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Original Article

Formulation and evaluation of polymer based, rapid onset, patient friendly, oral film of domperidone maleate

Deepak S Khobragade[1], Uday Bhasker Goud G[2], J. S. V. Prakash[2], Pranav Kumar A. V. R[3], G. R. Sreenivas Reddy[3], Mrunali Potbhre[3]

[1]Department of Pharmaceutics, Vijaya College of Pharmacy, Hyderabad, Telangana, India
[2]Department of Industrial Pharmacy, Bharat Institute of Technology, Hyderabad, Telangana, India
[3]Department of Pharmaceutics, Bharat Institute of Technology, Hyderabad, Telangana, India

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ABSTRACT

Mouth dissolving films have emerged as an advanced alternative to the traditional oral solid drug delivery systems. Generally the films are prepared using hydrophilic polymers that dissolves or hydrate on the tongue or buccal cavity, releasing the drug for enhanced absorption. The present study was undertaken with the objective of formulating mouth dissolving film(s) of anti-emetic drug Domperidone maleate to impart immediate action and enhance the convenience and compliance by the patients specifically elderly and paediatric. The films were formulated by solvent casting method with different concentrations of HPMC 15cps, Methyl Cellulose and Hydroxy Ethyl Cellulose as film forming polymers and glycerin as plasticizer. Prepared films were evaluated for their dissolution, *disintegration*, and physico-mechanical properties and short-term stability study. The formulations having polymers at low concentrations showed better results. Among these, formulation containing HPMC 15cps was found to show much superior film properties compared to Methyl Cellulose and Hydroxy Ethyl Cellulose. HPMC based film showed the high drug dissolution (99.54% or more within 5 min), satisfactory *in vitro* disintegration time (85 sec) and physico-mechanical properties that are indicative of good mouth dissolving films.

Key words: Mouth dissolving Film, Domperidone Maleate, HPMC, Methyl Cellulose, Hydroxy Ethyl Cellulose

INTRODUCTION

Amongst the different routes of administration, the oral route of administration continues to be most preferred route due to various advantages like self-administration, ease of administration, avoidance of pain, versatility and most importantly patient compliance. Many pharmaceutical dosages are administered in the form of oral pills, granules, powders, and liquids. Generally, a pill is designed for swallowing intact or chewing to deliver a precise dosage of medication to patients. The pills generally include tablets and capsule. Some patients, particularly paediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms[1].Many paediatric and geriatric patients are unwilling to take these solid preparations due to fear of choking[2]. These dosage forms also have slow onset of action as they need to reach at least to stomach to get absorbed. Therefore it is important in this context to develop new dosage forms that avoids the choking hazard and present advantage of rapid onset.

Formulation of mouth dissolving oral film (MDF) is one such relatively new approach. Recently, mouth dissolving drug delivery system have started gaining .popularity and acceptance as new drug delivery systems, because these delivery systems either dissolve or disintegrate in mouth rapidly, without requiring any water to aid in swallowing[3]. They also impart unique product differentiation, thus enabling use as line extensions for existing commercial products. This novel drug delivery system can also be beneficial for meeting the current needs of the industry such as improved solubility, stability, biological half-life and bioavailability enhancement of drugs[4,5]. A MDF is prepared using hydrophilic polymers that rapidly dissolves on contact with the tongue or fluids in buccal cavity. Patients who suffer from vomiting cannot be administered the conventional oral

***Corresponding Author Address: Dr. Deepak S. Khobragade,** Professor; Pharmaceutics, Vijaya College of Pharmacy, Munuganoor(v), via sanghi nagar post, Hyderabad-501511, R.R.Dist, (Telangana), Email: ksdeepak312yahoo.co.in*

formulations and need fast acting formulation. In general, emesis is preceded with nausea and in such condition it is difficult to administer drug with a glass of water; hence it is beneficial to administer drugs as mouth dissolving films with good mouth feel[6,7,8].

Domperidone maleate is prescribed for prevention of chemotherapy-induced nausea and for pre-and post-surgical nausea and vomiting. It is an antiemetic drug that blocks the action of dopamine and has strong affinities for the D_2 and D_3 dopamine receptors. It is well absorbed from GIT, but its bioavailability is low due to extensive first pass metabolism. This condition makes it a suitable drug candidate for MDF.

In order to provide a convenient and effective mean of administration of drug to patients suffering from vomiting and nausea, the present study was aimed at developing a rapid onset, fast acting, "patient friendly" and stable mouth dissolving film of Domperidone maleate using different hydrophilic polymers.

MATERIALS

Domperidone maleate was obtained as research sample from Lupin Pharmaceutical Pvt Ltd, India. Hydroxy propyl methyl cellulose (HPMC15 cps), Methyl cellulose, Hydroxy ethyl cellulose, DMSO, DMF, glycerine, sodium saccharin were procured from SD Fine-Chem Ltd, Mumbai, India. All other reagents used were of analytical grade.

METHODS

Formulation of mouth dissolving films of domperidone maleate

Mouth dissolving films were prepared by solvent casting method.

Solution- I (Aqueous) was prepared by dissolving polymer (HPMC 15cps, MC, HEC) in 10 mL water with stirring to produce a clear solution and kept for 1 hour to remove all the air bubbles that might have formed.

Solution- II (Aqueous) was prepared by dissolving sweetener, flavouring agent, surfactant, and saliva stimulating agent in specific proportion in distilled water.

Solution III was prepared by dissolving pure drug in mixer of 1ml DMSO and 1ml DMF.

The solutions I, II and III were mixed and stirred for 1 hour. Glycerine was added to this solution. The solutions were cast on to 9-cm diameter Petri dish and were dried at room temperature under light for 48 hours. The films were carefully removed from the Petri dish and checked for any imperfection and cut according to size required for testing (square film 2 cm length, 2 cm width) so that each film contained 10mg of the drug. The samples were stored in a glass container maintained at temperature 30 °C and relative humidity 60% ± 5% until further analysis.

Various formulations evaluated for film formation are given in Table No.1

RESULTS AND DISCUSSION

Physical appearance and surface texture of films: These parameters for all these formulations were checked simply with visual inspection of films and by feel or touch. The observations suggest that the films were having smooth and rough surface and they were elegant with acceptable appearance.

Mechanical properties:

Thickness: The general observation is that the thickness of the films increases as the total quantities of the polymers increase. The results suggest that the thickness of film at all the areas of individual films was uniform and within predetermined limits. The thickness of the film ranges from 0.15 – 0.37 mm as shown in Table No.2.

Tensile Strength: The films have shown good tensile strength and no sign of cracking in the films was observed. The tensile strength of all the batches ranged from 5.727- 6.693 g/mm^2 .The data of the tensile strength is presented in the Table no. 2. Formulation MC4 had highest tensile strength.

Percent Elongation: Percent elongation is mainly based on tensile strength of films. The nature of polymer affects tensile strength and % elongation. The percent elongation of all the batches ranged from 16-36 and percentage elongation of all films was given in Table No 2. It increased upon increasing the amount of polymer in the formulations. Formulation MC4 had highest percentage elongation.

Weight Uniformity. From this study the films exhibited uniform weight and there was no deviation in the weight of any formulation. The data of the individual weights are shown in the Table No. 2.

Folding Endurance: The results were reported in the Table No.2, The Folding endurance in the films was found to be ranged from 121 to 198. Formulations MC1 was found to have more folding endurance.

Surface pH: The pH of all the films was found to be around 6.8 that is close to the saliva pH. The surface pH of the films was ranging from 6.7 to 7 as shown in Table-3.

Percentage Drug Content: The drug content uniformity test was performed to ensure uniform and accurate distribution of drug. The content

uniformity was performed for all the formulations, results are tabulated in Table No.2. The results indicated that in all the formulations the drug content was uniform and within limits. The ranges of drug content in all the formulations were 99 % to 103%.

Moisture Content (Percentage Moisture Loss-(PML): The PML of the film containing HPMC was optimum. With different polymers, low concentration was giving low PML. Formulation HP3 was the best formulation having low moisture loss. The PML of the films ranged from 3.68-5.92 as shown in Table-3.

Moisture Uptake (Percentage moisture Absorption (PMA): The PMA of the film containing HPMC was optimum. With different polymers, low concentration was giving low PMA. Formulation HP3 is the best formulation having low moisture uptake. The Percentage moisture absorption of the films ranged from 4.52 to 8.22 as shown in Table No. 2.

In-vitro Disintegration time: The results were reported in the Table No. 2. The disintegration time of the films were found to be decreased with decrease in the concentration of the polymer. The DT ranges from 85 seconds to 105 seconds. Indicating that all formulations were god with respect to disintegration time.

In-vivo Dissolution time: The results suggest that in-vivo dissolution time of the films decreased as the total quantities of the polymers were decreased. The in-vivo dissolution time of the film containing HPMC 15cps was optimum. With different polymers, low concentration showed lesser in-vivo dissolution time i.e. HP3, MC3 and HE3. The in-vivo dissolution time for the formulations HP3, MC3, HE3 was found to be less among all the formulations i.e., 58, 90, 62 seconds respectively. Out of these three formulations HP3 was the best formulation having less in-vivo dissolution time. The in-vivo dissolution time of the films ranged from 58 to 150 as shown in Table No 2.

Taste Evaluation by Panel Method: The prepared films were given to volunteers of different age groups between 20 to 40yrs and evaluated for effectiveness of taste masking. Results showed that excellent taste masking was achieved with all formulations. Taste evaluation study of mouth dissolving films by panel method revealed that about 90% of the volunteers sensed no bitter taste.

The results of taste evaluation by panel method are shown in Table No.3.

The results are classified as below,

+ = excellent taste masking. ; ++ = slightly bitter;+++ = very bitter.

In Vitro Drug Release : From the results it is observed that the in-vitro drug release of the films was increased as the total quantities of the polymers were decreased. In-vitro drug release studies revealed that the release of Domperidone maleate from different formulations varies with characteristics and composition of film forming polymers as shown in Figure-2.

The release rate of Domperidone maleate increased with decreasing concentrations of HPMC 15cps, MC and HEC as in formulations HP3, MC3, and HE3 respectively. The in-vitro drug release from the formulation HP3 is complete and total amount of drug was released in within 5 min. Formulations HP3 was the best formulation having highest drug release. Maximum drug release was observed in HP3 that is 99.56%.

Stability Studies: The selected film formulations were evaluated for stability studies which was stored at 40 ^{0}C at 75% RH tested for 1 month and were analyzed for their physical parameters, in-vitro disintegration time and drug content at 1 month interval for total of three months. The residual drug contents of formulations were found to be within the permissible limits and the results were shown in the Table-4.

Films stored at 40 ^{0}C/ 75% RH were also evaluated for in vitro drug release for three months. The results of dissolution study are given in Table No. 5. The results of only three batches with highest polymer concentration are given for convenience.

The results indicate that there was no significant change in drug release pattern. The results of stability study show that the film formulations were having good stability.

Differential Scanning Calorimetric: The DSCthermo gram of Domperidone maleate exhibited an endothermic peak at 237.8 ^{0}C corresponding to its melting point. The DSC thermograms of Domperidone maleate with other excepitents doesnot show profound shift in peaks which indicates compatibility. The DSC study for HPMC based formulation is only given in the results for convenience.The DSC thermo gram of the individual drug, Hydroxy propyl methyl cellulose and drug with Hydroxy propyl methyl cellulose shown in figure.15,16 and 17. The thermo-grams show that the formulation has no interactions between its components and is stable.

Scanning Electron Microscopy (SEM): The SEM studies were carried out to study surface characteristics of the films. The film shows a smooth appearance without any signs of crystallization of drug. The film indicate sufficient blending of ingredients and no apparent segregation.

CONCLUSION

From the present investigation it can be concluded that taste masked mouth dissolving films can be a potential novel drug dosage form for paediatric,

geriatric populations to provide quicker onset of action and fast relief to treat general conditions of nausea and vomiting. The films can be formulated with hydrophilic polymers with combination of plasticizer and taste masking /taste enhancing agents successfully.

Table No . 1: Different Formulations of HPMC 15cps, MC and HEC films

Ingredients	FORMULATION BATCH CODE								
	HP 1	HP 2	HP 3	MC4	MC5	MC	HE 7	HE 8	HE 9
Domperidone maleate (mg)	202.5	202.5	202.5	202.5	202.5	202.5	202.5	202.5	202.5
HPMC 15cps (mg)	500	400	300	-	-	-	-	-	-
MC (mg)	-	-	-	500	400	300	-	-	-
HEC (mg)	-	-	-	-	-	-	500	400	300
DMSO (ml)	1	1	1	1	1	1	1	1	1
DMF (ml)	1	1	1	1	1	1	1	1	1
Ethanol (ml)	1	1	1	1	1	1	1	1	1
Plasticizers (%)	15	15	15	15	15	15	15	15	15
Saccharine Sod. (%)	5	5	5	5	5	5	5	5	5
Citric acid (%)	1	1	1	1	1	1	1	1	1
Sodium Chloride (%)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Table no. 2: Evaluation of mouth dissolving film formulations.

TEST PARAMETERS	FORMULATION BATCH CODE								
	HP 1	HP 2	HP 3	MC4	MC5	MC6	HE 7	HE 8	HE 9
Thickness (mm)	0.27	0.20	0.15	0.37	0.29	0.26	0.30	0.26	0.19
Tensile strength:	6.461	6.177	5.916	6.693	5.850	5.727	6.544	6.300	5.948
Percent elongation:	30	24	20	36	34	32	24	20	16
Folding endurance	198	169	141	148	130	121	181	171	142
Weight Uniformity	0.073	0.051	0.038	0.070	0.054	0.048	0.056	0.047	0.039
% Moisture content	3.81	3.71	3.68	4.82	4.61	4.42	5.92	5.81	5.56
%Moisture uptake	5.10	4.90	4.52	6.20	6.00	5.91	8.22	7.82	7.51
Disintegration time (sec)	103	90	85	110	105	98	107	92	86
Surface PH	6.8	6.7	6.8	6.9	6.8	6.8	6.7	7	6.9
Dissolution time (sec)	121	80	58	150	130	90	110	72	60
%Drug content	99.3	101.9	103.2	99.21	99.60	101.9	99.30	99.91	101.3

Table No. 3 Taste evaluation by panel method.

VOLUNTEERS	FORMULATION BATCH CODE								
	HP 1	HP 2	HP 3	MC 4	MC 5	MC 6	HE 7	HE 8	HE 9
V 1	+	+	+	+	+	+	+	+	++
V 2	+	+	+	+	+	+	+	++	+
V 3	+	+	+	+	+	+	+	+	++
V 4	+	+	++	+	+	+	+	+	++
V 5	+	+	+	+	+	+	+	+	+
V 6	+	+	+	+	+	+	+	+	+
V 7	+	+	++	+	+	+	+	+	+
V 8	+	+	+	+	+	++	+	+	++
V 9	+	+	++	+	+	+	+	+	+
V 10	+	+	+	+	+	+	+	+	++

Table No.4: Results of stability study of films stored at Formulations stored at 40 ^{0}C/ 75% RH

formu-lation	Test parameters															
	Initial				1st Month				2nd Month				3rd Month			
	A	B	C	D	A	B	C	D	A	B	C	D	A	B	C	D
HP1	Good	No	103	99.3	Good	No	103	99.3	Good	No	104	99.3	Good	Less	106	99.3
HP2	Good	No	90	101.9	Good	No	90	101.9	Good	No	91	101.9	Good	Less	91	101
HP3	Good	No	85	103.2	Good	No	85	103.2	Good	No	85	103.2	Good	No	84	103.2
MC1	Good	No	110	99.21	Good	No	110	99.21	Good	Less	111	99.2	Good	More	112	99.2
MC2	Good	No	105	99.60	Good	No	105	99.60	Good	No	105	99.60	Good	More	105	99.60
MC3	Good	No	98	101.9	Good	No	98	101.9	Good	No	98	101.9	Good	Less	98	101.9
HE1	Good	No	107	99.30	Good	No	107	99.30	Good	No	108	99	Good	Less	110	99
HE2	Good	No	92	99.91	Good	No	92	99.91	Good	No	92	99.91	Good	Less	92	99.91
HE3	Good	No	86	101.3	Good	No	86	101.3	Good	No	86	101	Good	No	86	101

A- **Physical appearance, B- Shrinkage, C-** ***In vitro*** **disintegration time(sec), D-% Drug content.**

Table No.5: In vitro drug release from films stored at 40 ^{0}C/ 75% RH

Time (sec)	% Drug Release											
	HP3 Batch				MC 3 Batch				HE 3 Batch			
	Initial	1 month	2 month	3 month	Initial	1 month	2 month	3 month	Initial	1 month	2 month	3 month
0	0	0	0	0	0	0	0	0	0	0	0	0
30	13.40	13.40	13.20	13.20	10.20	10.18	10.00	9.90	12.9	12.80	12.8	12.8
60	29.50	29.49	29.00	29.00	21.90	21.90	21.82	21.62	27.2	27.2	26.92	26.90
90	48.40	48.40	47.80	47.11	32.50	32.38	31.89	31.67	38.2	38.15	38.10	38.00
120	64.20	64.12	64.00	63.89	45.80	45.80	45.27	45.00	55.3	55.3	55.12	54.96
150	75.47	75.47	74.81	74.81	58.40	58.40	58.08	58.08	69.1	69.00	68.91	68.91
180	89.21	89.21	89.10	89.01	69.40	69.11	68.94	68.83	75.2	75.2	74.99	74.81
210	93.69	93.69	92.69	92.60	78.40	78.40	78.04	78.00	85.9	85.88	85.79	85.65
240	96.08	96.07	96.08	96.00	87.50	87.50	87.00	87.00	90.1	90.00	89.91	89.78
270	98.04	98.04	97.94	97.90	91.10	91.09	91.04	91.04	95.65	95.64	95.63	95.63
300	99.56	99.55	99.45	99.44	96.90	96.89	96.79	96.78	99.34	99.34	99.33	99.31

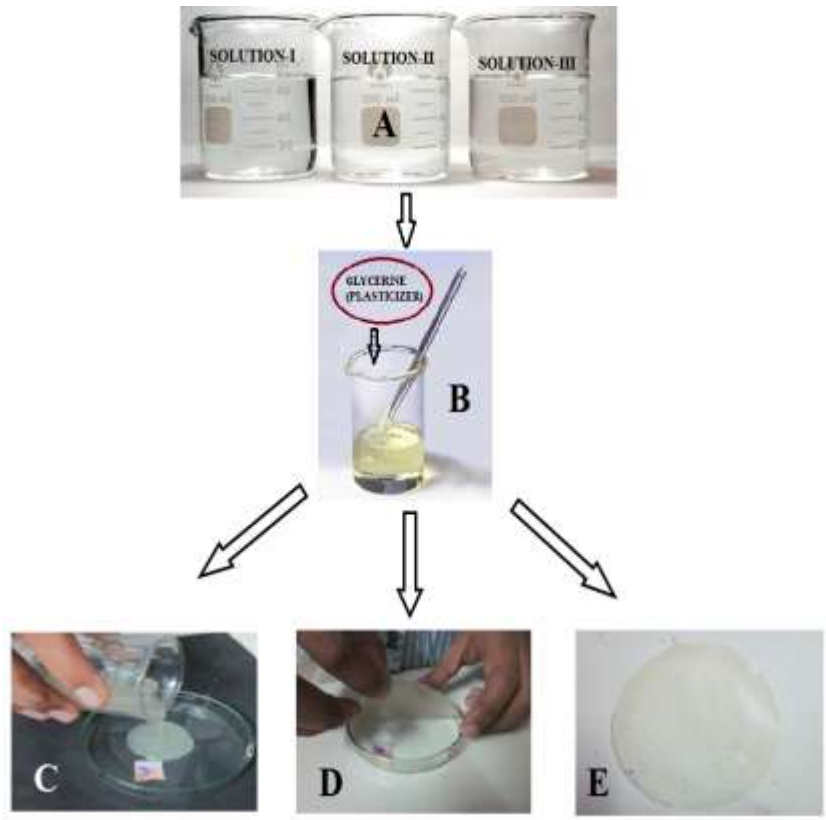


Fig. No-1: Diagrammatic representation of method of preparation of MDF

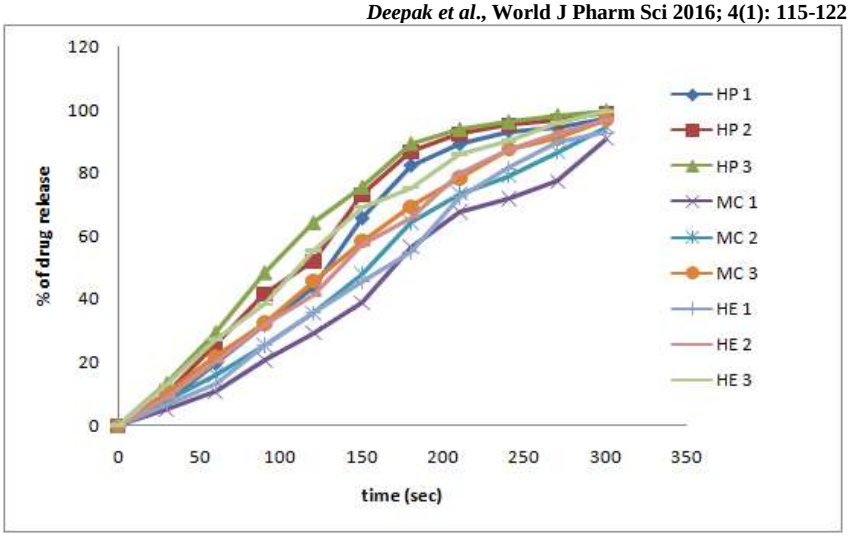
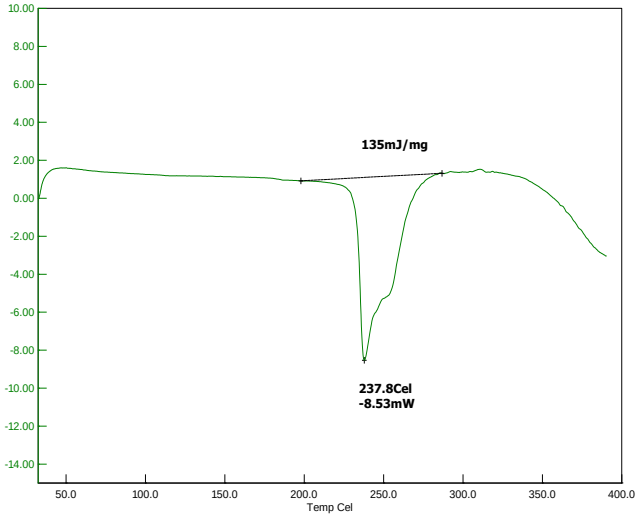
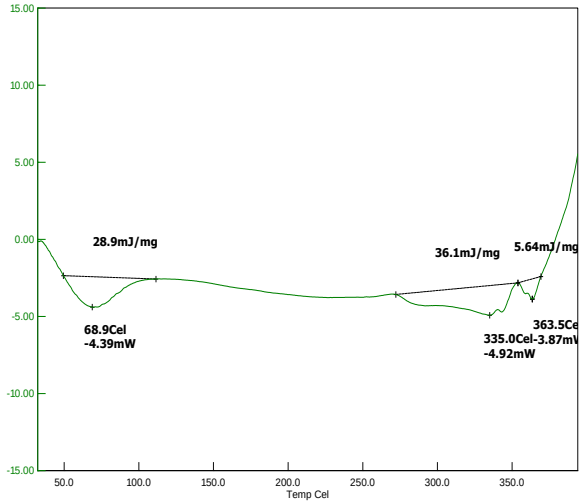


Fig.-2: In-vitro dissolution data for different formulations of mouth dissolving films of Domperidone Maleate



A



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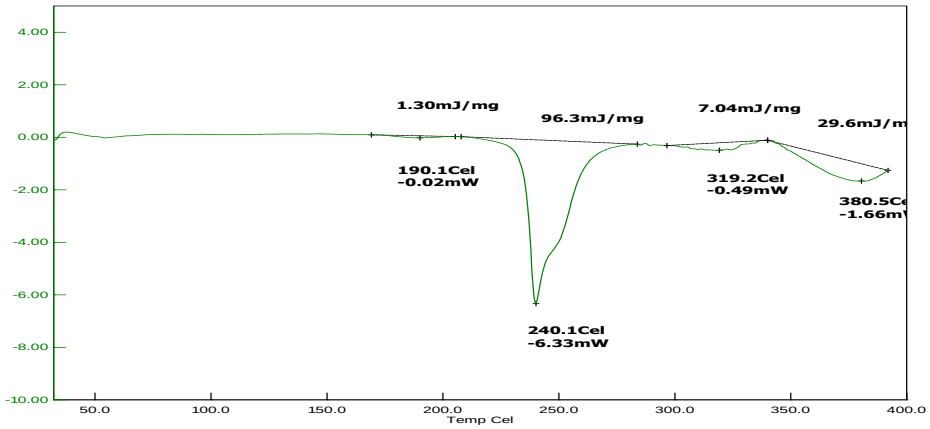
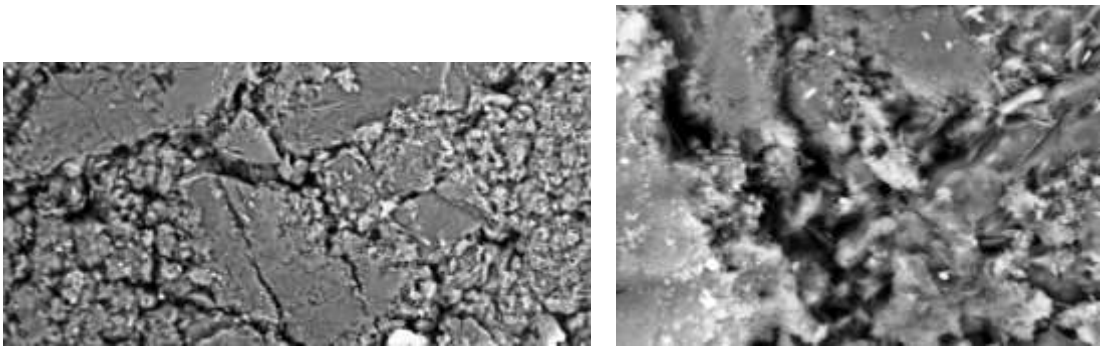


C

Fig. 3: DSC thermo-grams of A) Domperidone maleate, B) HPMC and C) film



(A) (B)

Fig.4: SEM of Domperidone maleate + Hydroxy propyl methyl cellulose. A) 500x B) 1000x

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