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Research Article

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Formulation and evaluation of domperidone embedded floating matrix tablets using various release retardants from natural and synthetic origin

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ABSTRACT

The aim of the current investigation was to fabricate domperidone floating matrix tablets by using various release retardants from natural and synthetic origin. Domperidone is a synthetic benzimidazole compound and weak base in nature, acts as a dopamine D_2 receptor antagonist and used as pro-kinetic agent. Its short biological half-life (4-7H), low bioavailability and rapid absorption characteristics in proximal part of GIT enable it as a suitable candidate for floating matrix tablets. Floating matrix tablets were prepared by direct compression method employing several hydrophilic swellable polymers like HPMC K100M, Carbopol-934P, Sodium alginate, Guar gum and Gellan gum in various combinations. $NaHCO_3$ and Citric acid were used as gas forming agents. Prepared tablets were evaluated for parameters such as swelling study, lag time, buoyancy time, in vitro dissolution studies etc. A modified buoyancy lag time for tablets was determined in order to include the effect of bioadhesion on initial buoyancy. Fourier transform-infrared spectroscopy, Differential scanning calorimetry and X-ray diffraction studies were also carried out for the optimized batch F7. From this investigation, it was observed that for optimized batch F7 the buoyancy time was achieved up to 12 H and the amount of drug release was around 96.25% within 12H. After linearization of the results obtained in the dissolution test, the best fit with higher correlation coefficients (r^2) was shown in zero order for optimized batch F7 and the mechanism was found to be non-Fickian or anomalous diffusion according to Korsemeyer's-Peppas equation.

Key words: Floating systems, modified floating lag time, normal floating lag time, buoyancy, swelling behaviour.

INTRODUCTION

Drugs with high rate of gastrointestinal absorption and short half-life are eliminated rapidly from the systemic circulation, resulting in frequent dosing. Oral controlled release formulations have been developed in order to avoid the rapid release of the drug into the gastro intestinal tract and maintain a steady drug-serum concentration for longer period. Administration of the drug through oral route has a constraint due to fluctuation in the gastric emptying process, a physiological limitation. Therefore, prolongation of gastric retention time is essential to attain control over the residence time as it helps to retain the dosage form in the proximal part of the GIT for a longer period with a predictable manner [1]. During past few years, scientific and technological revolutions have been made in the area of oral controlled drug delivery systems by overcoming physiological variations, such as short and variable gastric residence time. The GRT is the time taken by the dosage form to release the drug within GIT [2]. Several approaches have been developed to prolong the residence time of dosage forms in the stomach [3]. Many approaches are utilised in the development of gastroretentive drug delivery systems, which includes floating systems, swelling systems, expandable systems, high density systems, super porous hydrogels systems, bioadhesive systems, modified shape systems, ion exchange systems and raft systems [4]. Prolongation of gastric residence time

leads to sustained pharmacological action. A floating drug delivery system can be formulated for drugs which are act locally in the stomach, primarily absorbed at the proximal small intestine as well as in the stomach, poorly soluble at an alkaline pH, having narrow absorption window and which are unstable in the intestinal or colonic environment [5]. The floating matrix tablets may be of two types i.e. gas forming and non-gas forming. Non-gas forming floating matrix tablets contains low density excipients. The gas forming floating matrix tablets contain base and acid as gas forming agents, which lead to the formation of CO_2 bubbles to provide buoyancy for the floating matrix tablets [6]. Domperidone is a synthetic benzimidazole compound and weak base in nature, acts as a dopamine D_2 receptor antagonist [7]. Domperidone is also used as a prokinetic agent for the treatment of upper gastrointestinal motility disorders such as GERD, gastro paresis and also for the treatment of Parkinson's disease owing to its less extra pyramidal symptoms [8-10]. Domperidone has short biological half life i.e., 7 H and low bioavailability 15% [11]. After oral administration, domperidone is rapidly absorbed from the stomach and upper part of GIT with fewer side effects. It is a weak base and good soluble in acidic pH but significantly it is less soluble in alkaline medium [12]. Therefore, we could formulate into oral controlled release dosage forms to target the upper gastro intestinal tract. The aim of the current study was to develop gastric floating matrix tablet of domperidone. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug leads to higher bioavailability, more therapeutic efficacy, reduced frequent intervals for drug administration and also reduced dose size thus improved patient compliance.

EXPERIMENTAL SECTION

2.1. Materials

Domperidone was obtained from Yarrow chem. Products Pvt. Ltd, Mumbai, Hydroxypropylmethylcellulose (HPMC K100M), Guar gum, Gellan gum, Carbopol 934P were obtained from Yarrow chem. Products Pvt. Ltd, Mumbai, Sodium alginate and Sodium bicarbonate were obtained from Finar chemicals limited, Ahmedabad, Citric acid from Merck specialities Pvt. Ltd, Mumbai, Magnesium stearate from Molychem Ltd, Mumbai, Microcrystalline cellulose from Chemika-biochemika reagents, Mumbai. All ingredients used were pharmaceutical grade.

2.2. Methods

2.2.1. Preparation of floating matrix tablet by direct compression technique

Different batches of Domperidone embedded floating matrix tablets were prepared by direct compression method as represented in table 1. All the ingredients were powdered separately and dried for 30 min at 50˚C and cooled to room temperature. Then the powders were passed through #22 sieves separately. The drug, polymers and gas forming agents were mixed in polyethylene pouches to get a uniform mixture and kept aside. Then the Magnesium stearate (2%) was mixed before compression of the tablet. Compression was carried out by using 8mm flat faced punches on rotary compression machine (Rimek tablet mini press, Ahmedabad, India). Hardness was maintained at 5-6 kg/cm^2 throughout all formulations [12].

Table 1. Composition of various batches Domperidone floating matrix tablets

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
Domperidone (mg)	10	10	10	10	10	10	10	10	10	10
HPMC K100M (mg)	30	30	30	30	30	30	15	15	15	15
Sodium alginate (mg)	-	-	-	-	-	-	15	-	-	-
Carbopol-934P (mg)	-	-	-		-	-	-	15	-	-
Guar gum (mg)	-	-	-	-	-	-	-	-	15	-
Gellan gum (mg)	-	-	-	-	-	-	-	-	-	15
$NaHCO_3$ (mg)	-	7.5	10	15	15	15	15	15	15	15
Citric acid (mg)	-	7.5	5	-	-	-	-	-	-	-
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3	3
Microcrystalline cellulose (mg)	107	92	92	92	46	-	46	46	46	46
Lactose (mg)	-	-	-		46	92	46	46	46	46
Total weight (mg)	150	150	150	150	150	150	150	150	150	150

2.2.2. Swelling index study

Initially one tablet from each batch was weighed then placed in a Petri dish which contains 0.1N HCl. After every one hour, the tablet was withdrawn, wiped out with tissue paper and then again weighed. This process was continued till the 12th hour [12].

$$Swelling\ index = \frac{(wet\ weight) - (dry\ weight)}{(wet\ weight)} \times 100$$

2.2.3. Normal floating lag time and *in vitro* buoyancy study
The time taken by the dosage form to float on the surface of the dissolution medium is called floating lag time. And the time taken by the dosage form to remain buoyant on the surface of the medium is known as total buoyancy time. The test was performed by using 1000 ml beaker contains 900 ml of 0.1N HCl as dissolution medium [13].

2.2.4. Modified floating lag time
Agar medium was prepared and placed in Petri dish and allowed to keep in oven until the medium was dried. Later Petri dish was placed in 1000 ml beaker where 900 ml of 0.1N HCl was taken dissolution medium. The time taken by the dosage form to detach from the agar medium and to float on the surface of the dissolution medium is called modified floating lag time [13].

2.2.5. *In vitro* Dissolution studies
In vitro drug release study was performed in USP dissolution apparatus type II - paddle type containing 900 ml of 0.1N HCl, the temperature maintained at 37 ± 0.5°C with 50rpm. Samples of 5 ml were withdrawn at predetermined time intervals of 0.5 to 12 H and replaced with fresh medium each time. The samples were analyzed spectrophotometrically [14].

2.2.6. Kinetics of drug release studies
The drug release data were fitted into following kinetic equations: Zero order, First order, Higuchi, Korsemeyer's-Peppas equation and Hixson-Crowell model kinetics to know the drug release mechanism or pattern [15].

2.2.7. Fourier Transform – Infrared spectroscopy
Drug-polymer interactions were studied by FT-IR spectroscopy using the instrument Shimadzu, Japan, FTIR-8400S. The spectra were recorded for pure drug domperidone and also formulation of matrix tablet containing drug, polymer combination. Samples were prepared in KBr discs (2mg of sample in 200mg KBr) with a hydrostatic press at a force of 5.2 N/m^2 for 3 min. The scanning range was 400-4000 cm^{-1} and the resolution was 4 cm^{-1} [16].

2.2.8. Differential scanning calorimetric studies
The thermal behaviour of the floating matrix tablets were investigated using differential scanning calorimeter (DSC 60, Shimadzu, Japan). Samples of about 5 mg were placed in 50 μm perforated aluminium pans and covered with pans. All samples were run at a heating rate of 10 ˚C/min over a temperature range of 5-300 ˚C in atmosphere of nitrogen as purging gas at a flow rate of 25 ml/min [16].

2.2.9. X-ray diffraction analysis
Formulations were subjected to X-ray diffraction analysis, using Philips PW 170 system (Philips USA) with Cu-Kα radiation (400 kV, 30 mA, and scan speed 1˚/min) to investigate the physical state of domperidone in the formulations [16].

RESULTS AND DISCUSSION

3.1. Swelling behaviour
The swelling index for formulation F1 which was devoid of swelling agent and gas forming agents was found to be less i.e., 88.68% due to diffusion of water into the HPMC K100M resulted in expansion of HPMC matrix by the polymeric chain relaxation. The increase in swelling index (F2<F3<F4) due to increased concentration of sodium bicarbonate from 5- 10% of the total tablet weight. Swelling behaviour was further influenced by the addition of swellable polymers. Among F8, F9, F10 formulations, F8 has more swelling index (99.7%) because of presence of carbopol, which is a hydrating swellable agent. The swelling index for F6 was found to be more (98.5%) when compared to F5 owing to presence of hydrophilic filler lactose. The swelling index for optimized formulation F7 (98.29%) was found to be satisfactory and all the batches were performed in triplicates as shown below [table 2].

3.2. Floating lag time studies
The objective of the primary study was to optimization of lag time. The floating lag time was characterized between two parameters normal floating lag time (NFLT) and modified floating lag time (MFLT). The least possible lag time was optimized by changing the ratio of $NaHCO_3$ (base) and citric acid (acid) to the polymer. The lag time studies were carried out in 0.1N HCl. In case of formulation F1 (without gas forming agents) more lag time (2H 10M) was observed due to the presence of only low-density polymer which causes more time for expansion of matrix tablet. But MFLT observed was 3H 20M because of adhesion of tablet to the agar medium, takes more time to float over the surface of medium. When compared to F2, F3 the addition of sodium bicarbonate influences the lag time. The MFLT values decreased with increased amounts of base (F2>F3). The inclusion of an acid in formulations does not have any major effect on lag time. This may be due to the presence of 0.1N HCl as dissolution medium is sufficient

for reaction with $NaHCO_3$ in order to generate the gas. By taking 10% base for formulation F4 has got less modified floating lag time (35S). So the proportion of only base 10% was considered to achieve desired lag time for all remained formulations (F5-F10). Presence of swelling agents also influences lag time. Desired NFLT and MFLT (<30 and 35S) was obtained for F7 batch, may be because of higher swelling capacity of sodium alginate. All the batches were performed in triplicates shown in table 2.

Table 2. Data showing floating lag time, buoyancy time and swelling index

Batch code	Normal floating lag time	Modified floating lag time	Total buoyancy time(H)	Swelling index (%)
F1	2H 10M	3H 20M	-	88.68± 0.26
F2	<60S	2M 15S	6H	96.86 ± 0.28
F3	<40S	56S	9H	95.82 ± 0.03
F4	<30S	42S	12H	99.2 ± 0.23
F5	<30S	54S	9H	90.80 ± 0.21
F6	<30S	58S	11H	98.5 ± 0.35
F7	<30S	35S	12H	98.29 ± 0.32
F8	<30S	40S	12H	99.7 ± 0.5
F9	<30S	45S	9H	98.12 ± 0.36
F10	<30S	38S	7H	96.28 ± 0.16

3.3 *In vitro* buoyancy study

F1 batch was unable to achieve the desired buoyancy time. This may be because of absence of any gas forming agents. Variation in the concentration of base and acid influences the floating duration. For F2, F3 and F4 the buoyancy time obtained were 6, 9 and 12H respectively. So, F4 was considered for further studies. Addition of hydrophilic filler greatly influences the floating duration. For F5, F6 the total buoyancy time was 9H and 11H obtained respectively. Based on the type of swelling agents the buoyancy time was influenced. In case of F10 (consisting of gellan gum) the total buoyancy time was very less and the tablet disintegrated within 7H. This may be due to the rapid swelling and disintegrating characteristics of gellan gum, but presence of HPMC in the same batch F10 may be the cause of intactness of the tablets for 7H. For F7, F8, F9, F10 the total buoyancy time obtained was 12H, 12H, 9H and 7H respectively. All the batches were performed in triplicates as shown in table 2.

(After 0 second) (After 8 seconds) (After 26 seconds)

(After 35 seconds)

Figure 1. Floating behaviour of optimized formulation F7 at different time intervals

3.4. *In vitro* drug release studies

The high viscosity of hydrophilic swellable polymers employed for the present investigation was responsible for formation of high viscosity gel layer in order to retard the release of the drug. Gel forming capacity and extent of swelling of different polymers like HPMC K100M, Carbopol 934P, Guar gum, Gellan gum, Sodium alginate were observed during this study.

3.4.1. Effect of increasing concentration of bicarbonate on drug release

In the current investigation, 20% of HPMC K100M was taken alone without any gas forming agents in F1 batch. The amount of drug release was very low (58%). In order to enhance the floating characteristics, when increasing amount of base was added, a significant increase in the drug release was observed. In case of F2, where concentration of bicarbonate was 5%, drug release (69.12%). In case of F3 and F4 when concentration of bicarbonate was increased, drug release was found to be increasing respectively. The amount of drug release for F3 and F4 were 74.25% and 78.56% respectively. This may be due to the fact that increase in bicarbonate concentration makes the tablet more reactive with 0.1N HCl and the evolution of amount of the gas also increases. Increasing amount of gas evolution helps in the enhancement of the permeability of the gel barrier layer resulting in increased amount of drug release.

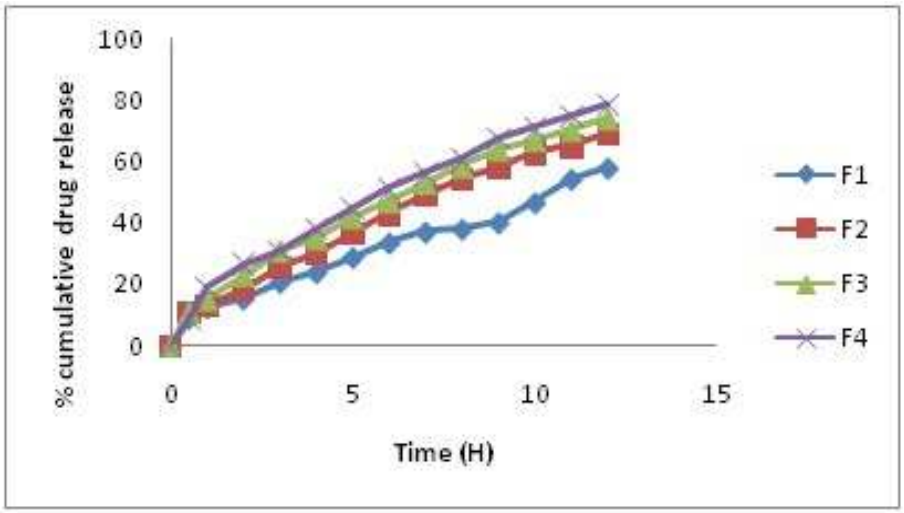

Figure 2. Showing %CDR values for (F1-F4)

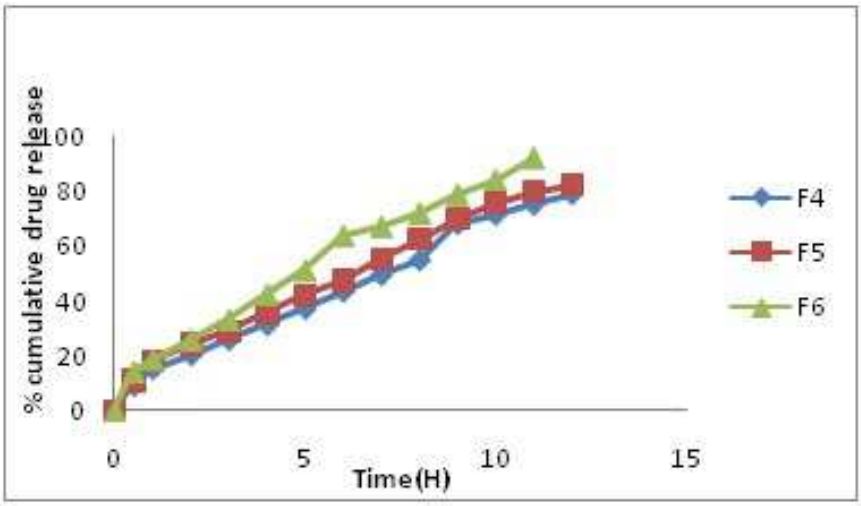

Figure 3. Showing %CDR values for (F4-F6)

3.4.2. Effect of type of filler on drug release

In the current study, it was found that use of different type of filler greatly influences the amount of drug release. When hydrophilic filler 'lactose' was added in F5 in combination with hydrophobic microcrystalline cellulose, the drug release was found to be (82.08%) better than F4. In F6 hydrophilic filler lactose was used alone. When compared with F5 the amount of drug release was more (i.e. about 92% within 11H) in case of F6. This may be due

to the fact that lactose being hydrophilic in nature instead of micro crystalline cellulose; it helps in the enhancement of hydrophilicity of the matrix.

In F7, binary blend of polymers HPMC and sodium alginate were used in equal proportion (10% + 10%), along with a mixture of hydrophilic and hydrophobic fillers, was able to provide a desired drug release of 96.25% in 12H with satisfactory floating lag time and buoyancy time. In F8, F9, F10 the total concentration of polymer was kept constant along with a variation in the composition of polymer blend by changing the type of polymer as given in the table 1. The amount of drug release obtained for F8 was 88.12% in 12H, F9 was 95.04% in 11H and F10 was 95.52% in 10H.

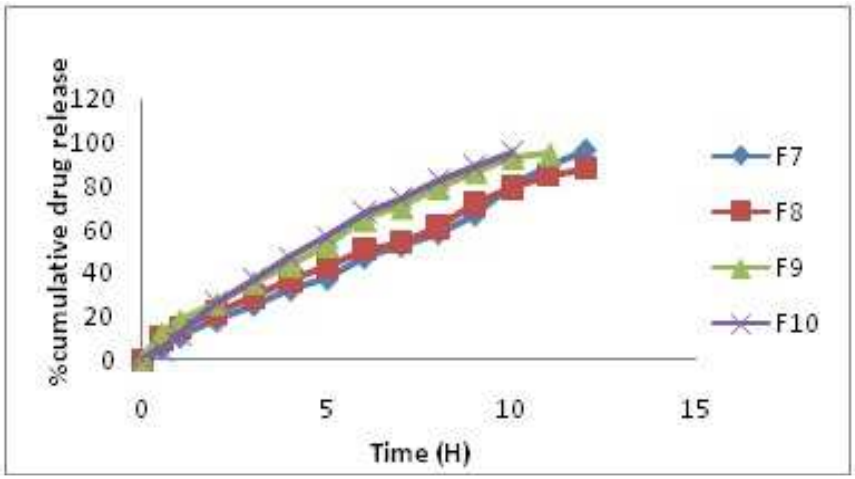

Figure 4. Showing %CDR values for (F7-F10)

3.5. Kinetics of drug release studies

The mechanism of drug release for various batches was determined by finding the coefficient of determination (r^2) by applying kinetic model equations (zero order, first order, Higuchi model, Korsmeyer's-Peppas model and Hixon-Crowell cubic root model). After linearization of the results obtained in the dissolution test, the best fit with high coefficient of determination (r^2) was observed in zero order, followed by Higuchi plots and first order (i.e. drug release was independent of concentration). Formulation (F10) follows Hixon-Crowell drug release pattern i.e. erosion type of drug release, which may be because of presence of gellan gum, which is highly disintegrating in nature. Further it can be supported by the result observed during the buoyancy study and *in-vitro* drug release study. The data obtained were also put in Korsemeyer-Peppas model in order to find out 'n' value, which describes the drug release mechanism. In the current investigation 'n' values of various batches were within 0.5-1, indicating the probable mechanism for drug release following anomalous or non-Fickian diffusion i.e., the rate of solvent penetration and drug release are in the same range. The results were shown in the table 3.

Table 3. *In vitro* release kinetic parameters for different formulated batches

Formulations	Zero order plot		First order plot		Higuchi model plot		Korsemeyer- Peppas plot		Hixson- Crowell plot	
	r^2	K_0	r^2	K_1	r^2	K_H	r^2	n	r^2	K
F1	0.978	4.246	0.907	-0.059	0.958	16.04	0.976	0.571	0.887	-0.132
F2	0.981	5.538	0.914	-0.094	0.974	21.07	0.979	0.605	0.616	-0.096
F3	0.990	5.916	0.869	-0.096	0.962	22.26	0.978	0.630	0.682	-0.011
F4	0.989	6.360	0.928	-0.119	0.950	23.81	0.982	0.673	0.753	-0.128
F5	0.987	6.882	0.904	-0.131	0.937	25.39	0.973	0.697	0.816	-0.146
F6	0.982	7.863	0.937	-0.195	0.972	28.50	0.979	0.628	0.934	-0.202
F7	0.993	7.717	0.798	-0.207	0.918	28.33	0.940	0.843	0.808	-0.202
F8	0.992	7.232	0.881	-0.151	0.928	26.73	0.972	0.696	0.839	-0.169
F9	0.986	8.600	0.927	-0.253	0.969	31.05	0.983	0.673	0.965	-0.250
F10	0.986	9.76	0.921	-0.269	0.963	33.37	0.990	0.998	0.991	-0.289

3.6. Fourier Transform - Infrared spectroscopy

The FT-IR of pure drug was characterized by N-H stretching at 3122 cm^{-1} and C = O stretching at 1714.60 cm^{-1}, indicating the presence of -CONH group, asymmetric C-H stretching at 2937.38 cm^{-1}, symmetric C-H stretching at 2817.81 cm^{-1}, N-H deformation at 1693.38 cm^{-1}, aromatic C-H stretching at 3024.18 cm^{-1} and C = C at 1622.02 cm^{-1}. Similar type of result was obtained by (Dananjay *et al.*, 2011) which indicates that the drug was pure domperidone [17]. From the above interpretation, it was concluded that there was no major shifting in the frequencies of above said functional groups. Since there was no significant shifting in band peak & intensity of the peaks with the

excipients, signs of incompatibility were not observed. The FT-IR spectra of pure drug and formulation mixture F7 was shown in figure 5.

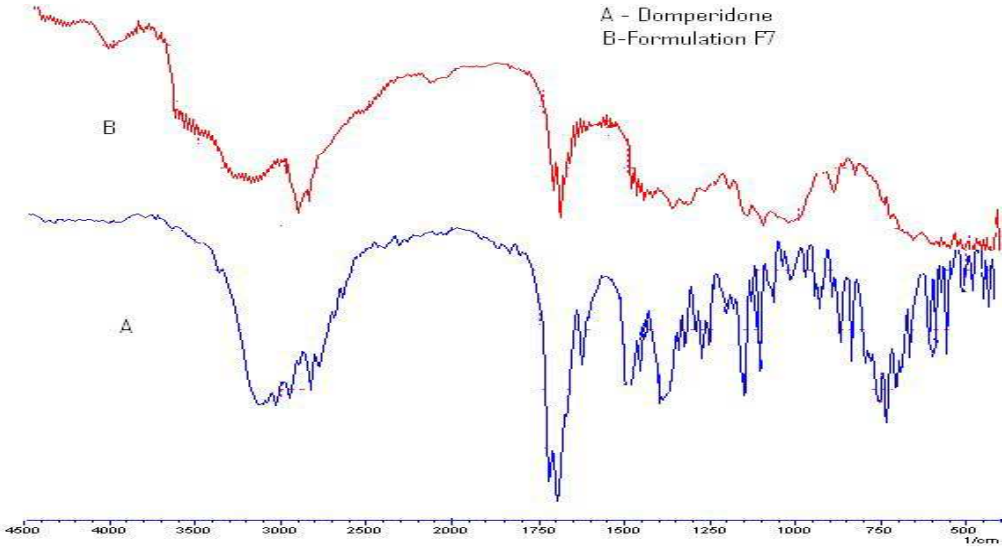

Figure 5. FTIR spectra of Domperidone and F7

3.7. Differential scanning calorimetry studies

The thermal curve of domperidone (Tpeak = 245.98°C) indicated its crystalline anhydrous state. The DSC endotherm peak supports the melting point of the domperidone, as shown in figure 6. Dananjay *et al.* 2011, obtained similar type of result [17]. From the DSC analysis, it was observed that there was no significant interaction between drug and other excipients used in the formulation of floating tablets.

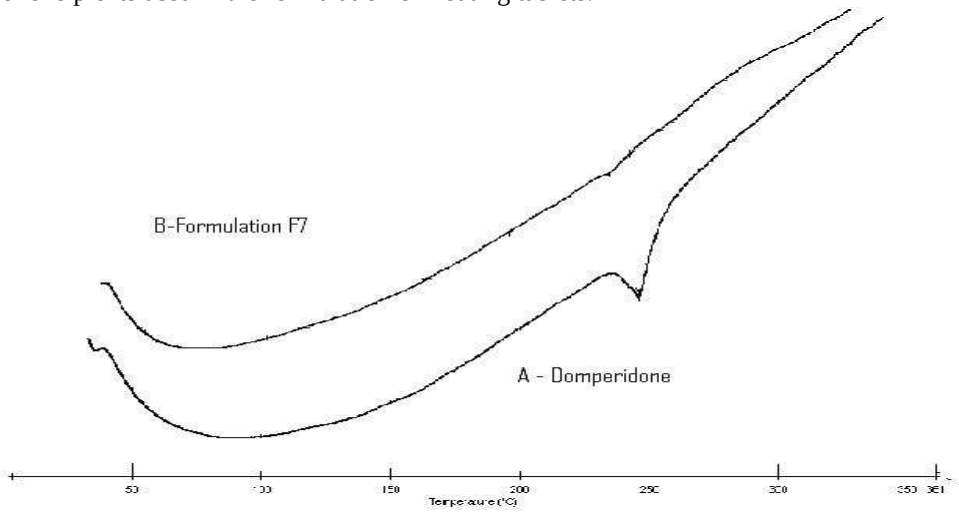

Figure 6. DSC spectra of domperidone and F7

3.8. X-ray diffraction analysis

The X-Ray diffraction pattern of domperidone exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug, as shown in figure 7. The diffractogram of floating matrix tablets shown a similar pattern with a slight decrease in the intensity of the peaks, which suggests that the drug was able to disperse almost homogenously through the tablet. This result confirms a partial change in the solid state of domperidone from crystalline to amorphous. Similar type of results result was obtained by Dananjay *et al.*, 2011 having same type of interpretation [17].

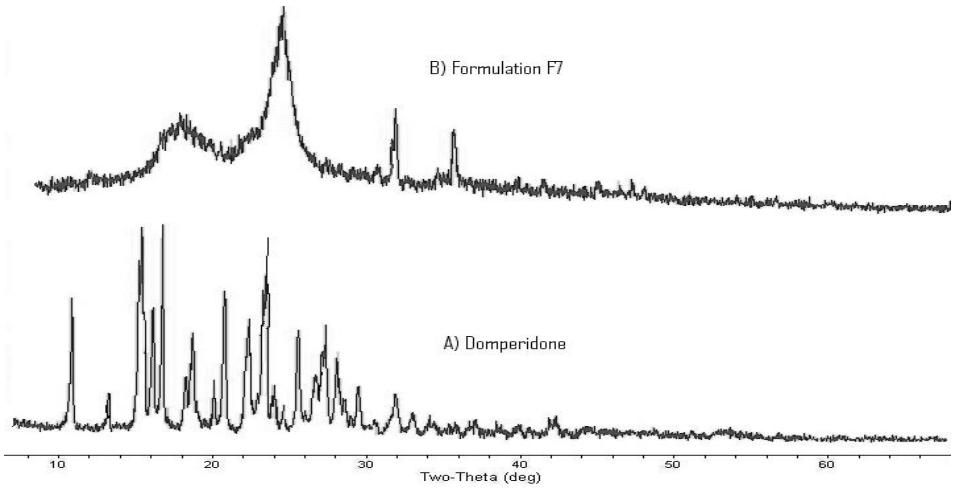

Figure 7. XRD spectra of domperidone and F7

CONCLUSION

Controlled release floating matrix tablets of domperidone were successfully designed and characterized by using various release retardants of natural and synthetic origin, which has the advantage to retain the dosage form for longer period of time at proximal part of GIT and to increase the bioavailability of the drug. HPMC K100M, Sodium alginate and Carbopol 934P significantly affect the normal, modified floating lag time and total buoyancy time. Finally it can be concluded that blend of various natural polymers along with synthetic polymers can be used successfully in the design of floating matrix tablets.

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REFERENCES

[1] KS Soppimath; AR Kulkami; TM Aminabhavi. *Drug Dev Ind Pharm*. **2001**; 27(6), 507-527.
[2] KJ Sunil; AM Awasthi; NK Jain; GP Agrawal. *J Control Release*. **2005**; 107, 300-309.
[3] AJ Moes. *Crit Rev Ther Drug*. **1993**; 10, 143-195.
[4] B Chandrasekhar. *Int J App Pharm*. **2012**; 4(2), 1-13.
[5] BM Singh; KH Kim. *J Control Release*. **2000**; 63, 235-259.
[6] G Manoj; P Rajesh; K Purohit. *J Curr Pharm Res*. **2011**; 5(11), 7-18.
[7] H Michael; C Malcolm; Margaret Y. *Br J clin Pharmacol*. **1986**; 135, 453-460.
[8] HJ Francois. *Can J Anaesth*. **1988**; 32(2), 162-173.
[9] SW Christopher; DF Christopher. *Gastroenterol Clin North Am*. **2003**; 32, 619-658.
[10]JS Shindler; GT Finnerty; K Towlson; AL Dolan; CL Davies; JD Parkes. *Br J clin Pharmacol*. **1984**; 18, 959-962.
[11]R Biswas. *J PharmaSci* Tech. **2011**; 1(1), 28-34.
[12]S Prajapathi; P Laxmanbhai; P Changanbhai. *Iranian J Pharm Res*. **2011**; 10(3), 447-455.
[13]ST Prajapati; DP Laxmanbhai; MP Dasarath. *Acta Pharm Sinic*. **2008**; 58, 221-229.
[14]SN Jeetendra; K Praveen; T Abhinav; N Vandana. *J Adv Pharm Tech Res*. **2011**; 2(2), 121-127.
[15]D Suvakanta; MP Narasimha; C Prasantha. *Acta Pharm Sinic*. **2010**; 67(3), 217-223.
[16]M Jelvehgari; A Nokhodchi; M Rezapour; H Valizadeh. *Indian J Pharm Sci*. **2010**; 72(1), 72-78.
[17]SD Dhananjay; NK Premchand; GY Pramod; SN Nilofer; SM Chandrakant; RS Rohit. *Iranian J Pharm Res*. **2009**; 8(3), 145-151.