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MELT GRANULATION: AN APPROACH TO ENHANCE THE DISSOLUTION RATE OF DOMPERIDONE

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ABSTRACT
Melt granulation is one of the most widely applied processing technique in the array of pharmaceutical manufacturing operations. The wide spread interest in this technique is because it offers a means of facilitating the dissolution and bioavailability of poorly soluble drugs when combined with hydrophilic meltable polymers. Advantage of this technique over conventional granulation is that it negates the risk originating from residual solvents and is less time consuming. The focus of the present study was to evaluate the feasibility of this technique to improve the dissolution characteristics of domperidone, a BCS class II drug indicated for treatment and prevention of nausea and vomiting especially in cytotoxic and radiotherapy. Granules were prepared using hydrophilic polymers like Myrj S40, Pluronic F 127, and Pluronic F 68 with primellose as disintegrant. Prepared granules were subjected to preformulation studies and were compressed into tablets. These tablets were evaluated for various parameters and a remarkable increase in dissolution rate was observed compared to their commercial counterparts. Physicochemical characterization was done by FTIR, DSC and XRD. Stability studies performed as per ICH guidelines ascertained that the formulations are stable. Mathematical modeling of dissolution data indicated best fitting with first order kinetics.

KEY WORDS: Domperidone, Myrj S40, Pluronic F 68, Similarity Factor.

INTRODUCTION
Poorly water soluble drugs are allied to slower rate of absorption from oral route; hence dissolution is the rate limiting step for lipophilic drugs[1]. So, there is a necessity to enhance the dissolution of these drugs to ensure maximum therapeutic utility of these drugs[2, 3]. As oral route is considered most natural, uncomplicated, convenient, safe means of administering drugs due to its immense advantages like flexibility in dosage form design, ease of production and low cost e.g. tablets, capsules. But, nearly one third of drugs in development are poorly water soluble, thus these poorly water soluble drugs show slow drug absorption leading to inadequate and variable bioavailability and gastro intestinal mucosal toxicity of drugs[4].

As these solid dosage forms are convenient for many drugs but they are challenging to formulate if the active substances has poor dissolution rate or low bioavailability. Hence to overcome such problems various techniques have been introduced to enhance the dissolution rate and solubility of the drug[5]. These techniques include physical modification of lipophilic drugs using several carriers like cyclodextrins, carbohydrates, hydrotropes, dendrimers, polyglycolized glycerides, acids[6] and other methods by the use of superdisintegrants, solid dispersions, surfactants, melt granulation, particle size reduction etc.[7]

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[8]. The present study was aspired to enhance the dissolution of Domperidone using melt granulation technique.

There is a wide spread in melt granulation technique because it offers a means of facilitating the dissolution and bioavailability of poorly water soluble drugs when combined with hydrophilic meltable binder. This increase in dissolution rate is achieved by combination of effects, the most significant of which is reduction of particle size to an extent that cannot be readily achieved by convention comminuting approaches.

MATERIALS AND METHODS

Materials

Domperidone was supplied as gift sample from Sri Krishna Pharmaceuticals, Hyderabad, India. Polymers Pluronic F 127 and Pluronic F 68 were purchased from Sigma life sciences USA and Myrj S40 from Croda India, Mumbai. Fructose, Primellose, Talc, Magnesium stearate were purchased from SD Fine, Mumbai, India.

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 THE GRANULES

Melted granules were prepared in a porcelain dish. Firstly, the mixture of Domperidone with surfactants Myrj S40, Pluronic F 127 and Pluronic F 68 in 1:5 and 1:10 ratios (Table 1) was dry blended for 10 min. Then, this mixture was placed in a hot porcelain dish and supply the heat around 60^0C on temperature controlled water bath so as to melt the surfactant in which the drug was dispersed. The formed molten mass is then cooled to room temperature and were allowed to solidify at room temperature by spreading them in thin layers on glass plates. Pass the melted mass through sieve no # 20 so as to form uniform granules. The cooled granules were stored in sealed bags for their evaluation.

Table 1: Formulation of Domperidone Melt Granules

Formulation code	Drug (mg)	Myrj S40 (mg)	Pluronic F 127 (mg)	Pluronic F 68 (mg)
F1	10	50	---	---
F2	10	100	---	---
F3	10	---	50	---
F4	10	---	100	---
F5	10	---	---	50
F6	10	---	---	100
F7	10	50	50	---
F8	10		50	50
F9	10	50	---	50

EVALUATION OF GRANULES

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 (θ) was measured using fixed funnel method and tapped density was determined using bulk density apparatus.

In-vitro Dissolution studies of granulates

In-vitro dissolution studies for prepared melt granules 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 optimized formulation were obtained. Sample about 5 mg was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 ρsi 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.

Powder X-Ray Diffraction Analysis (XRD)

X- ray diffraction of drug, placebo and optimized formulation were obtained on a D-5000 Semens X-ray diffractometer, using Cu K_a radiation (wave length=1.5406A^0). The data were recorded over a scanning 2ϕ range of 2^0 to65^0 at step time of 0.045 steps/0.5 sec. The relative intensity I/I_0 and the inter planner distance (d) corresponding to the 2ϕ values were reported and compared.

Differential Scanning Colorimetry (DSC)

DSC analysis of drug, placebo and optimized formulation 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 a closed, flat bottom, aluminium sample pans. Thermograms were obtained by heating the sample at a constant rate 10.00^0C/min. A dry purge of nitrogen gas (20ml/min) was used for all runs. Samples were heated from 32.00^0C to 350.00^0C with a hold time for 1.0 min at

32.00^{0}C. The melting point, peak maxima, appearance of any new peak and peak shape was noted.

PREPARATION AND EVALUATION OF SUBLINGUAL TABLETS

Based on the dissolution profile, Domperidone with Myrj S40 & Pluronic F 68 (F9) was selected for the preparation of sublingual tablets. Tablets were formulated as shown in Table 2 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.

Table 2: Formulation of Domperidone sublingual tablets

Ingredients	Quantity (mg)
Domperidone	10
Myrj S40	50
Pluronic F 68	50
Advantose FS 95	72
Talc	4
Magnesium Stearate	4
Primellose	10
Tablet weight	200

Stability studies

To evaluate the drug and formulation stability, stability studies were done according to ICH guidelines. Optimized formulation was sealed in aluminum packaging coated inside with polyethylene, and three replicates were kept in the humidity chamber maintained at 40 ± 2°C and 75 ± 5% RH for six months [9]. Samples were collected after six months of storage and analyzed for the drug content and *in vitro* dissolution rate. Then to prove the stability of dosage form, the similarity index was calculated between dissolution rates of optimized tablets before and after storage[10].

RESULTS AND DISCUSSIONS

Calibration curve of Domperidone was obtained in 0.1N HCl with a slope of 0.0256 and was shown in "Fig 1". Hydrophilic meltable surfactants like Myrj S40, Pluronic F 125 & Pluronic F 68 were selected for the study. All the prepared granules were found to be free flowing powders as shown in Table 3.

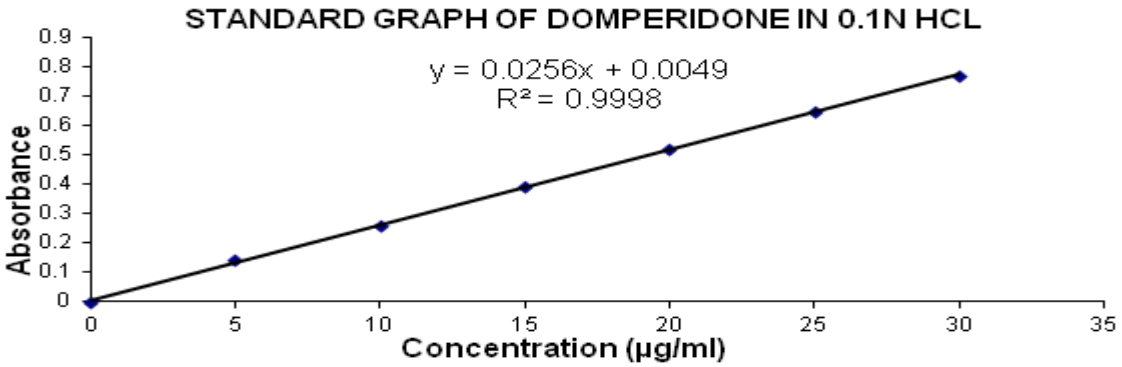

Fig 1: Calibration curve of Domperidone

Table 3: Flow properties prepared melt granules

Formulation code	Bulk Density (g/cc)	Tapped Density (g/cc)	Angle of repose (θ)	Carr's Index	Hausner's ratio
F1	0.257 ± 0.047	0.297 ± 0.043	29.68 ± 1.44	13.4 ± 1.52	1.15 ± 1.2
F2	0.256 ± 0.042	0.304 ± 0.042	31.24 ± 1.45	15.78 ±1.59	1.18 ± 1.47
F3	0.256 ± 0.044	0.301 ± 0.051	29.24 ± 1.36	14.6 ± 1.46	1.17 ± 1.42
F4	0.245 ± 0.043	0.287 ± 0.054	31.12 ± 1.52	14.63 ± 1.48	1.17 ± 1.50
F5	0.256 ± 0.045	0.286 ± 0.044	29.68 ± 1.76	10.48 ± 1.36	1.11 ± 1.51
F6	0.264 ± 0.051	0.291 ± 0.045	28.24 ± 1.72	9.27 ± 1.29	1.10 ± 1.46
F7	0.271 ± 0.050	0.292 ± 0.047	28.36 ± 1.45	7.19 ± 1.46	1.07 ± 1.45
F8	0.259 ± 0.047	0.291 ± 0.046	29.24 ± 1.36	10.9 ± 1.39	1.12 ± 1.38
F9	0.289 ± 0.046	0.319 ± 0.046	28.24 ± 1.39	9.40 ± 1.52	1.10 ± 1.42

Invitro dissolution studies of melt granules

All the surfactants selected showed rapid and higher dissolution of Domperidone as compared to pure drug as shown in "Fig 2". Table 4 shows the comparison of dissolution profile of melt granules with pure drug. Melt granules prepared with Myrj S40 & Pluronic F 68 displayed increased dissolution profile compared to other formulations. So F9 is considered as optimized formulation for preparation of sublingual tablets.

Table 4: Dissolution profile of prepared melt granules & Pure drug

Formulation code	T5	T15	T30	DE 30
F1	43.03	49.27	58.02	46.22
F2	44.46	52.15	63.82	48.55
F3	45.54	53.95	66.73	50.40
F4	46.25	54.31	71.40	50.92
F5	49.48	57.59	73.29	53.81
F6	53.07	60.49	76.25	56.79
F7	55.22	64.11	77.05	59.62
F8	56.65	64.83	79.59	60.61
F9	59.88	71.69	99.57	70.04
Pure drug	17.93	24.24	36.18	23.64

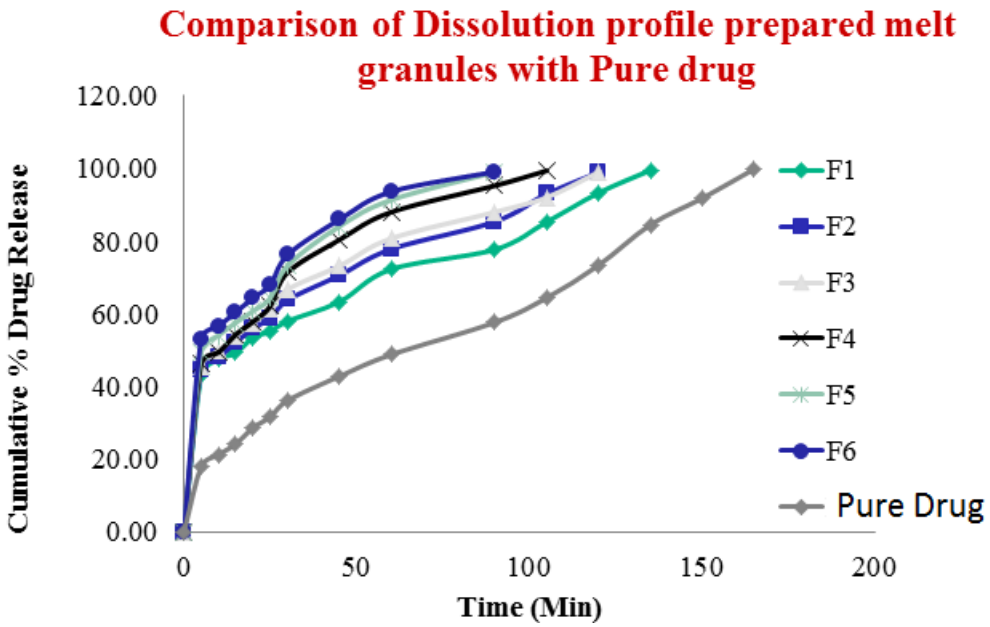

Figure 2: Comparison of Dissolution profile of Domperidone melt granules with pure drug

FT-IR spectroscopy

It was performed by KBR pellet method. The principal peaks of domperidone were observed at 3435, 1694, 1454 and 1105 cm^{-1}. The characteristic peaks for optimized formulation were found at 3435, 1693, 1455 and 1103 cm^{-1} indicating no interaction between drug and the excipients therein. The results are shown in "Fig 3".

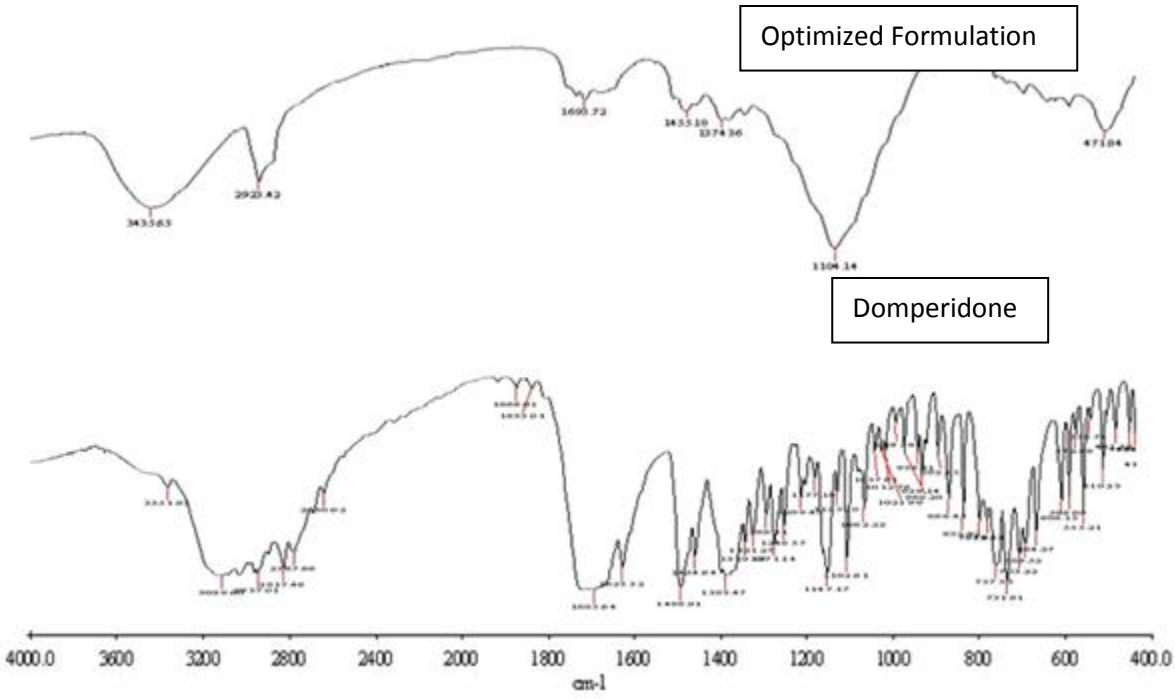

Fig 3: Characterization by FTIR

Differential Scanning Colorimetry (DSC)

The DSC plot of pure domperidone "Fig. 4" shows a sharp endothermic peak near 255°C, which is attributed to its melting temperature. The Optimized Formulation also show the melting point at same temperature indicating no interaction between the drug and excipients.

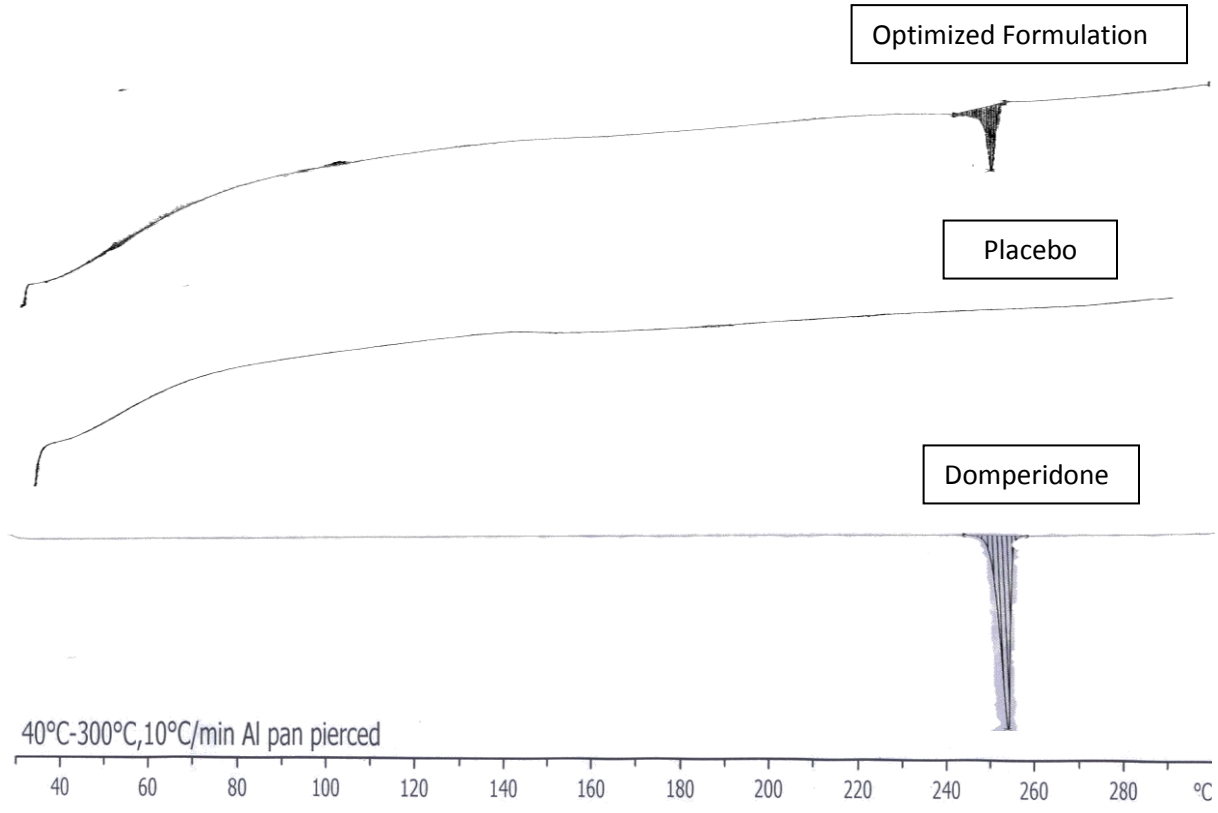

Fig 4: Characterization by DSC

Powder X-Ray Diffraction Analysis (XRD)

XRD of optimized formulation reveals a reduction in peak intensity when compared with XRD of plain drug. The characteristic peaks identified in the drug XRD were not detected in Formulation. Optimised formulation (F9) showed reduced crystalline properties, indicating of possible conversion into amorphous form as shown in "Fig 5".

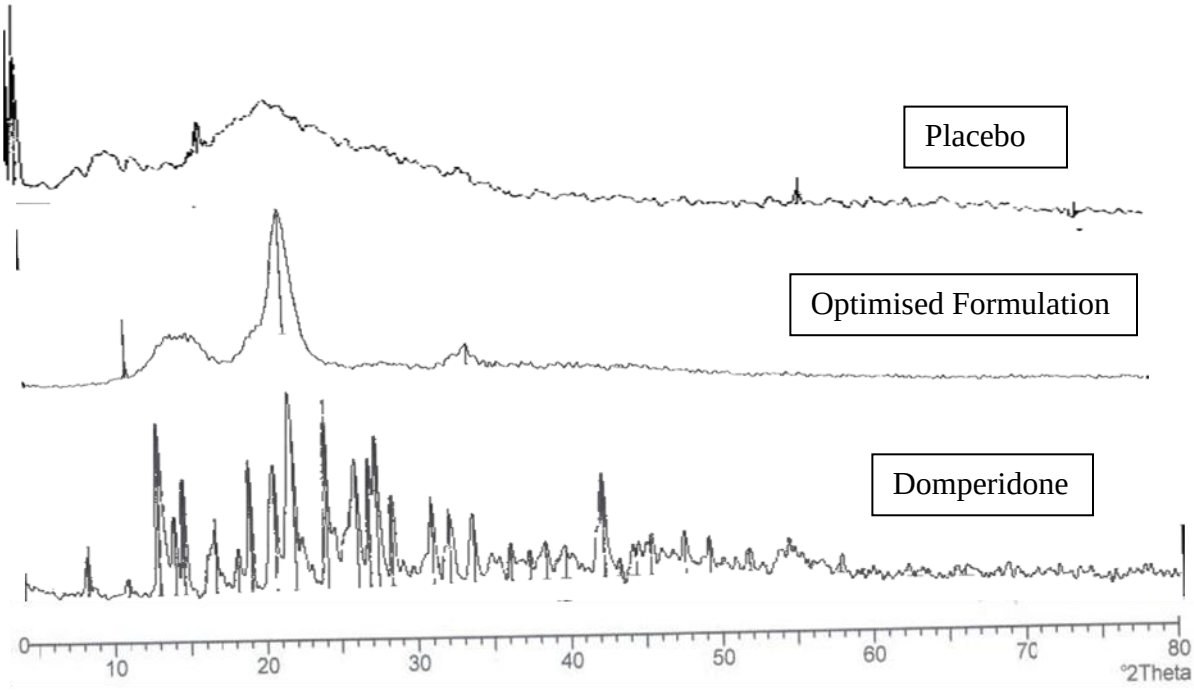

Fig 5: Characterization by XRD

Evaluation of Domperidone Sublingual Tablets

Domperidone sublingual Tablets were prepared by direct compression method. Table 5 reveals that all the prepared tablets have acceptable physical properties according to the IP.

Table 5: Evaluation of Prepared sublingual tablets & Marketed product

S.No	Evaluation Tests	Sublingual Tablets by Melt Granulation	Mkt.Pdt (Motinorm 10mg)
1	Weight Variation	198 ± 1.94 mg	199 ± 1.87 mg
2	Hardness	4.8 ± 0.52 Kg/cm2	4.6 ±0.56 Kg/cm2
3	Friability	0.611%	0.615%
4	Disintegration Time	33 ± 0.79 sec	60 ± 0.56 min
5	Assay	99.07 ± 1.64%	99.01 ± 1.62%
6	Content uniformity	98.01 ± 1.62	98.99 ± 1.46

Tablets prepared with melt granules exhibited higher dissolution rate as compared to marketed tablets. Marketed tablets showed 40.34% drug release in 30 mins whereas sublingual tablets prepared with melt granules showed 99.54 % drug release as shown in "Fig 6". There is a two fold increase in Dissolution efficiency when compared to marketed product. From Table 7 it is clear that the drug release followed first order kinetics.

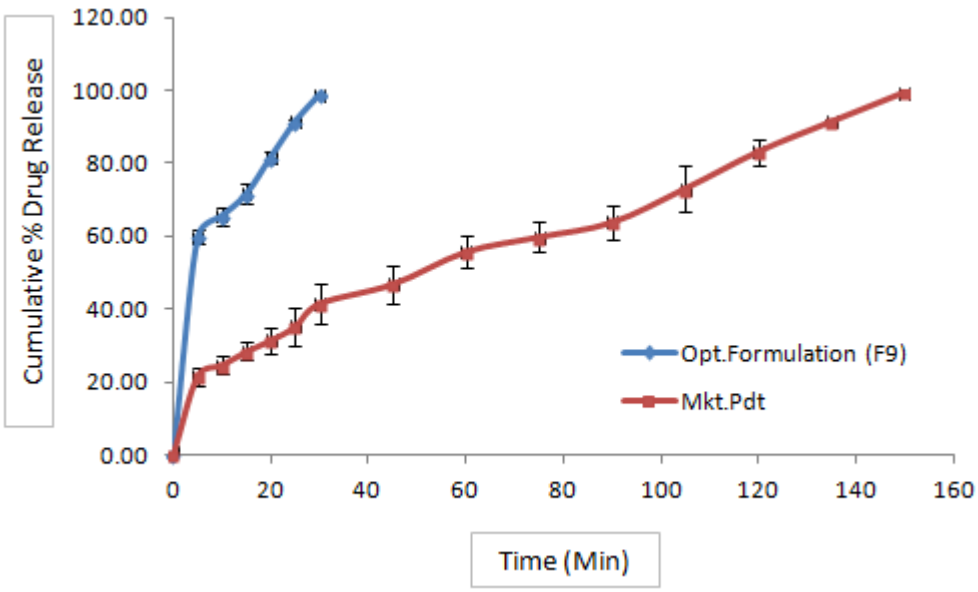

Fig 6: Comparative Dissolution studies of optimized Formulation & Marketed product

Table 6: Dissolution profile of prepared sublingual tablets & Marketed product

Formulation	T5	T15	T30	DE30
Sublingual Tablets	59.88 ± 1.63	71.69 ± 2.44	98.9 ± 0.47	70.4
Mkt. Pdt (Motinorm 10mg)	21.59 ± 2.51	28.34 ± 2.51	41.5 ± 5.13	22.64

Table 7: Kinetic analysis of drug release data

Formulation	Parameters	Zero order	First order	Hixson Crowell ($Q^{1/3}$ -$Qt^{1/3}$)
Opt. Formulation	K	3.76	-0.043	0.107
	r^2	0.627	0.820	0.745
MKT.PDT	K	3.02	0.024	0.069
	r^2	0.604	0.6922	0.659

Stability studies

To check the stability of tablet formulations, stability studies were carried out for six months. After storage of six months, the formulation was subjected to a drug content and *in vitro* dissolution studies and from the statistical analysis there was no significant difference between before and after storage (P<0.05). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 80.5 (Table 9).

Table 9: Accelerated stability studies data

Parameters	Observation						
	Initial	30 Days	60 Days	90 Days	Similarity Factor (f2)	Difference Factor (f1)	P value
Drug content	**99.12**	**98.97**	**98.97**	**98.94**	--	---	---
T5	47	46.99	46.85	45.97	80.5	2.74	Not significant
T15	54.69	53.68	53.43	52.99			
T30	67.41	66.89	66.40	65.98			
DE30	50.14	50.12	49.78	49.76			

CONCLUSION

Melt Granulation was found to be a viable process in improving the dissolution rate of poorly soluble drug like Domperidone. Prepared Sublingual tablets with melt granules of Domperidone displayed significantly increased dissolution rate compared to conventional tablets. FTIR and DSC studies indicate there were no interactions between drug and excipients. XRD studies revealed that there is a change in crystallinity of drug to amorphous form. Mathematical modeling of drug release data fitted into first order kinetics. From the stability studies, the similarity index was found as above 50

indicated the stability of drug in the formulation. The increased dissolution rate may be due to increased wetting and increased surface area of the particles. Thus the melt granulation technique can be a promising approach to improve the dissolution rate of poorly soluble drugs.

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