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SURFACE SOLID DISPERSION OF DOMPERIDONE FOR DISSOLUTION RATE ENHANCEMENT

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ABSTRACT

The main objective of the study was to enhance the dissolution rate of poorly water soluble drug Domperidone by Surface solid dispersion (SSD) technique. Water-insoluble carriers like Sodium starch glycolate (SSG), Crospovidone, Avicel PH 102, Pre-gelatinized starch, Cab – o-sil M5 and Florite R were used in different ratios to prepare SSD by solvent evaporation method. SSD prepared with Florite R as carrier in the ratio of 1:10 showed the highest dissolution rate as compared to pure drug. Increase in the dissolution rate may be attributed to the reduced particle size of drug deposited on the surface of carrier and enhanced wettability of the drug particles by the carrier. The optimized formulation was evaluated by X-ray diffractometry (XRD), Differential scanning colorimetry (DSC) and Fourier transform infrared spectroscopy (FTIR). These tablets, apart from fulfilling the official and other specifications, exhibited higher rates of dissolution and dissolution efficiency values compared to their commercial counter parts. Mathematical modeling of dissolution data shows fitting into first order kinetics. Accelerated stability studies performed on optimized formulation indicated no significant change in the drug content and dissolution rate.

KEYWORDS: Domperidone, Sodium starch glycolate, Crospovidone, Surface Solid Dispersion, In-vitro dissolution, Florite R.

INTRODUCTION

Formulation of poorly water soluble drugs for oral delivery is an ongoing challenge for scientists.[1] Oral bioavailability of a drug depends on its solubility and dissolution rate which is the rate determining step for the onset of therapeutic activity. Several methods have been introduced to increase dissolution rate and thereby oral absorption and bioavailability of such

drugs. Among various approaches, solid dispersion has shown promising results in improving the solubility, wettability, dissolution rate and subsequently its bioavailability. Only a few commercial solid dispersion products are available inspite of the many advantages it offers.[2]

Surface solid dispersion (SSD) technique overcomes the shortcomings of solid dispersion prepared like tackiness and difficulty in handling of the product.[3] This technique disperses one or more active ingredients on a water insoluble carrier of extremely high surface area to achieve increased dissolution rates of practically insoluble drugs.[4] The carriers used in surface solid dispersion are hydrophilic, water insoluble, porous materials.[5] Common tablet excipients like sodium starch glycolate, crospovidone, croscarmellose sodium, kyron T-314, cab-o-sil and silicified microcrystalline cellulose have been used as carriers for surface solid dispersions.[6]

Deposition of drug on the surface of an inert carrier leads to reduction in the particle size of the drug thereby providing a faster dissolution rate. Larger the surface area of carrier available for adsorption of drug, better is the release rate.[7] This technique has been extensively used to increase the solubility, dissolution and bioavailability of many insoluble or poorly water soluble drugs such as Piroxicam[8], Simvastatin[9], Meloxicam[10] and Itraconazole[11], Nifedipine[12], celecoxib[13], ketoprofen.[14]

Domperidone (DMP), the model drug of this research, is an antiemetic drug that has the chemical structure of 5- Chloro-1-{1-[3-(2-oxobenzimidazolin-1-yl)propyl]-4- piperidyl} benzimidazolin-2-one. It is described as a peripheral antidopaminergic drug that is mainly used as an antiemetic for the treatment of nausea and vomiting of various etiologies. DMP has low systemic bioavailability about 13-17% of the orally administrated dose due to the extensive hepatic metabolism.[15]

The main objective of this study was to enhance the dissolution rate of poorly water soluble drug Domperidone by using various hydrophilic carriers. SSDs were prepared by solvent evaporation method using different drug to carrier ratios. The optimized SSD was formulated into sublingual tablets to overcome the pre systemic metabolism and dissolution rate compared to that of pure drug and marketed tablets.

MATERIALS AND METHODS

Materials: Domperidone was supplied as gift sample from Sri Krishna Pharmaceuticals, Hyderabad, India. Sodium starch glycolate (SSG) and crospovidone (CPV), Avicel PH 102,

Pre gelatinized starch, Cab – o- sil M5 were purchased from SD FINECHEM, Mumbai (India). All the reagents used were of analytical grade.

Method

PREPARATION OF CALIBRATION CURVE

100 mg of drug was dissolved in methanol in a volumetric flask and volume made upto 100 ml with methanol (1000µg/ml). From this stock solution, solutions of different concentrations were prepared with 0.1N HCl and absorbances measured at 283 nm using systronics UV-VIS Spectrophotometer. Beer-Lambert law was obeyed in the concentration range of 5 to 30µg/ml.

PREPARATION OF DOMPERIDONE SURFACE SOLID DISPERSION (SSD)

Surface solid dispersion of Domperidone were prepared by solvent evaporation method using different hydrophilic carriers such as Sodium starch glycolate(SSG), Crosspovidone, Avicel PH 102, Pre-gelatinized starch, Florite R and Cab – o- sil M5. Surface solid dispersions were prepared with drug to carrier ratios of 1:5, 1:10, 1:15 and 1:20. The required amount of drug was dissolved in methanol to get a clear solution. Water insoluble carrier was added to this clear drug solution and dispersed. The solvent was removed by continuous trituration until a dry mass was obtained. The obtained mass was further dried at 50^0C for 2 hrs in an oven. This product was crushed, pulverized and sifted through a 60# sieve. The obtained product was stored in desiccators containing $CaCl_2$.

EVALUATION OF SURFACE SOLID DISPERSIONS

Flow properties: Flow properties must be optimum for the formulation and industrial production of tablet dosage form. The flow properties of surface solid dispersion were estimated by Tapped density, Bulk density, Angle of repose, Carr's index and Hausner's ratio. Angle of repose (ɵ) was measured using fixed funnel method and tapped density was determined using bulk density apparatus.

In-Vitro Dissolution Studies: In-vitro dissolution studies for drug Domperidone and prepared SSDs were carried out using USP Apparatus 2 (Paddle type). Sample equivalent to 10 mg of Domperidone was placed in the dissolution vessel containing 900 ml of 0.1N HCl (pH 1.2) at 37 ± 0.5° C and stirred at 50 rpm. Aliquots of 5 ml were withdrawn at specified time intervals and replaced with an equal volume of dissolution medium. The filtered samples were analyzed spectrophotometrically at 283 nm. Amount of drug released at 5, 15 and 30

minutes were calculated and tabulated as T5, T15 and T30 respectively. A model independent parameter, the dissolution efficiency (DE) was employed to compare dissolution profiles of different samples.

FTIR Spectroscopy: FTIR spectra of drug and SSD were obtained. About 5mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 4000 cm-1 to 625 cm-1 in a scan time of 12 minutes. The resultant spectra were compared for any spectral changes.

DIFFERENTIAL THERMAL ANALYSIS (DSC)

DSC analysis of drug, Placebo and SSD prepared using methanol as solvent were obtained on a PerkinElmer Thermal Analyzer equipped with a monitor and printer. The instrument was calibrated with indium standard. Accurately weighed about 3.5mg of sample was placed in an open, flat bottom, aluminum sample pans. Thermo grams were obtained by heating the sample at a constant rate 10.00^0C/min. A dry purge of nitrogen gas (20 ml/min) was used for all runs.

POWDER X-RAY DIFFRACTION ANALYSIS (XRD)

X- ray diffraction of drug, Placebo and SSD prepared using methanol as solvent were obtained on a D-5000 Siemens X-ray diffractometer, using Cu Ka radiation (wave length=1.5406A0). The data were recorded over a scanning 2f range of 20 to 65^0 at step time of 0.045 steps/0.5 sec.

SOLVENT RESIDUE

The residual solvent; methanol was monitored by gas chromatography on a Agilent GC 6890N with 7694E Head space sampler, fitted with flame ionization detector. Packed column was BD-624 capillary column. Carrier gas was nitrogen. Headspace GC is used to detect solvent residues. Temperature of oven was 60^0C injection port 140^0C and detector 250^0 C. Oven was programmed at 5^0C/min for 10min., 15^0C/min upto 250^0C.

PREPARATION AND EVALUATION OF TABLETS

Based on the dissolution profile, Domperidone SSD on Florite R (1:10) was selected as the carrier for the preparation of sublingual tablets. Tablets were formulated as shown in Table 1

by direct compression method on a 10 station rotary tablet compression machine. The tablets prepared were evaluated for parameters like weight variation, hardness, friability, disintegration time, assay, content uniformity, drug release and compared with marketed product. Results were confirmed on three independent batches. Dissolution data obtained was fitted into zero order, first order, Hixson-Crowell cube root model to analyze the mechanism of drug release rate kinetics from the prepared SSD and marketed product.

Stability studies: Stability studies for the tablets were carried out as per ICH guidelines. The tablets (n=3) were kept for stability studies at 40 ± 2 ^{0}C and 75 ± 5% RH for a period of 3 months in environmental test chamber (HMG INDIA, Mumbai). The samples were kept in glass vials sealed with rubber plugs. After 30, 60 and 90 days, the samples were taken out and analyzed for appearance, drug content and dissolution study.

RESULTS AND DISCUSSION

Table 1: Formulation of Domperidone sublingual tablets

Ingredients	Quantity (mg)
Domperidone + Florite R	110
Advantose FS 95	72
Talc	4
Magnesium Stearate	4
Primellose	10
Tablet wt.	**200**

Calibration curve of Domperidone was obtained in 0.1N HCl with a slope of 0.0256 and was shown in "Fig 1". Water dispersible carriers like Sodium starch glycolate(SSG), Crospovidone(CPV), Avicel PH 102, Pre-gelatinized starch, Florite R and Cab – o- sil M5 were selected for the study. All SSDs were found to be free flowing powders as shown in Table 2.

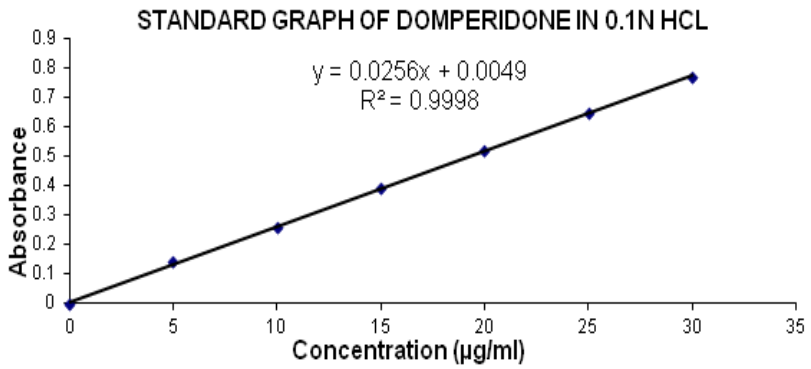

Fig 1: Calibration curve of Domperidone

Invitro dissolution studies of SSD's

All the carriers selected showed rapid and higher dissolution of Domperidone as compared to pure drug. Dissolution rate observed with various carriers were in following increasing order: Florite R> Cab – o – sil M5> SSG> CPV> PGS> Avicel PH 102 as shown in "Fig 2" and "Fig 3". Table 3 shows the comparison of dissolution profile of different formulations of surface solid dispersions. There is no remarkable increase in the dissolution rate of SSD's prepared with drug : Florite R in 1:15 and 1:20 ratios compared to 1:10 ratio. So drug : Florite R of 1:10 ratio is considered as optimized formulation for preparation of sublingual tablets.

Table 2: Evaluation of flow properties of prepared SSD's

Formulation		Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (Ɵ)	Carr's index	Hausners ratio
Avicel PH 102	1:5	0.258 ± 0.044	0.301 ± 0.051	27.44 ±0.04	14.28 ± 0.9	1.16 ± 0.9
	1:10	0.245 ± 0.043	0.287 ± 0.054	31.13 ± 0.14	14.63 ± 1.6	1.17 ± 0.50
	1:15	0.257 ± 0.047	0.297 ± 0.043	30.68 ± 0.44	13.4 ± 1.02	1.15 ± 1.0
	1:20	0.256 ± 0.042	0.304 ± 0.042	31.24 ± 0.45	15.78 ± 0.59	1.18 ± 0.47
PGS	1:5	0.257 ± 0.047	0.297 ± 0.043	29.68 ± 0.44	13.4 ± 0.52	1.15 ±0.7
	1:10	0.256 ±0.042	0.304 ± 0.042	31.24 ± 0.45	15.78 ± 1.09	1.18 ± 1.02
	1:15	0.256 ± 0.044	0.301 ± 0.051	29.24 ±0.36	14.6 ± 0.06	1.17 ± 0.09
	1:20	0.245 ± 0.043	0.287 ± 0.054	31.12 ±0.52	14.63 ±0.48	1.17 ± 0.05
SSG	1:5	0.256 ± 0 .044	0.301 ± 0.051	27.44 ± 0.04	14.95 ± 0.12	1.17 ± 0.9
	1:10	0.249 ± 0.043	0.287 ± 0.054	31.12 ± 0.14	13.24 ± 1.01	1.15 ± 0.7
	1:15	0.257 ±0.047	0.300 ± 0.043	30.68 ±0.44	14.33 ± 1.02	1.16 ± 0.09
	1:20	0.256 ± 0.042	0.304 ± 0.042	31.24 ± 0.45	15.78 ± 0.59	1.18 ± 0.12
CPV	1:5	0.257 ± 0.047	0.297 ± 0.043	29.68 ± 0.44	13.4 ± 0.52	1.15 ± 0.7
	1:10	0.256 ± 0.042	0.304 ± 0.042	31.24 ± 0.45	15.78 ± 0.09	1.18 ± 1.0
	1:15	0.256 ± 0.044	0.301 ± 0.051	29.24 ± 0.36	14.6 ± 0.46	1.17 ± 0.09
	1:20	0.245 ± 0.043	0.287 ± 0.054	31.12 ± 0.52	14.63 ± 0.48	1.17 ± 0.05
Cab – o- sil M5	1:5	0.248 ± 0.12	0.280 ± 0.03	27.47 ± 0.05	11.42 ± 0.16	1.12 ± 0. 07
	1:10	0.290 ± 0.12	0.319 ± 0.10	29.24 ± 0.07	9.40 ± 0.05	1.1 ± 0.07
	1:15	0.269 ± 0.14	0.291 ± 0.03	28.36 ± 0.10	7.56 ± 0.05	1.08 ± 0.06
	1:20	0.271 ± 0.05	0.292 ± 0.03	28. 24 ± 0.14	7.19 ± 0.10	1.07 ± 0.03
Florite R	1:5	0.289 ± 0.11	0.319 ± 0.14	29.24 ± 0.10	9.40 ± 0.03	1.10 ± 0.08
	1:10	0.264 ± 0.07	0.291 ± 0.03	29.68 ± 0.11	9.27 ± 0.14	1.10 ± 0.04
	1:15	0.256 ± 0.10	0.280 ± 0.07	29.68 ± 0.03	8.57 ± 0.07	1.09 ± 0.05
	1:20	0.269 ± 0.06	0.291 ± 0.05	28.36 ± 0.07	7.56 ± 0.05	1.08 ± 0.09

Table 3: Dissolution profiles of prepared SSD's

Formulation	Ratio	T5	T15	T30	DE30
Avicel PH 102	1:5	24.14	27.86	39.15	26.91
	1:10	28.69	32.60	43.95	31.67
	1:15	30.76	36.05	45.56	32.89
	1:20	33.35	41.21	46.32	33.78
PGS	1:5	24.38	32.21	41.75	30.03
	1:10	29.76	33.69	44.70	32.64
	1:15	32.56	40.97	49.65	37.45
	1:20	36.76	47.39	51.13	37.89
SSG	1:5	33.35	40.91	52.77	38.80
	1:10	35.86	42.01	54.58	39.87
	1:15	38.11	49.45	56.67	42.45
	1:20	41.23	53.46	58.87	44.32
CPV	1:5	31.91	37.66	47.65	35.37
	1:10	32.27	39.82	48.05	36.63
	1:15	35.54	43.21	52.23	38.45
	1:20	39.21	50.69	55.56	41.35
Cab – o- sil M5	1:5	35.86	43.45	55.34	40.95
	1:10	38.37	46.70	57.20	43.10
	1:15	40.76	52.34	58.08	44.79
	1:20	44.44	57.76	60.98	46.75
Florite R	1:5	38.73	46.71	57.94	43.70
	1:10	43.03	50.70	62.35	47.45
	1:15	44.01	51.21	63.23	47.89
	1:20	45.54	52.23	64.43	48.98
Pure Drug		17.93	24.24	36.18	23.64

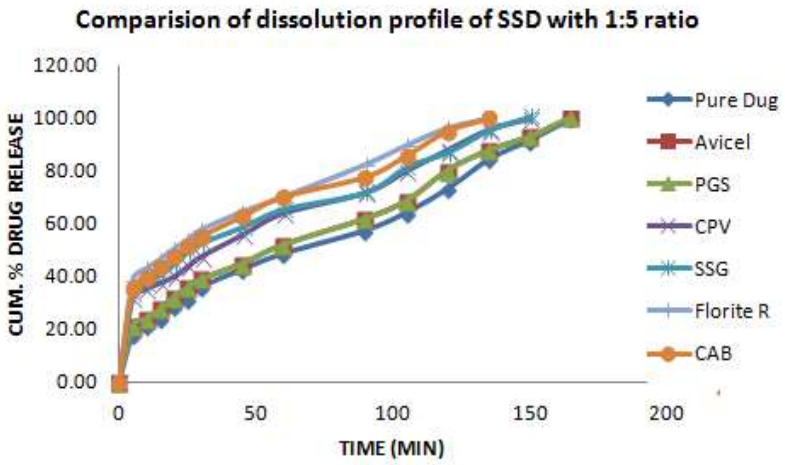

Fig 2: Dissolution profile of SSD's with 1:5 ratio

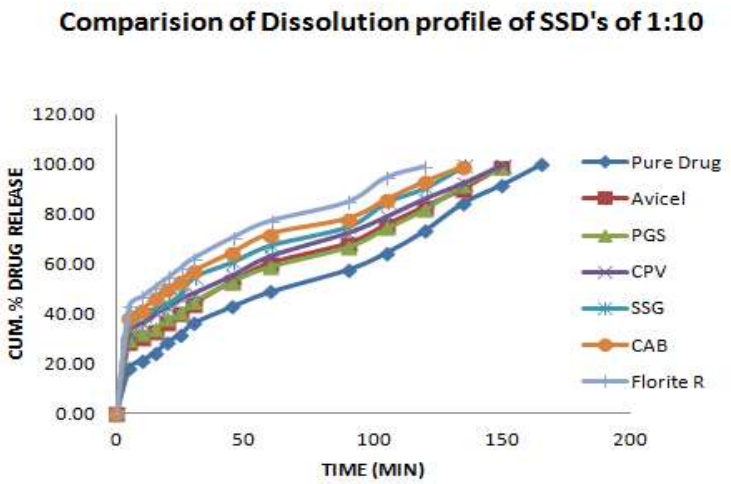

Fig 3: Dissolution profile of SSD's with 1:10 ratio

FT-IR spectroscopy: It was performed by KBR pellet method. The principal peaks of domperidone were observed at 1685, 1102 and 481 cm^{-1}.The characteristic peaks for SSD and physical mixture were found at 1693, 1106 and 471 cm^{-1} indicating no interaction between drug and the excipients therein. The results are shown in "Fig 4".

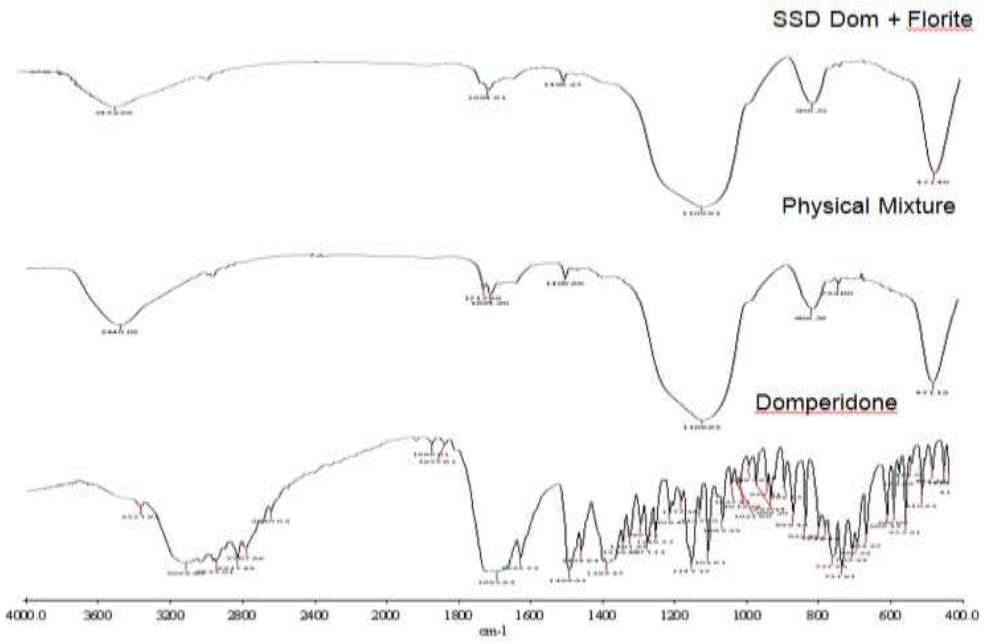

Fig 4: FTIR Spectrum of Domperidone, physical mixture & Optimised formulation

Differential Scanning Colorimetry (DSC)

The DSC plot of pure domperidone "Fig. 5" shows a sharp endothermic peak near 255°C, which is attributed to its melting temperature. The SSD and physical mixture also show the melting point at same temperature indicating no interaction between the drug and excipients.

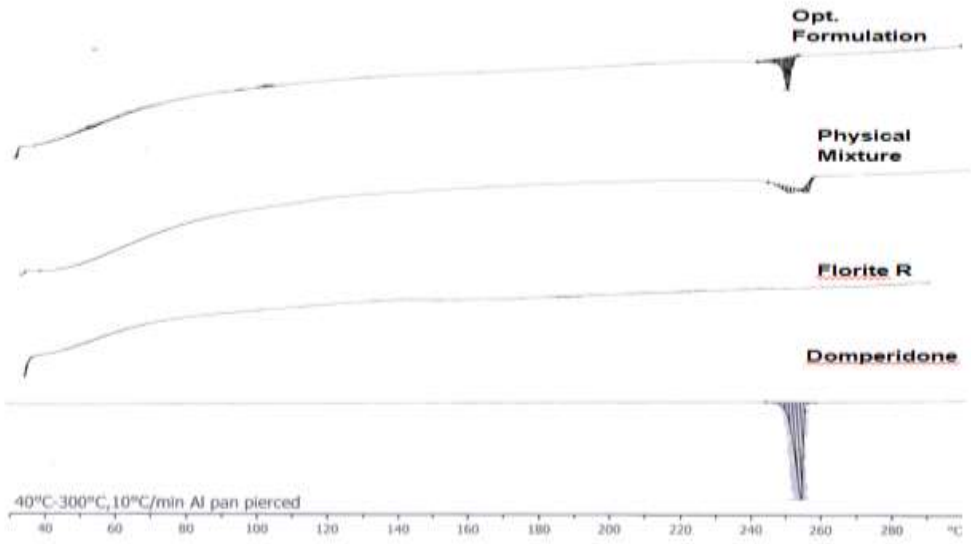

Fig 5: DSC Plots of Domperidone

Powder X-Ray Diffraction Analysis (XRD): XRD of SSD reveals a reduction in peak intensity when compared with XRD of excipient and plain drug. The characteristic peaks identified in the drug XRD were not detected in SSD. SSD showed reduced crystalline properties, indicating of possible conversion into amorphous form as shown in "Fig 6".

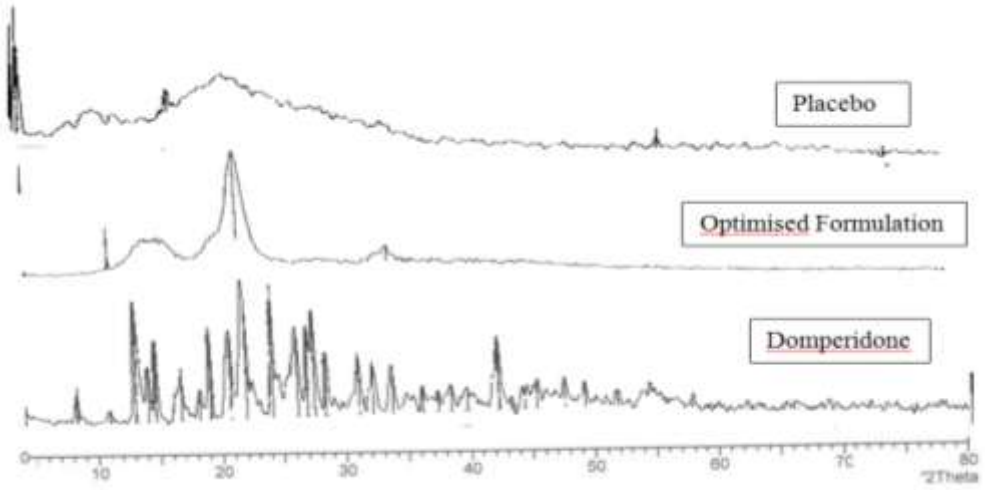

Fig 6: XRD graphs of SSD of domperidone

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, can be concluded that solvent deposition method was efficient in removal of solvents from SSD well below permissible levels. "Fig 7" shows a standard chromatogram for residual solvent obtained during the study. "Fig 8" the chromatogram obtained after residual analysis.

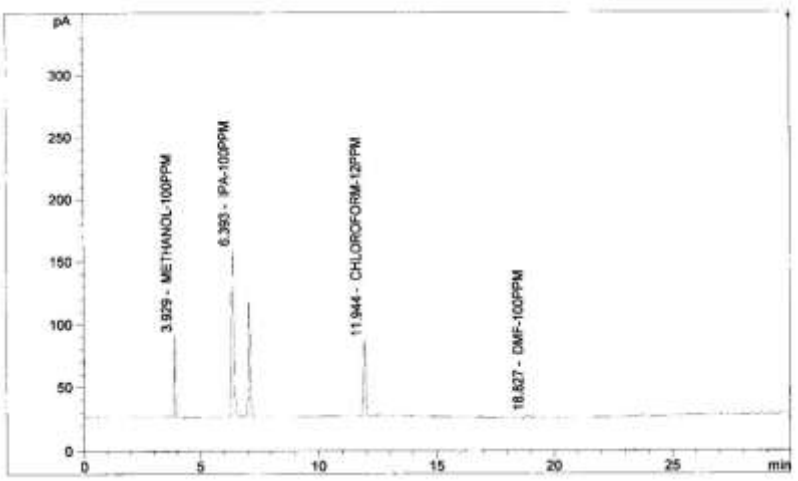

Fig 7: Standard chromatogram for residual solvents

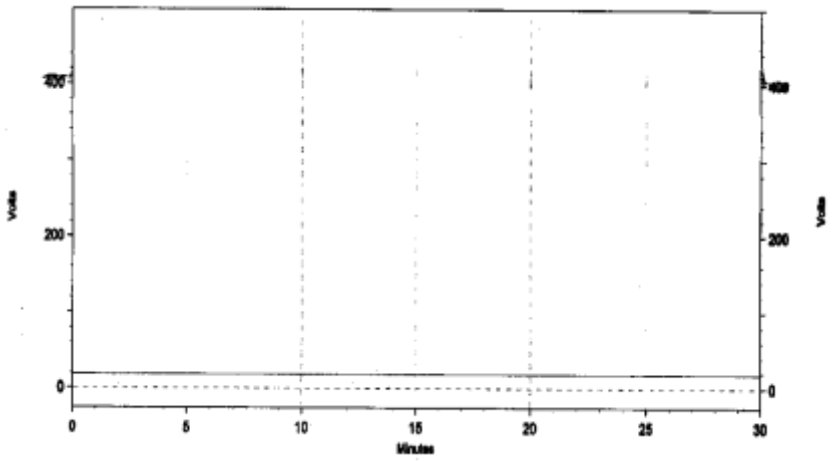

Fig 8: Chromatogram of SSD for residual solvents

Evaluation of SSD Tablets: Domperidone tablets of drug with Florite R as carrier were prepared by direct compression method. Table 4 reveals that all the prepared tablets have acceptable physical properties according to the IP.

Table: 4 Evaluation of Surface solid dispersion tablets & Marketed product

S. No	Evaluation Tests	SSD Tablet	Marketed Product
1	Weight Variation	199 ± 1.92 mg	199 ± 1.87 mg
2	Hardness	4.8 ±0.65 Kg/cm2	4.6 ±0.56 Kg/cm2
3	Friability	0.631% (0.5-1%)	0.615% (0.5-1%)
4	Disintegration Time	31 ± 0.79 sec	60 ± 0.56 min
5	Assay	99.03 ± 2.72%	99.01 ± 1.62%
6	Content uniformity	97.62 ± 1.67	98.99 ± 1.46

Tablets prepared from SSD having Florite R as the carrier exhibited higher dissolution rate as compared to marketed tablets. Marketed tablets showed 83.53% drug release in 120 mins

whereas tablets prepared from SSD with Florite R as the carrier showed 99.54 % drug release as shown in "Fig 9". From Table 6 it is clear that the drug release followed first order kinetics.

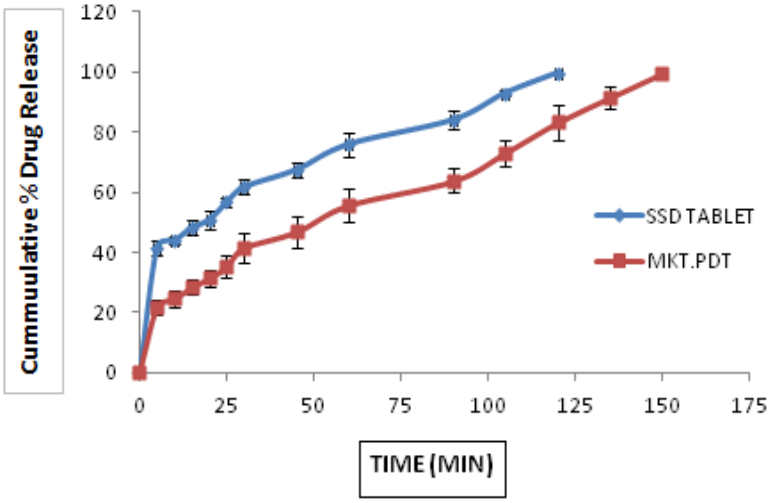

Fig 9: Comparative Dissolution studies of prepared SSD's & Marketed product

Table 5: Dissolution profile of SSD Tablet & Marketed product

Formulation	T5	T15	T30	DE30
SSD Tablet	41.76 ± 2	48.2 ± 1.52	61.67 ± 1.73	47.34
Mkt. Pdt (Motinorm 10mg)	21.59 ± 2.51	28.34 ± 2.51	41.5 ± 5.13	22.64

Table 6: Kinetic analysis of drug release data

Formulation	Parameters	Zero order	First order	Hixson Crowell $(Q^{1/3}-Qt^{1/3})$
SSD Tablet	K	5.79	-0.08	0.813
	r^2	0.67	0.868	0.787
MKT.PDT	K	3.02	0.024	0.069
	r^2	0.604	0.6922	0.659

Table 7: Accelerated stability studies data

Parameters	Observation			
	Initial	**30 Days**	**60 Days**	**90 Days**
Drug content	**99.03**	**98.97**	**98.97**	**98.94**
T5	41.76	41.56	41.54	40.87
T15	48.2	48.09	47.89	47.86
T30	61.67	61.6	60.97	60.87
DE30	47.34	47.30	47.28	47.27

Stability Studies: The accelerated stability studies indicated that there were no visible and physical changes observed in the tablets after storage. It was also observed that there was no significant change in drug release from the tablets Table 7. The drug release characteristics of the optimized tablets remained unaltered.

CONCLUSION

Surface solid dispersion technique was successful in improving the dissolution rate of poorly water-soluble drug Domperidone. SSDs of drug with Florite R as carrier showed significantly higher dissolution rate as compared to pure drug. The nature and amount of carrier used played an important role in the enhancement of dissolution rate. FTIR and DSC studies showed no evidence of interaction between the drug and carrier. XRD studies revealed that there is a change in crystallinity of drug to amorphous form. SSD tablets prepared with Florite R as carrier showed an enhancement of dissolution rate of drug as compared to marketed tablets. Mathematical modeling of drug release data fitted into first order kinetics. Accelerated stability studies indicated that there was no significant change in the drug content and % drug release.

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