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Original Article

Formulation and Evaluation of Mucoadhesive Microbeads of Domperidone.

S.S. Deshmukh[a,*], K.K. Mali[a], V.S. Ghorpade[a]

[a]*Department of Pharmaceutics, GES's Satara College of Pharmacy, Satara, Maharashtra, India.*

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Abstract

Hydroxy propyl methyl cellulose and citric acid were used in preparation of solid dispersion by kneading method. The drug release was found to be dependent on concentration of polymer in solid dispersion and modification of micro environmental pH by citric acid in dissolution medium. Amorphous dispersed form of domperidone was due to homogeneous dispersion of drug in carriers by kneading method. Mucoadhesive microbeads containing domperidone was prepared by Ionotropic gelation method. Beads was prepared, employing mucoadhesive polymer carbopol 934 in different ratio with sodium alginate. The drug release from formulation C10 was almost zero order which favors development of a sustained release formulation to improve short biological half life of drug which is 7 hour.

Keywords: *Domperidone, Solid dispersion, Dissolution.*

1. Introduction

Domperidone (DMP), a dopamine antagonist, can used in the treatment of nausea and vomiting in dose of 10-40 mg daily. It is weak base with good solubility in acidic pH but in alkaline pH solubility is significantly reduced. Oral controlled release dosage forms containing weakly basic drug, when exposed to environment of increased pH, leads to the precipitation of drug at higher pH in intestine. Precipitated drug is no longer capable of being eliminated release from formulation which may further decrease its bioavailability [6]. The study was planned to prepare solid dispersion incorporated microbeads of domperidone which will remain for 2 hours in stomach with controlled drug release and then controlling drug release in gastrointestinal tract.

3. Materials and methods

3.1. Materials

Domperidone was received as gift sample from Vasudha Pharma Pvt. Ltd. Hydrabad, Andra Pradesh, India. Hydroxy propyl methyl cellulose (HPMC E 15 LV) was obtained from Panacea Biotech, Mumbai. Citric acid, Sodium alginate, Carbopol 934, calcium chloride was purchased from Loba Chemie, Mumbai.

3.2. Methods

3.2.1 Preparation of DOM/ HPMC/CA solid dispersion

The solid dispersion of DOM and HPMC in presence of citric acid was prepared in the ratio of 1:0.5:1, 1:1:1, 1:1.5:1, 1:2:1, 1:1:0 as F1, F2, F3, F4, F5 by kneading method [2,7,8]. Accurately weighed quantity of HPMC was mixed with sufficient quantity of water to obtain a smooth and homogeneous paste. Weighed quantity of DOM with citric acid was added slowly by grinding. The mixture was ground for half an hour by adding appropriate quantity of water to maintain suitable consistency. Finally the paste was dried in hot air oven at 60˚C for 6 hrs. The dried solid dispersion was powdered, passed through sieve number 30 and stored in air tight container.

3.2.2 Physical characterization of solid dispersion

The IR spectrum of DOM and solid dispersion formulations was recorded using Fourier transform infrared spectroscopy (ALPHA E Bruker). The spectrum was recorded over the wavelength of 4000 to 500 cm-1. Thermograms of pure DOM, HPMC, citric acid, DOM/ HPMC/CA solid dispersion F2 and DOM/ HPMC/CA (physical mixture) were recorded using instrument. Samples were sealed in aluminium pans and heated at the rate of 10˚C/min from 30˚C to 300˚C under nitrogen atmosphere. X-ray diffraction pattern of pure DOM, HPMC, citric acid and solid dispersion were recorded using X-ray diffractometer (Bruker axs D8).

3.2.4 Dissolution rate study of domperidone and its solid dispersion

Dissolution study of DOM and its solid dispersion formulations were performed in 900 ml of 0.1 N HCl and phosphate buffer pH 6.8 using USP XXIII dissolution apparatus (Electrolab, TDT- 06P, Mumbai, India) for 30 minutes under sink conditions

*Corresponding author.
E-mail address: deshmukh.shilpa84@gmail.com (S.S.Deshmukh)

at stirring speed of 100 rpm at 37±0.50C. Powder samples of solid dispersions equivalent to 30 mg of drug was clamped between infusion filter paper and immersed in dissolution medium. Sample of pure drug (30 mg) was also tested similarly. 5 ml of aliquot was withdrawn at different time intervals and replaced with same volume of fresh dissolution medium. Filtered samples were assayed spectrophotometrically [8].

3.2.5 Preparation of floating mucoadhesive Microbeads

Sodium alginate and carbopol 934 P were dissolved in purified water (50 ml) to form a homogeneous polymer solution. Core material, optimized DOM: HPMC: CA solid dispersion equivalent to 400 mg was added to polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resultant dispersion was then added dropwise to about 200 ml of calcium chloride solution (10% w/v) using 5 ml syringe (21 gauge needle) with mild agitation for period of 10 minutes [9]. The beads were then separated and washed with water repeatedly and dried at room temperature for 24 hours. Composition of variables is given in Table 4.

Table 1.
Formula for different batches of DOM: HPMC: CA solid dispersion loaded sodium alginate-carbopol mucoadhesive microbeads.

Formulation variables	C1	C2	C3	C4	C5	C8	C9	C10
Domperidone (mg)	400	-	-	-	-	-	-	-
Domperidone (mg) equivalent solid dispersion	-	400	400	600	800	400	400	400
Sodium alginate (% w/v)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Carbopol (ratio with sodium alginate)	9:1	-	9:1	9:1	9:1	8:2	7:3	9:1
Calcium chloride solution (% w/v)	10	10	10	10	10	10	10	15

3.2.6 Determination of entrapment efficiency
The beads (30 mg) loaded with domperidone solid dispersion was dissolved in solvent. It was stirred for 6 hrs using magnetic stirrer. The resulting solution was then filtered and filtrate was suitably diluted with dissolution medium solvent. Domperidone content was determined spectrophotometrically at 284 nm from which entrapment efficiency was determined [10].

3.2.7 Determination of surface morphology
Surface morphology of microbeads was studies by using scanning electron microscopy (JEOL 5400, Japan). Microbeads were sprinkled on to double side tape, sputter coated with gold ions and examined in the microscope at 5 kV.

3.2.8 Study of mucoadhesion
The sheep mucosa was washed with physiological saline. After 15 min. the mucosa was held in inclined position and fixed to glass slide with cynoacrylate glue and 50 beads (N_0) hydrated with little amount of water and dispersed on mucosal tissue and left on it for 20 min. for the interaction with mucosal surface. Then system was washed with 0.1 N HCl by using IV infusion set at the rate of about 22ml/min. After 20 min., 60 min, 120 min beads detached from the mucosa (Ns) were visually observed and percent mucoadhesion were calculated using following formula [11].

% mucoadhesion strength = $(N_0 – Ns / N_0) \times 100$

3.2.9 In Vitro drug release study
The in vitro drug release from different batches of microbeads was evaluated (in triplicate) in 900 ml of 0.1 N HCl and phosphate buffer pH 6.8 using USP XXIII dissolution apparatus (Electrolab, TDT- 06P, Mumbai, India) for 8 hrs under sink conditions at 37±0.5^{0}C. The rotation speed of the paddle was adjusted to 100 rpm [11]. 5 ml of aliquot was withdrawn at different time intervals and replaced with same volume of fresh dissolution medium. Filtered samples were assayed spectrophotometrically at 284 nm.

Results and discussion

Physical characterization of solid dispersion

Figure 9 illustrates the FTIR spectra of DOM, HPMC E15LV, citric acid and solid dispersion formulation F2. The IR spectrum of DOM shows principal absorption peaks at 3019.05 cm^{-1} (N-H stretching), 2818.53 cm^{-1} (C-H stretching), 1689.62 cm^{-1} (C=O stretching), 1621.03 cm^{-1} (C=C stretching), 1384.61 cm^{-1} (C-H bending), 832.17 cm^{-1} (C-Cl bending). The IR spectrum of HPMC E15LV shows prominent absorption peaks at 3729.23 cm^{-1} (O-H stretching), 1451.01 cm^{-1} (C-H bending), 1637.95 cm^{-1} (Saturated cyclic six membered ring), 940.55 cm^{-1} (Cyclic C-H bending). The IR spectrum of citric acid shows prominent absorption peaks at 1287.59 cm^{-1} (C-H bending), 3224.37 cm^{-1} (O-H stretching of acid), 1721.67 cm^{-1} (C=O stretching of acid), 1430.17 cm^{-1} (aliphatic C-H bending).

(A)

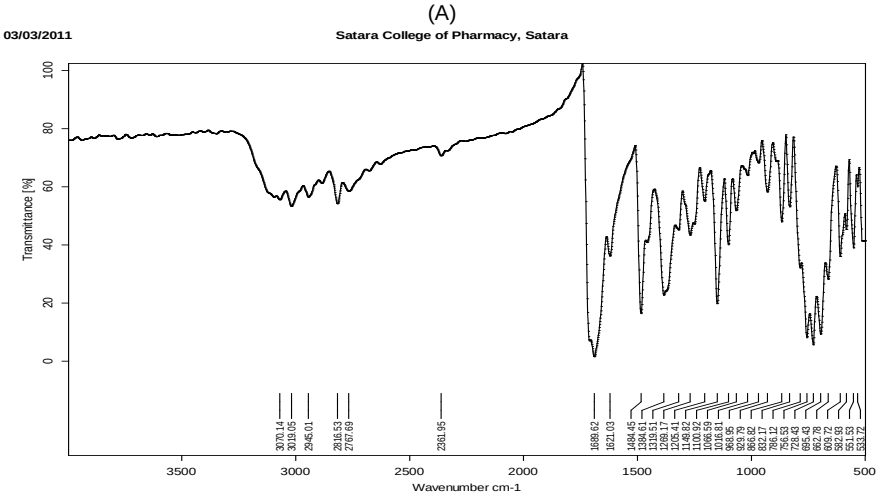
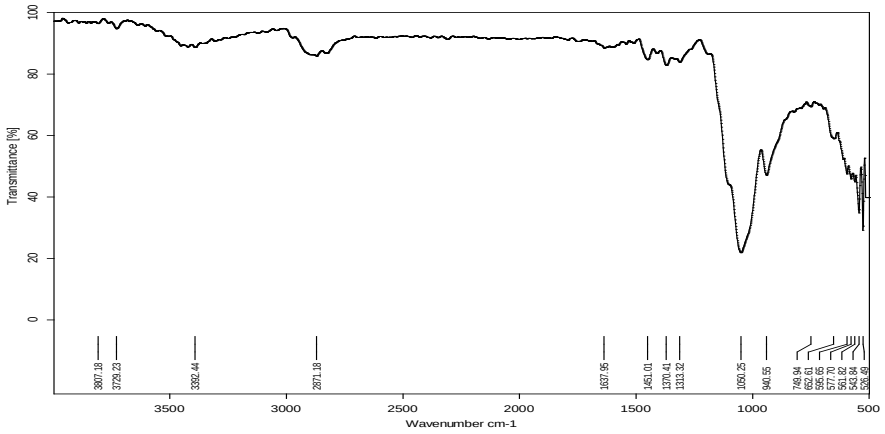


Fig.1. IR analysis of DOM (A), HPMC E15LV (B), citric acid (C) and solid dispersion formulation F2 (D).

(B)



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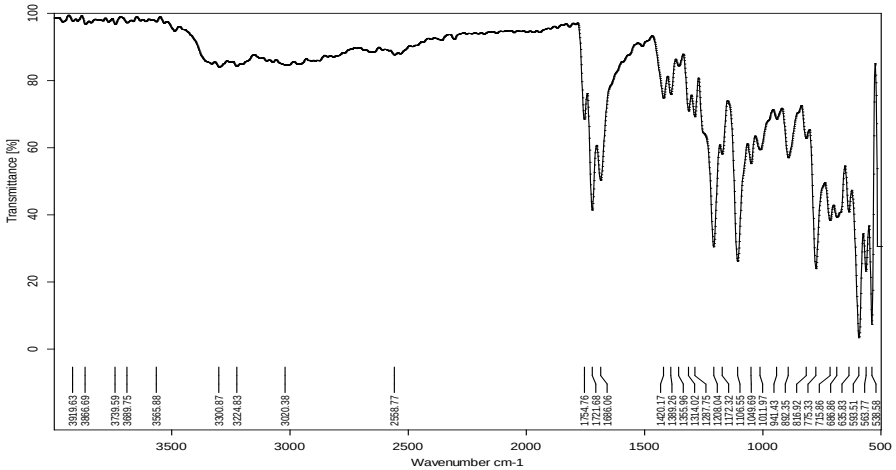

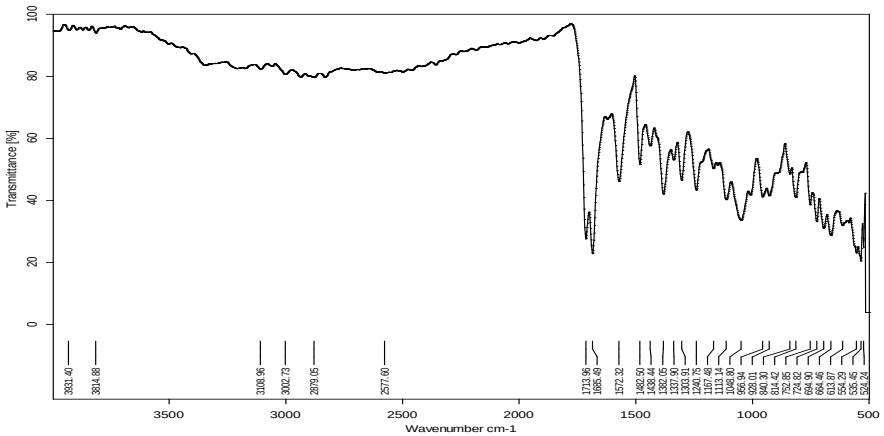

From the IR spectral analysis it was observed that the spectra of solid dispersion formulation F2 showed the presence of characteristic peak of DOM and there were no additional peaks which indicates that there was no any unusual interaction between drug and other excipients. Differential scanning calorimetric analysis shows that no more shifting of endothermic peak of drug was observed in the physical mixture, indicating that drug did not interact with the other carriers. Also decrease in intensity and sharpness of endothermic peak of domperidone in DOM/HPMC/CA solid dispersion was observed indicating molecular interaction of drug with the carriers and thus homogeneous dispersion in the carriers resulting in amorphous dispersed form of domperidone.

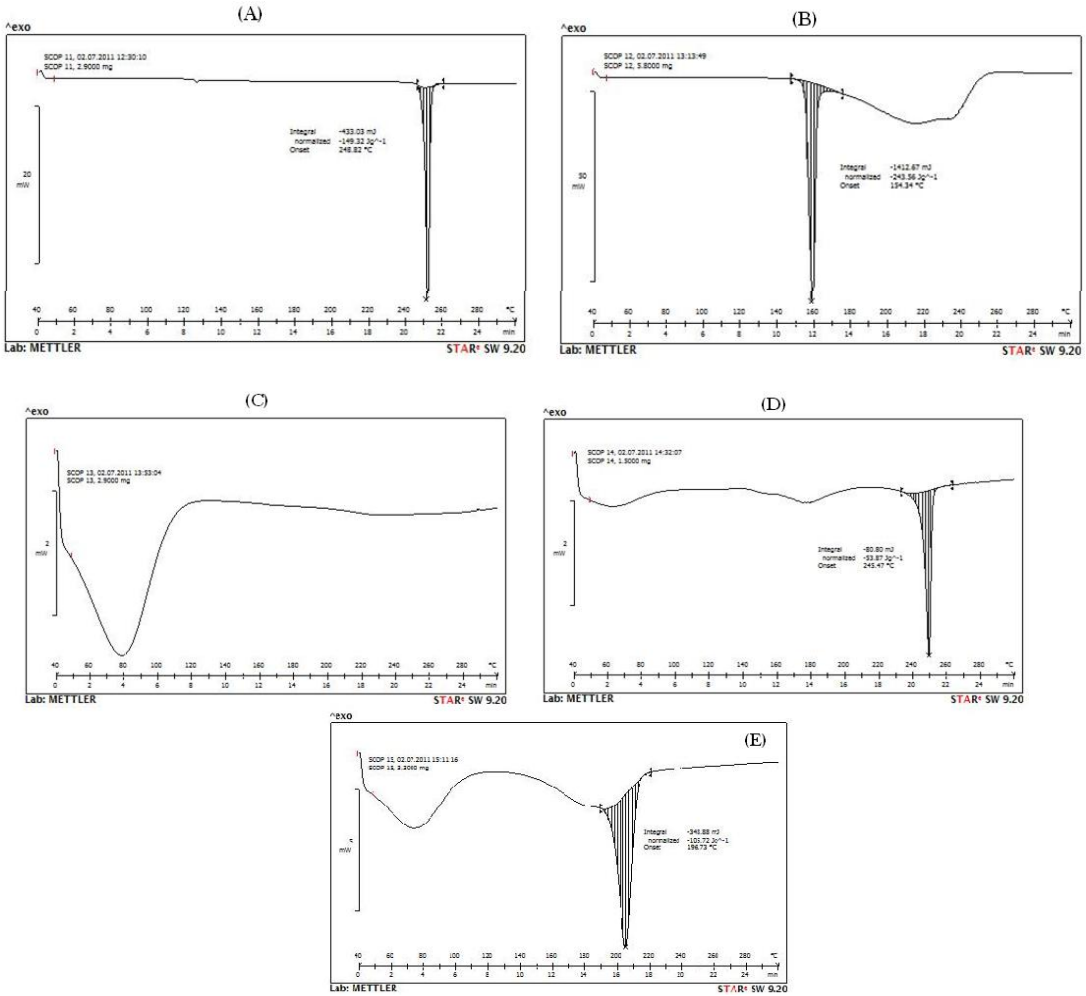

Fig. 2. DSC analysis of DOM (A), CA (B), HPMC (C), DOM/HPMC/CA physical mixture (D) and DOM/HPMC/CA solid dispersion (E).

No more shifting of endothermic peak of drug was observed in the physical mixture, indicating that drug did not interact with the other carriers. Also decrease in intensity and sharpness of endothermic peak of domperidone in DOM/HPMC/CA solid dispersion was observed indicating molecular interaction of drug with the carriers and thus homogeneous dispersion in the carriers resulting in amorphous dispersed form of domperidone. The XRD pattern of DOM (see fig. 3) showed peaks that were intense and sharp, indicating its crystalline nature.

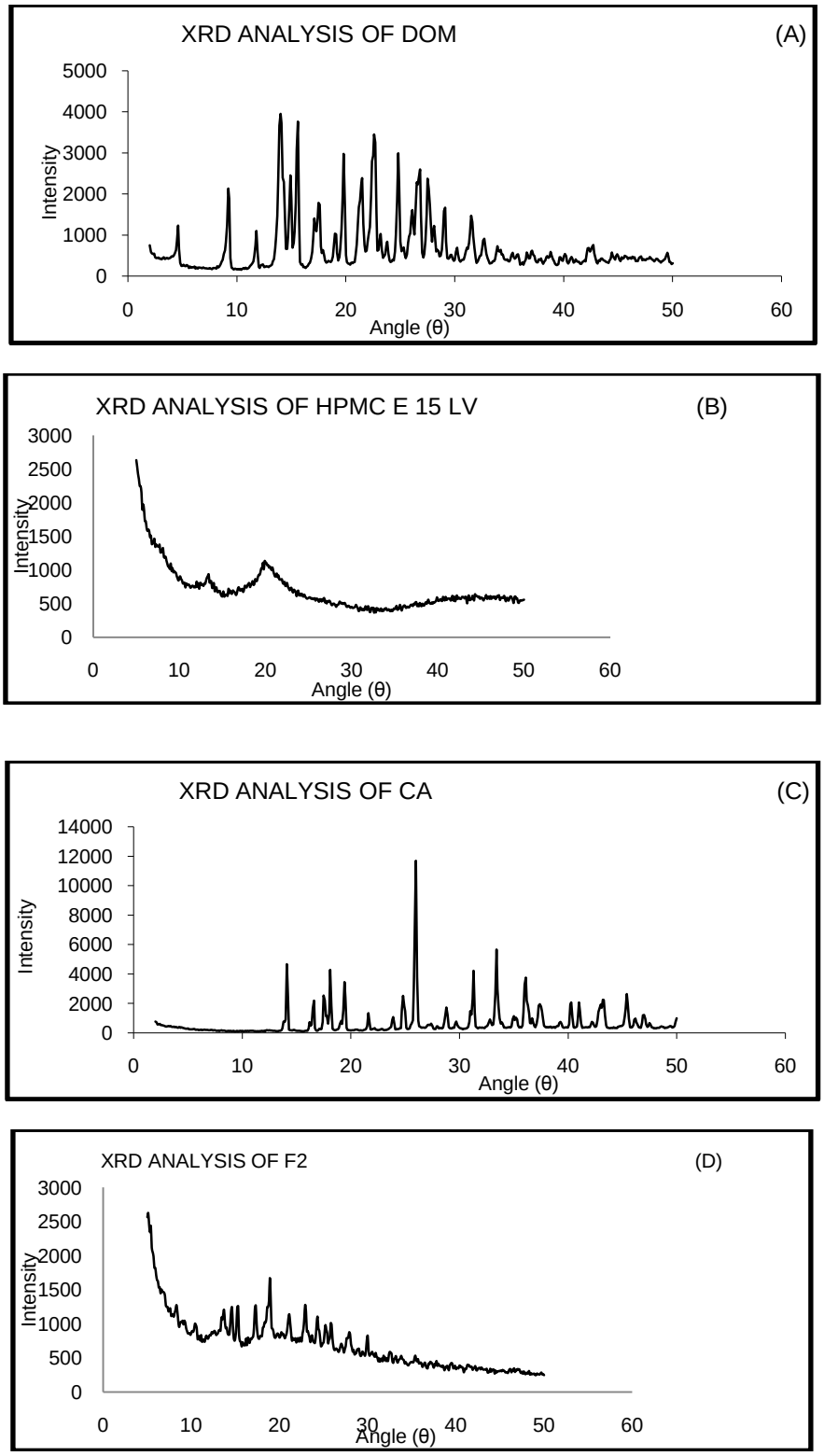

Fig. 3. XRD analysis of DOM (A), HPMC E15 LV(B), Citric acid (C) and DOM/HPMC/Citric acid solid dispersion (D).

Crystallinity was determined by comparing some representative peak heights in the diffraction patterns of the solid dispersion F2 with those of reference. DOM showed sharp peak at 14˚ (2θ) with peak intensity 3952. Solid dispersion formulation F2 showed peak at 14˚ (2θ) with peak intensity 947.The relative degree of crystallinity (*RDC*) was calculated according to equation,

$$RDC = I_{Sample} / I_{reference}$$

Where I_{Sample} is the peak height of the sample (F2) and $I_{reference}$ is the peak height at the same angle for the reference (DOM) with the highest intensity.

The RDC value of DOM/HPMC/CA (1:1:1) solid dispersion was found to be 0.23962. Thus the XRD analysis revealed that there was reduction in the diffraction intensity of DOM/HPMC/CA solid dispersion. This indicates reduced crystallinity of drug.

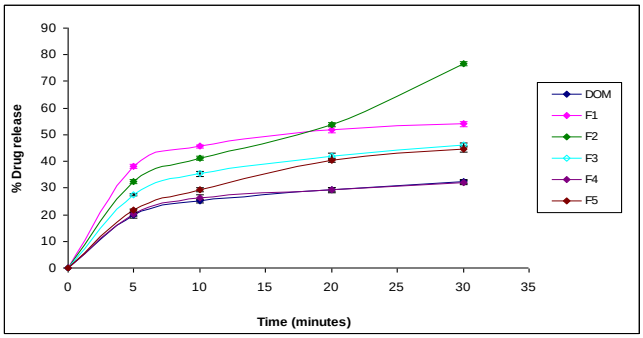

Fig. 4. Dissolution profile of DOM and its solid dispersion in 0.1 N HCl.

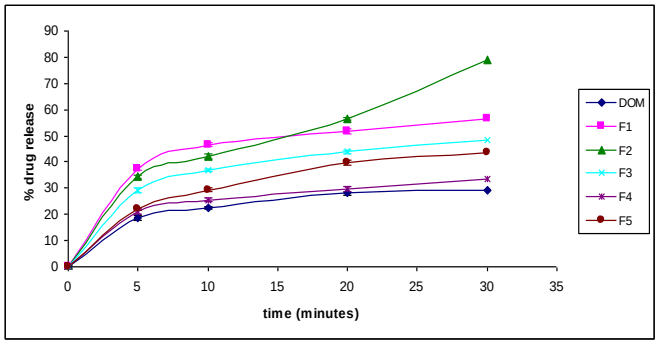

Fig. 5. Dissolution profile of DOM and its solid dispersion in phosphate buffer pH 6.8.

Table 2.
Dissolution profile of DOM and its solid dispersion in 0.1 N HCl.

Sr. no.	Time (min)	% Drug release (mean ± SD)					
		DOM	F1	F2	F3	F4	F5
1	0	0	0	0	0	0	0
2	5	19.66± 0.86	38.21± 0.81	32.44± 0.82	27.38± 0.46	20.07± 0.73	21.6 ± 0.70
3	10	25.04± 0.58	45.58± 0.49	41.30± 0.76	35.36± 0.86	26.39± 0.90	29.32± 0.86
4	20	29.34± 0.93	51.86 ± 0.9	53.68 ± 0.6	41.9 ± 1.10	29.49± 0.82	40.33± 0.73
5	30	32.36± 0.77	54.07 ±1.00	76.77 ±0.80	46.31 ±0.78	32.08 ±0.84	44.72 ± 1.14

Table 3.
Dissolution profile of DOM and its solid dispersion in phosphate buffer pH 6.8.

Sr. no.	Time (min)	% Drug release (mean ± SD)					
		DOM	F1	F2	F3	F4	F5
1	0	0	0	0	0	0	0
2	5	18.62± 0.83	37.41± 0.83	34.29 ± 0.62	29.21± 0.91	21.1± 0.74	22.12± 0.82
3	10	22.41± 0.95	46.61± 0.77	42.27±0.75	36.75±0.84	25.56±0.79	29.36±0.40
4	20	28.02± 0.55	51.65± 0.65	56.38±0.99	43.85±0.58	29.55±0.87	39.78±0.84
5	30	29.31± 0.66	56.43± 0.81	79.03±0.46	48.45±0.83	33.66±0.92	43.42±0.78

The solid dispersion formulation F2 showed higher dissolution rate as compared to other solid dispersion formulations and pure drug (DOM). Solid dispersion formulation F1 show higher dissolution rate for 15 min. whereafter the extent of dissolution decreased. This may be attributed to reason that proportion of citric acid is more than HPMC which may gives crystallinity to formulation [12]. Solid dispersion formulation F2 showed initial slow dissolution rate however showed rapid increase in dissolution of DOM after 20 min. at the end of 30 min 76.77 % of DOM was found to be dissolved. This may be attributed to the presence of drug, carrier and citric acid in same ratio. The enhancement of dissolution of drug is due to molecular dispersion of drug molecules in the polymeric carrier which may lead to higher level of particle size reduction and surface area enhancement and presence of citric acid in equal proportion to HPMC so that citric acid molecules homogeneously dispersed surrounds the drug particles for efficient modulation of microenvironmental pH in dissolution medium may provide proper acidic microenvironment which in turns result in improved dissolution rate [2,13]. Increase in proportion of HPMC in formulation lead to decrease in dissolution rate, the reason may attribute to swelling characteristic of HPMC [14]. Formulation F5 showed only 44.72 % dissolution of DOM at the end of 30 min which may be due to the absence of acidic microenvironment. A solid dispersion formulation shows same kind of dissolution pattern in phosphate buffer 6.8.

Characterization of DOM/ HPMC/CA solid dispersion containing mucoadhesive microbeads for Gastroretentive drug delivery

Study of entrapment efficiency

Entrapment efficiency was calculated and reported in table 4.

Table 4.
Entrapment efficiency of microbeads.

Sr. no.	Batch code	Entrapment efficiency (%w/w) (mean ± SD)
1	C1	48.96 ± 0.87
2	C2	52.83 ± 0.70
3	C3	48.62 ± 0.83
4	C4	55.26 ± 0.90
5	C5	61.28 ± 0.73
8	C8	46.4 ± 0.83
9	C9	43.85 ± 0.74
10	C10	54.25 ± 0.90

The formulation C5 showed more entrapment effieciency than C4 and C3 which may be attributed to fact that an increase in entrapment efficiency with increase in concentration of solid dispersion of DOM in formulation of microbeads. The increase in concentration of solid dispersion containing HPMC may be attributed to increase in viscosity, which results in increase in encapsulation of drug [15]. Formulation C9 showed less entrapment efficiency than C8 this may be due the fact that increase in proportion of carbopol decreases the viscosity of formulation thus beads become less rigid and thus leakage of drug from polymer matrix is more [15]. Formulation C10 showed 54.24 % encapsulation efficiency. At high concentration of crosslinking agent, the hydrogel matrix is rigid and leakage of drug from polymer matrix is low resulting in high drug entrapment efficiency [15]. The microbeads are more spherical in shape before solid dispersion loading. The drug loading and solid dispersion loading lead to formation of irregular microbeads with rough surface which may provide higher specific surface area [17]. SEM of the surface of sectioned solid dispersion loaded microbeads shows that many large pores are present in the gel matrix may be due to contraction of gel matrix caused by water evaporation is depressed by the presence of carbopol [4].

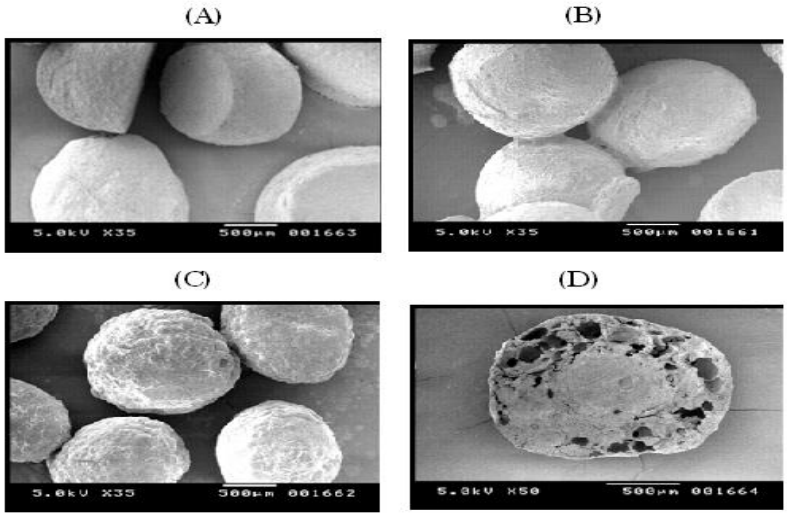

Fig. 6. SEM analysis of sodium alginate- carbopol microbeads (A) blank microbeads (B) drug loaded microbeads (C) solid dispersion loaded microbeads (D) sectioned surface of solid dispersion loaded microbeads.

Mucoadhesion study

Percent mucoadhesion in vitro is given in table 5.

It was observed from the result that as the concentration of mucoadhesive polymer carbopol increased, mucoadhesion also get increased. This can be due to the availability of more polymer chains for entanglement with the mucus[18].

The results also showed that increase in concentration of crosslinking agent decreases the percentage mucoadhesion; the reason may be attributed to less availability of polymer chains for entanglement with the mucus.

Table 5.

Percent in vitro mucoadhesion of microbeads.

Sr. no.	Batch code	Percent in vitro Mucoadhesion (mean ± SD) (20 Min.)	Percent in vitro Mucoadhesion (mean ± SD) (120 Min.)
1	C1	76.33 ± 0.57	11.6 ± 0.57
2	C2	21 ± 1	2 ± 1
3	C3	90.33 ± 0.57	13.5 ± 0.57
4	C4	86.33 ± 1.52	12.7 ± 1.5
5	C5	82.66 ± 0.57	12 ± 0.57
8	C8	88.33 ± 0.57	13.2 ± 0.57
9	C9	94 ± 1	16 ± 1
10	C10	80.33 ± 0.57	12± 0.57

In vitro drug release study

It was observed that formulation C1 shows only 37.18 % at the end of 8 hrs which contains pure drug which indicates drug molecules presenting difficulties in their solubility in dissolution medium [17].It was observed that formulation C5 showed more drug release than formulation C4 and C3, thus it was found from result that with the increasing concentration of DOM solid dispersion in formulation, % drug release also get increased.

The reason may be attributed to the facts that decrease in polymer concentration in microbeads. The drug in the bead might act as inert filler by occupying the free volume of swollen hydrogel. The release rate is correlated with diffusion coefficient which indicates that as the diffusion coefficient increases, the release rate also has increased [19].

Table 6.
In vitro release data from batch C1, C3, C4, C5.

Sr.no.	Time (hrs)	% Drug Release (mean ± SD)			
		C1	C3	C4	C5
1	0	0	0	0	0
2	0.5	0.083 ± 0.03	8.62 ± 0.75	12.36 ± 0.80	15.18 ± 0.53
3	1	0.6 ± 0.22	19.82 ± 0.84	25.77 ± 0.75	31.95 ± 0.94
4	1.5	7.31 ± 0.90	30.36 ± 0.54	39.22 ± 0.67	46.71 ± 0.74
5	2	14.58 ± 0.94	40.61 ± 0.95	52.47 ± 0.92	61.91 ± 0.81
6	3	27.08 ± 0.66	61.34 ± 0.84	78.19 ± 0.70	77.70 ± 0.94
7	4	36.28 ± 0.83	80.17 ± 0.44	87.95 ± 0.96	87.17 ± 0.74
8	5	36.35 ± 0.77	85.68 ± 0.93	91.22 ± 0.84	92.69 ± 0.70
9	6	37.16 ± 0.83	88.37 ± 0.76	93.2 ± 1.07	95.07 ± 0.93
10	7	36.99 ± 0.70	90.11 ± 0.63	94.04 ± 0.67	97.21 ± 1.04
11	8	37.18 ± 0.89	91.22 ± 1.12	95.8 ± 0.73	99.25 ± 0.88

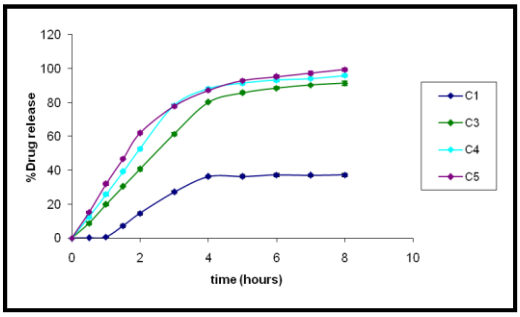

Fig. 6. In vitro release data from batch C1, C3, C4, C5.

Table 7.
In vitro release data from batch C1, C2, C3, C8, C9.

Sr.no.	Time (hrs)	% Drug Release (mean ± SD)				
		C1	C2	C3	C8	C9
1	0	0	0	0	0	0
2	0.5	0.083 ±0.03	6.55 ± 0.81	8.62 ± 0.75	11.01 ±0.65	12.41 ±0.75
3	1	0.6 ± 0.22	14.46 ±0.93	19.82 ±0.84	23 ± 0.80	25.86 ±0.57
4	1.5	7.31 ± 0.90	22.14 ±0.73	30.36 ±0.54	37.76 ±0.57	39.25 ±0.90
5	2	14.58 ±0.94	29.92 ±0.63	40.61 ±0.95	45.04 ±0.90	52.52 ±0.66
6	3	27.08 ±0.66	45.34 ±0.92	61.34 ±0.84	67.80 ±0.93	77.51 ±0.83
7	4	36.28 ±0.83	60.59 ±0.80	80.17 ±0.44	80.9 ± 0.73	84.43 ±0.71
8	5	36.35 ±0.77	74.86 ±0.76	85.68 ±0.93	87.21 ±0.67	89.57 ±0.84
9	6	37.16 ±0.83	81.65 ±0.97	88.37 ±0.76	90.74 ±0.93	92.39 ±0.75
10	7	36.99 ±0.70	85.28 ±1.07	90.11 ±0.63	92.44 ±0.59	93.79 ±0.74
11	8	37.18 ±0.89	88.48 ± 0.83	91.22 ± 1.12	93.56 ± 1.04	95.77 ± 0.56

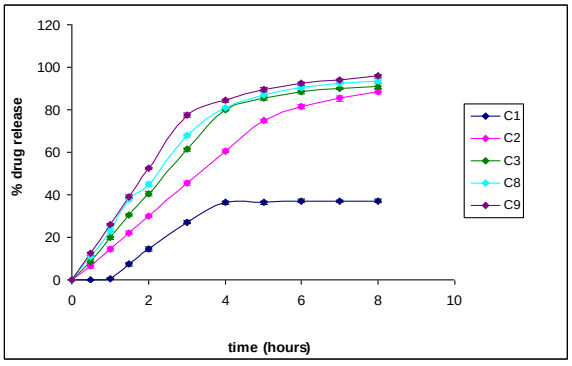

Fig. 7. In vitro release data from batch C1, C2, C3, C8, C9.

It was observed that formulation C9 showed more drug release than formulation C8, C3 and C2. The reason may be attributed to the fact that, when the proportion of carbopol increased while preparation of formulation, the polymer solution become less viscous and beads formed from such polymer solution when incorporated in dissolution medium, it may give more relaxation of polymer chains thus shows more drug release [18].

The drug release from formulation C10 was less as compared to formulation C3 and in almost zero order.Tthe rate and extent of drug release was decreased with the increasing concentration of calcium chloride. This can be attributed to formation of tight junction between mannuronic acid residues and glucuronic acid residues of sodium alginate with calcium [17].

Table 8.
In vitro release data from batch C3, C10.

Sr. no.	Time (hrs)	C1	C3	C10
1	0	0	0	0
2	0.5	0.083 ± 0.03	8.62 ± 0.75	3.89 ± 0.73
3	1	0.6 ± 0.22	19.82 ± 0.84	10.01 ± 0.90
4	1.5	7.31 ± 0.90	30.36 ± 0.54	14.70 ± 0.64
5	2	14.58 ± 0.94	40.61 ± 0.95	22.77 ± 0.80
6	3	27.08 ± 0.66	61.34 ± 0.84	34.64 ± 0.77
7	4	36.28 ± 0.83	80.17 ± 0.44	46.45 ± 0.74
8	5	36.35 ± 0.77	85.68 ± 0.93	58.26 ± 0.70
9	6	37.16 ± 0.83	88.37 ± 0.76	70.11 ± 0.84
10	7	36.99 ± 0.70	90.11 ± 0.63	81.96 ± 0.75
11	8	37.18 ± 0.89	91.22 ± 1.12	86.10 ± 1.00

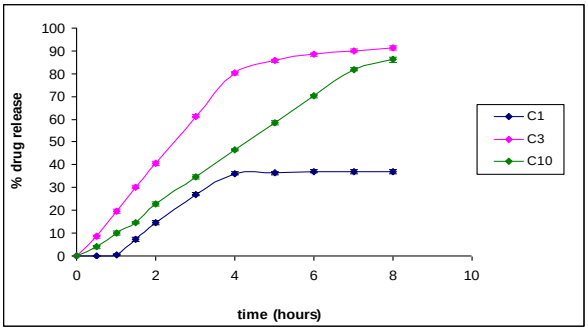

Fig. 9. In vitro release data from batch C1, C3, C10.

Table 9.
In vitro release data from batch C1, C9, C10.

Sr. no.	Time (hrs)	C1	C9	C10
1	0	0	0	0
2	0.5	0.01	11.28	2.35
3	1	0.07	23.6	9.72
4	1.5	3.74	38.63	13.01
5	2	10.58	50.13	21.02
6	3	21.38	82.1	37.89
7	4	30.2	90.28	50.18
8	5	31.17	97.68	64.1
9	6	30.59	97.56	76.22
10	7	30.39	97.55	88.54
11	8	30.26	97.49	90.23

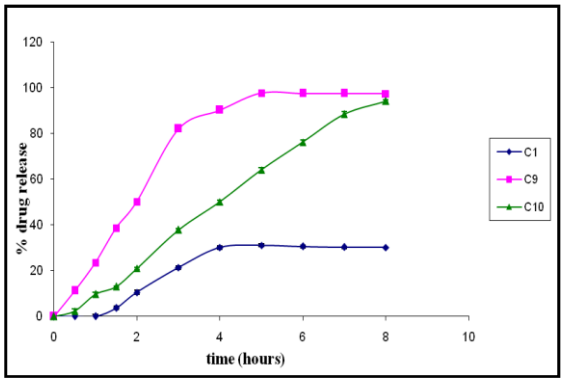

Fig. 10. In vitro release data from batch C1, C3, C10.

Conclusion

Domperidone is poorly water soluble D_2 antagonist widely used as antiemetic. It has short elimination half life of 7 hours hence effect last within 5 to 7 hours. It has poor bioavailability. It is rapidly absorbed from stomach and upper part of GIT. It was found that solid dispersion of domperidone with HPMC E 15 LV and citric acid in the ratio of 1:1:1 (domperidone: HPMC E 15 LV: citric acid) enhanced the dissolution rate of domperidone to maximum extent and hence oral bioavailability of domperidone. Increase in concentration of cross linking agent in beads indicated increased entrapment efficiency and less percentage mucoadhesion was found. Increase in proportion of solid dispersion showed increase in extent of drug release. Similarly when proportion of carbopol in formulation was increased, extent of drug release also gets increased. When we increased concentration of crosslinking agent, less extent of drug gets released. Thus it is indicated that developed mucoadhesive microbeads have potential to deliver the domperidone in stomach and upper part of GIT and further in intestine and improve its bioavailability and thus can be viewed as efficient alternative to conventional dosage forms.

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