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Enhancement of Dissolution Rate of Domperidone Using Melt Granulation Technique

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ABSTRACT

The present work describes the melt granulation technique to improve the solubility and dissolution characteristics of a poorly water-soluble drug Domperidone. Melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by a meltable polymers and surfactants. The advantage of this technique as compared to a conventional granulation is that no water or organic solvents is needed. Because of bypassing drying step, the process is less time consuming and uses less energy than wet granulation. Granules were prepared by using hydrophilic polymer polyethylene glycol-6000, 4000 and Myrj-52. The prepared granules were characterized using SEM, DSC and FTIR techniques. A significant enhancement in the solubility and in-vitro dissolution profiles of the melt granules was observed compared to the pure drug and marketed product. DSC results indicated change in internal energy of Domperidone with polymer and surfactant in the melted granules. In conclusion, the results of this work suggest that melt granulation is a useful technique to enhance the solubility and dissolution rate of poorly water-soluble drug like Domperidone.

Key Words: Melts granulation, Domperidone, Dissolution rate, polymer Myrj-52, PEG 4000, PEG 6000.

INTRODUCTION

Dissolution is the process by which a solid solute enters a solution. It may be defined as the amount of drug substance that goes into solution per unit time under standardized conditions of liquid/solid interface, temperature and solvent composition. Dissolution is considered one of the most important quality control tests performed on pharmaceutical dosage forms and now developing into a tool for predicting bioavailability and in some cases, replacing clinical studies to determine bioequivalency. Dissolution behavior of drugs has a significant effect on their pharmacological activity. In fact, a direct relationship between *in vitro* dissolution rate of many drugs and their bioavailability has been demonstrated and is generally referred to as in vitro-in vivo correlation (IVIVC).

Although, salt formation, solubilization and particle size reduction have commonly been use to increase dissolution rate of the drug, but there are particular limitations with these techniques. The desired bioavailability enhancement may not always be achieved. Therefore several approaches are being explored to enhance bioavailability of poorly water soluble drugs. One such formulation approach that has been significantly enhances the absorption of such drugs using melt granulation technique. Advantage of melt granulation technique are Neither solvent nor water used in this process, Fewer processing steps needed, thus time consuming drying steps are eliminated, no requirements for the compressibility of active ingredients and the entire procedure is simple, continuous and efficient, Uniform dispersion of fine particle occurs, Good stability at varying pH and moisture levels [1].

There is wide spread interest in melt granulation technique because that offers a means of facilitating the dissolution and the bioavailability of poorly water soluble drugs when combined with hydrophilic melting binder. This increase in dissolution rate is achieved by a 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 [2-4].

Melt granulation is one of the most widely applied processing techniques in the array of pharmaceutical manufacturing operations. Melt granulation process currently applied in the pharmaceutical research for manufacture of variety of dosage forms and formulation such as immediate release and sustained release pellets, granules and tablets [5-7].

MATERIALS AND METHODS

Materials

Domperidone was purchase from Rohani chemical Pvt. Ltd. Ghaziabad U.P, and polymers Myrj-52, PEG 4000, PEG 6000 (Sigma life science USA) and starch, lactose, magnesium stearates was purchase from CDH New Delhi.

Methods

Melt Agglomeration method was selected for preparation of meltable granules of Domperidone having a melting range of 244^0C- 248^0C. The granules were prepared in the laboratory by adding molten carriers Myrj-52 and PEG 4000, PEG 6000 to the physical mixture of the drug and Lactose and Starch (maize). The granulation process (sieving method) and the formulations were optimized on the basis of preliminary trials like drug-excipients interaction and drug-polymer ratio, Table-1. The drug and diluents were mixed well in the mortar pastel for 15 min. The mixture was then heated up to 50 °C using a hot plate. Next, molten carriers Myrj-52 and PEG 4000, PEG 6000 was added to prepare the granules with each polymer and with combination of polymer. The granulation was done using no. 20 sieves. At the end of the granulation process, granules were cooled at room temperature by spreading them out on trays, collected, and passed through a no 40 sieve [1, 9].

Rheological characterization of granules [10]

The rheological characterization of granules were evaluated using different parameters like bulk density (B.D.), tapped density (T.D.), hausner ratio (H.R.), Carr's index (C.I.), and flow properties (angle of repose).

Granule-size analysis

The size distribution of granules was evaluated using sieve analysis with a sieve shaker (Nippon) and #5 sieves in the 65–1200 μm range. The fractions were collected, stored in a desiccators' at 25 ± 2 °C, and further used for the dissolution studies.

Table-1: Drug-polymer % ratios for the preparation of matrix granules of Domperidone

Formulation code	Drug (%)	Myrj-52 (%)	PEG-4000 (%)	PEG-6000 (%)	Lactose (%)	Starch (maize) (%)
F_1	10	40	-	-	45	15
F_2	10	-	40	-	45	15
F_3	10	-	-	40	45	15
F_4	10	20	20	-	45	15
F_5	10	30	10	-	45	15
F_6	10	20	-	20	45	15
F_7	10	30	-	10	45	15
F_8	10	-	20	20	45	15
F_9	10	-	30	10	45	15

Determination of Drug content

Weigh accurately 10mg drug and melt granules was taken, prepared the 10μg/ml solution in 0.1N HCl and sonicate for 5 minute and kept for 2-3 hrs and filtered through whatman filter paper and measure the absorbance using U.V. Spectrophotometer at 284.0 nm (λ_{max}) [1, 2, and 14]. The drug content was calculated further and determined using calibration curve, Fig. 1.

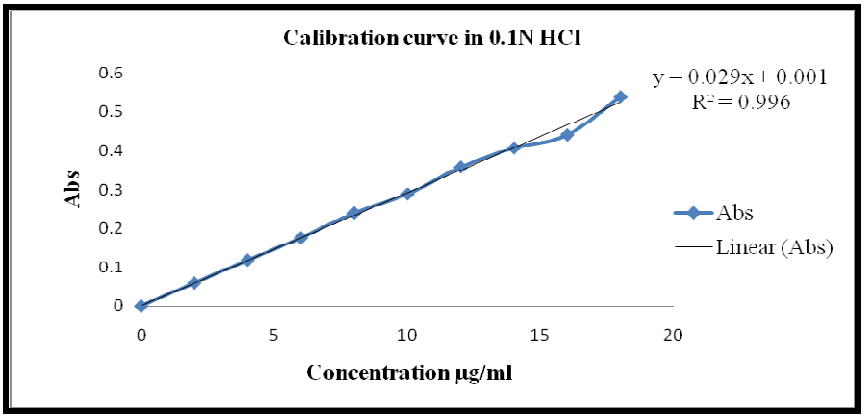


Fig. 1: Calibration Curve of Domperidone at λ_{max} 284.0nm

Fourier transforms infrared (FTIR) spectroscopy

The samples were mixed with potassium bromide in a ratio of 1:99 in mortar and pestle and mixed thoroughly. This mixture was then loaded in FTIR-8400 Shimadzu from MIET Meerut to get an IR spectrum [4, 13].

Scanning electron microscopy

The external and internal morphology of the granules were studied by scanning electron microscopy (SEM) using scanning electron microscope (EVO- 50, ZEISS, IIT Delhi). The samples for SEM were prepared by adhering granules on a double adhesive tape stuck to an aluminium stub. The stubs were then coated with silver under an argon atmosphere using a high-vacuum evaporator (Polaron SEM coating system). The coated sample was then randomly scanned and photomicrographs were taken with a scanning electron microscope [2, 7].

Differential scanning calorimetry (DSC):
A differential scanning calorimeter (DSC 7, *PERKIN-ELMER*) at IIT Delhi was used to obtain the DSC curves representing the rates of heat uptake. About 5 mg of sample was weighed in a standard open aluminum pan. An empty pan of the same type was used as the reference. Samples were heated from 30 to 300 °C at a heating rate of 10 °C/min while being purged with dry nitrogen. Calibrations of temperature and heat flow were performed with indium [2, 7].

Dissolution studies
Dissolution studies of the designed formulations were conducted using USP II paddle type dissolution apparatus by taking granules equivalent to 10 mg of drug. The dissolution medium used was 900 ml of 0.1N HCl, maintained at 37±0.5 ^{0}C at a speed of 50 rpm. The dissolution study was performed for 1 hr. 5 ml sample was withdrawn out at specified intervals of time and filtered. The volume of dissolution fluid was adjusted to 900 ml by withdrawing each 5 ml aliquot and by adding 5 ml 0.1N HCl to maintain a constant volume after each sampling. The samples were analyzed spectrophotometrically at 284.0 nm (λ_{max}). The concentration of drug was determined from cumulative release and % cumulative drug release. [13, 14]

Preparation and evaluation of capsules
The prepared capsules were then evaluated for weight variation, drug content, and In- vitro disintegration time according to Indian pharmacopoeia 2007; and In-vitro dissolution studies were performed similarly as for granules using USP type-II apparatus [13]

RESULT AND DISCUSION

Rheological characterization of granules
All tested formulations had a Carr's index ranging from 12% to 23.6% and optimized formulation was show good rheological properties of granules. Results of the characterization of the granules reported in Table-2.

Table-2: Rheological characterization of granules (F1-F9)

Formulation code	Bulk density (g/ml) ± SD	Tapped density (g/ml) ± SD	Carr's index± SD	Angle of repose± SD
F1	0.454±0.047	0.555±0.043	18.2%±1.86	29◦.74±1.82
F2	0.431±0.045	0.500±0.037	19.2%±1.83	26◦.53±1.76
F3	0.412±0.042	0.500±0.021	17.6%±1.85	27◦.96±1.65
F4	0.414±0.047	0.500±0.027	17.2%±1.76	25◦.94±1.81
F5	0.516±0.043	0.585±0.037	19.7%±1.46	23◦.22±1.44
F6	0.424±0.037	0.496±0.041	14.5%±1.52	22◦.83±1.36
F7	0.516±0.051	0.591±0.043	18.6%±1.85	25◦.20±1.68
F8	0.500±0.041	0.555±0.044	16.0%±1.62	26◦.72±1.55
F9	0.515±0.040	0.598±0.026	18.8%±1.76	27◦.76±1.35

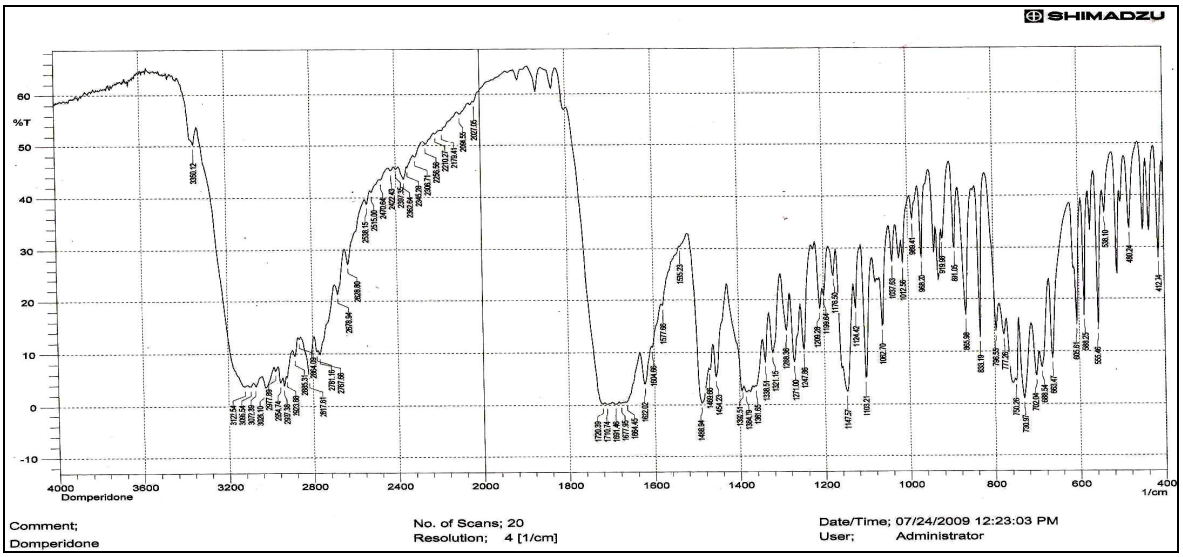
Granule-size analysis:
The amount of fine powder (< 70 μm) and the amount of big lumps (size > 1200 μm) are less than 2% and 6 %, respectively. This finding confirms that the parameters were correct. The main fraction was 150–400 μm, and more than 70% of the granules had a size in the range of 250–850 μm.

Drug content:

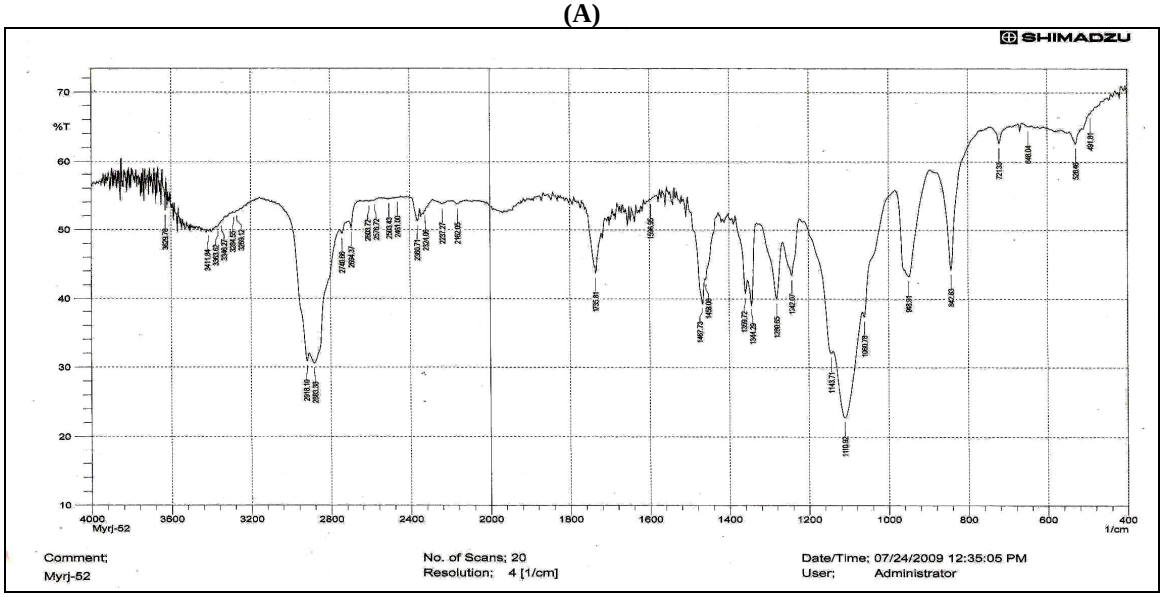
The drug content in the prepared melt granules were determined and found 99.96%±0.96 shows no or less wastage or deterioration of the drug in the melt granule formation, results reported in Table-3.

Table 3 % Drug content of optimize granules

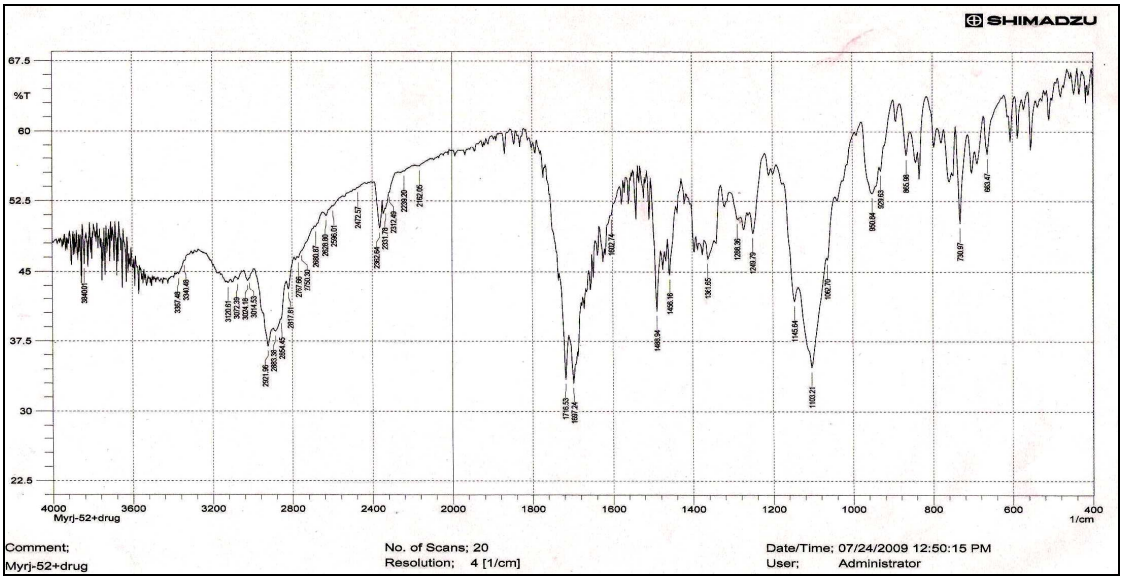
Formulation code	F1	F2	F3	F4	F5	F6	F7	F8	F9
% drug conten	99.83	99.98	99.33	98.92	98.85	101.18	99.99	99.98	98.91
Mean±SD	99.96%±0.955								



(A)



(B)



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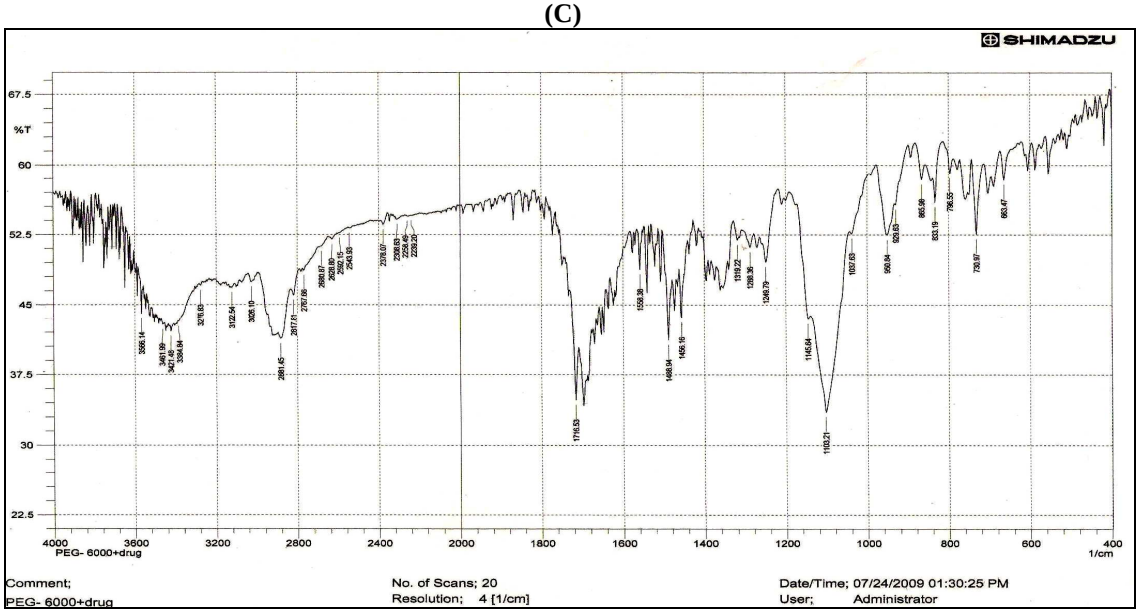

(D)

Fig. 2: (A) I.R. spectra of pure drug (Domperidone) (B) I.R. Spectra of Myrj-52 (C) I.R. Spectra of Myrj-52+Drug (D) I.R. Spectra of Myrj-52+Drug+PEG6000

Fourier transforms infrared (FTIR) spectroscopy

Fourier transform infrared spectroscopy was performed on Domperidone the prominent peaks were obtained at 3122,1720, 1677, 1488, and 1271cm because of stretching vibration bands of C=O, N-H, C-N, and two C-O, respectively. The group frequencies of drug confirmed to the respective structure. In case of melt granules of Domperidone and myrj-52 and PEG 4000, PEG 6000, both drug and polymers peaks were present. The spectra revealed no difference in the positions of the absorption bands, especially with respect to C-N, =O, NH, hence providing the evidence for the absence of hydrogen bonding interaction in solid state between polymers and Domperidone. When the ratio of Domperidone and polymer is same, the peak is sharp, where as in higher polymer, these peaks are not distinct, Fig. 2 (A-C).

Scanning electron microscopy

The scanning electron micrographs of Domperidone with Myrj-52, PEG 4000 and PEG 6000 in 1:1 ratio systems were reported in Fig. 2. Domperidone: Myrj-52, Domperidone: PEG 4000 and

Domperidone: PEG 6000 melt granules was relative have rough surface and spherical shape. Different surface morphology might be responsible for the enhanced drug dissolution rate found for melt granules, Fig. 3.

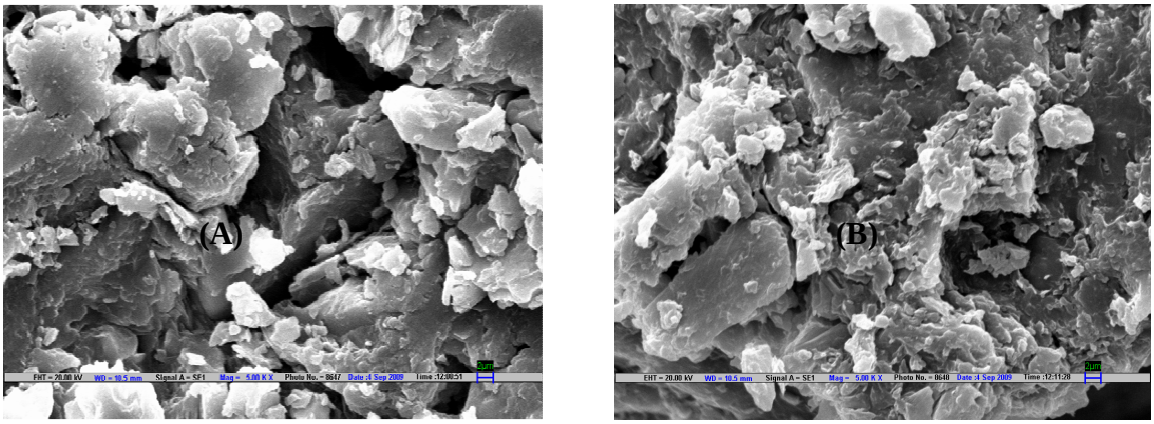

Fig. 3: (A) SEM image of melt granules of myrj-52 at 4×, (B) SEM image of melt granules of myrj-52 at 20x.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry scans of pure domperidone, and hydrophilic melting binder Myrj-52, PEG 4000, PEG 6000. Domperidone showed an endothermic peak at 257.90^{0}C corresponding to its melting point. Myrj-52 and PEG 4000, PEG 6000 shows the thermogram at 50^{0}C, 60^{0}C and 70^{0}C respectively corresponding to its melting point. Concerning the melt granules of Domperidone with Myrj-52, PEG 4000 and PEG 6000, endothermic peaks were found at 249.25, 248.9 and 241.36 respectively along with the broad peak of polymer. The phase transition thermal profile of Domperidone with the broaden and size reduced almost disappeared peak with a concomitant shift to lower temperature, indicating the formation of an amorphous nature and the molecular encapsulation of the drug inside the granules, Fig. 4.

Dissolution studies

Dissolution profile of pure drug and optimized of all granules is shown in Fig. 5. The figure indicated that the melt granule (F1) 1:4 of DOM:myrj-52 gives fast dissolution rate 86.024% of drug as compared to other polymers and plane drug. Melt granulation technique has improved the dissolution rate of Domperidone to a great extent.

Table-4: % Drug release of optimize batch

Time(min)	%Drug Release F1± SD	%Drug Release F5± SD	%Drug Release F6± SD	%Drug Release F7± SD
0	0±0.0	0±0.0	0±0.0	0±0.0
5	45.931±2.83	46.551±1.87	40.344±2.13	41.586±2.07
10	57.051±2.13	58.303±2.21	56.458±2.09	57.651±2.02
20	72.344±1.65	73.603±2.67	75.431±2.11	74.820±1.83
30	80.855±2.32	80.248±3.12	81.462±1.87	80.848±1.23
45	84.417±1.93	85.679±1.86	85.027±1.56	86.282±1.43
60	86.024±2.76	87.193±1.97	86.141±1.65	88.524±2.82

DOM:myrj-52:PEG4000 and DOM:myrj-52:PEG6000 melt granule system in 0.1N HCL the percentage of drug release in one hour were (F5) 87.193% , (F6)86.14% and(F7) 88.52%, for 1:2:1 ratio and 1:2:2, 1:3:1 respectively.

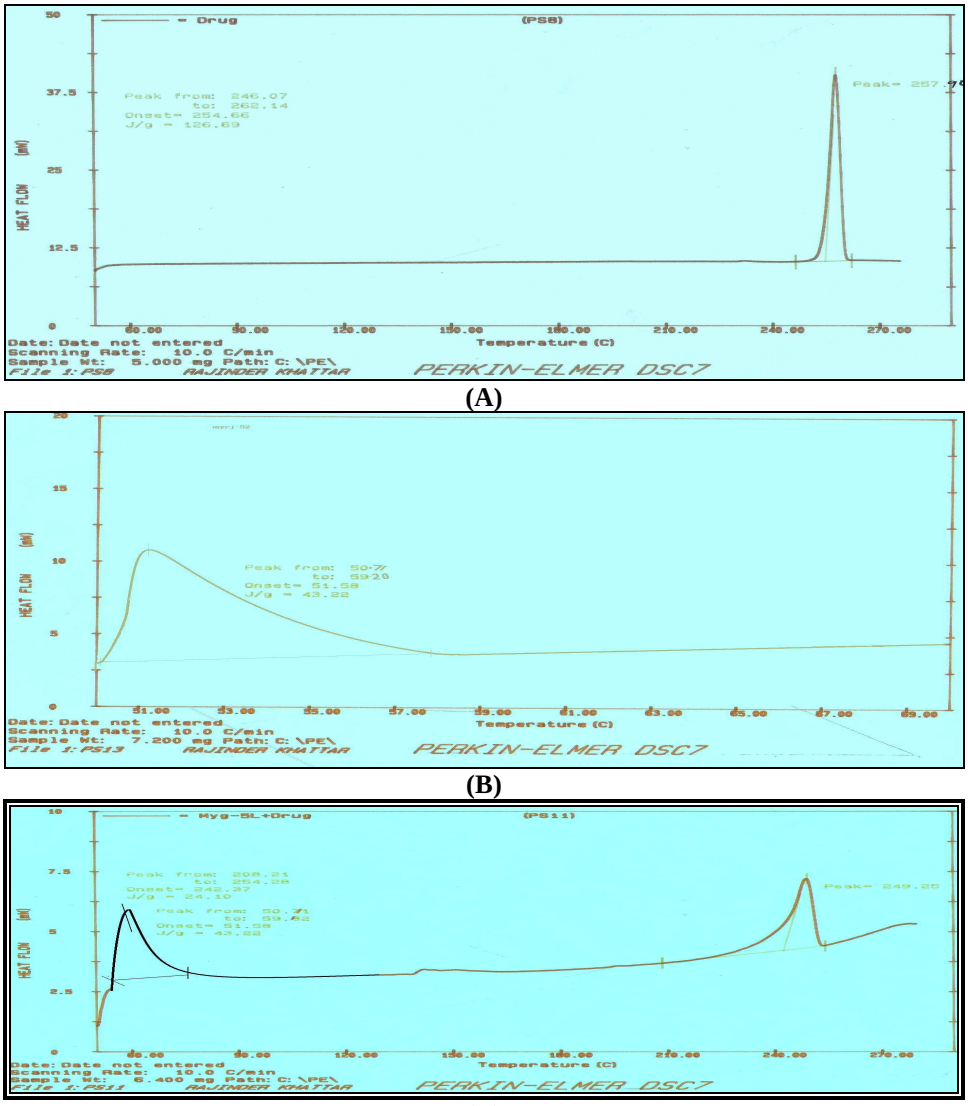

Fig. 4: (A) DSC curve of Domperidone (B) DSC curve of Myrj-52 (C) DSC curve of optimized batch

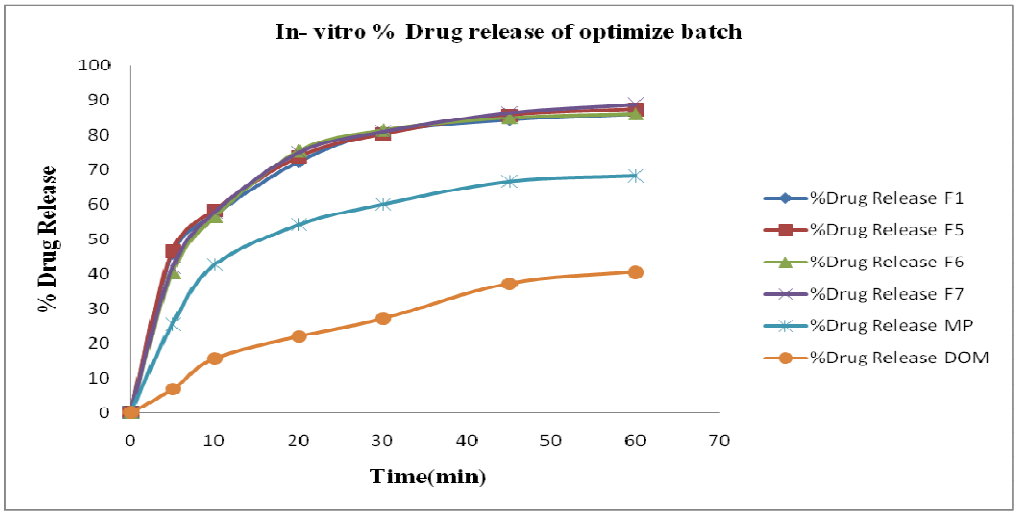

Fig. 5: Comparative dissolution profiles of optimize batch with Domperidone (DOM) & marketed product (MP)

The data indicates that the % drug release in one hour from melt granules increased with increasing concentration of myrj-52 and PEG 4000, PEG6000 in combination form than polymer use alone. (Table 4)

CONCLUSION

Melt granulation has been proved to be a viable process to produce a fast-release dosage form for Domperidone, using myrj-52, PEG 4000, PEG 6000 as a melting binder, without using solvents or water. It was found that formulation F7 (DOM: myrj-52, PEG6000) have best releasing of drug.

Acknowledgment

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REFERENCES

[1] P. D. Chaudhari, S. P. Chaudhari, G. S. Yeola, N. S. Barhate, *J. Pharm. Sci.*, **2005**, 8(2),132-140.
[2] P. Sharma, P. Chaudhari, H. Bhagat, N. Varia, *J. Pharm. Sci.*, **2007**, 1-10.
[3] N. V. Patel, P. Narendra, P. M. Patel, *Asian J. Pharm.*, **2008**, 22-25.
[4] W. S. Heng, T. W. Wong, *Pharm Tech.*, **2003**, 1-6.
[5] P. J. Sinko, Martin's physical pharmacy of pharmaceutical 5th-edition. Indian edition, Lippincott Williams Wilkins. BI-Publication Pvt Ltd., **2006**, 53-54.
[6] J. Swarbrick, J. C. Boylan, "Granulation", Encyclopedia of pharmaceutical technology, Marcel Dekker INC, New York, **1992**, Volume- 7, 121-123.
[7] V. B. Yadav, A. V. Yadav, *Int. J. Pharm. Tech Research*, **2009**, 1(2), 256-263.
[8] H. Eliasen, H. G. Kristensen, T. Schafer, *Int. J. Pharm.*, **1999**, 186, 149-159.
[9] M. E. Aulton, "The science of dosage form design, 2nd edition, published by Churchill Livingstone, **2002**, 113-138,181,187,188.
[10] T. Schafer, P. Holm, H. G. Kristensen, *Drug Devl. Ind. Pharm.*, **1990**, 16 (8), 1249 – 1277.
[11] M. Dilip Parikh, "Theory of Granulation", Handbook of Pharmaceutical Granulation Technology, Marcel Dekker INC, New York, **1997**, 8, 15, 16, 152.
[12] M. Dilip Parikh, "High Shear Mixer Granulators", Handbook of Pharmaceutical Granulation Technology, Marcel Dekker INC, New York, **1997**, 165-181.
[13] Indian Pharmacopoeia **2007**, Vol-II. Published by central institute of pharmacopoeial commission, Ghaziabad, pp.600-601.
[14] British Pharmacopoeia. **2004**, vol. I, 690-692.