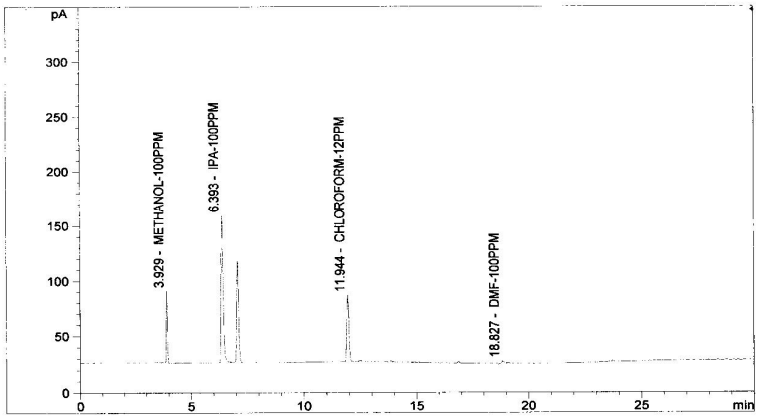
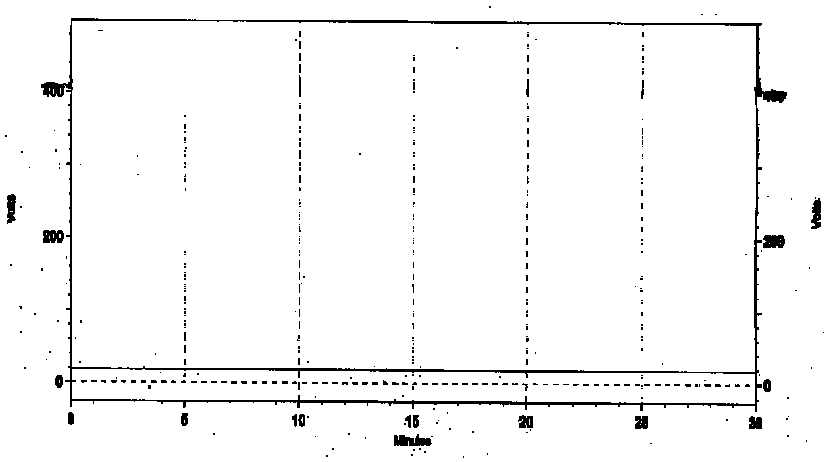


Fig. 6: Characterization of domperidone by GC
Standard chromatogram for residual solvents



Chromatogram for residual solvents obtained after analysis of SSD samples

REFERENCES

1. Yalkowsky SH. Technique in Solubilization, vol 12, Marcel Dekke. 122-137.
2. Serajiddin ATM. Solid dispersion of poorly water soluble drugs: early promises, subsequent problems and recent breakthroughs. J Pharm Sci. 1999;88:1058-1066.
3. Chowdary KPR and Srinivasa Rao SK. Investigation of Dissolution Enhancement of Itraconazole by Solid Dispersions in Superdisintegrants. Drug Development and Industrial Pharmacy. 2000;26(11):1207-1211.
4. Barzegar-Jalali. Enhancement of dissolution rate and anti-inflammatory effects of piroxicam using solvent deposition technique. Drug Dev. Ind Pharm. 2002;28(6):681-686.
5. Chowdary KPR and Hymavathi R. Enhancement of dissolution rate of meloxicam. Indian Journal of Pharmaceutical Sciences. 2001:152-155.
6. Chowdary KPR and Rama Krishna S. Improvement of dissolution efficiency of ketoprofen by solvent deposition technique. Indian Journal of Pharmaceutical Sciences. 1990:269-271.
7. Dixit RP and Nagarsenker MS. In vitro and in vivo advantage of celecoxib surface solid dispersion and dosage form development. Indian Journal of Pharmaceutical Sciences. 2007:370-377.
8. Adrian C. Williams, Peter Timins, Mingchu Lu, Robert T. Forbes, Disorder and Dissolution Enhancement: Deposition of Ibuprofen onto Insoluble Polymers. European Journal of Pharmaceutical Sciences. 2005;26:288-294.
9. Suporn Charumanee, Siriporn Okonoki and Jakkapan Sirithunyalug. Improvement of Dissolution Rate of Piroxicam by Surface Solid Dispersions. CMU Journal. 2004;3(2):77-84.
10. James I. Wells, Pharmaceutical Preformulation: The Physicochemical Properties of Drug substances, John Willy Publication, Edition 1987.