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Formulation and Evaluation of Gastroretantive Floating Tablet using Carbopol with Xanthan Gum and Guar Gum

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Abstract : The Floating tablets of Domperidone were prepared by wet granulation process. All tablets were evaluated for their physical parameters for both, pre-compression and post-compression. FTIR and DSC studies proved that no chemical interaction in Domperidone and polymers.All the batches evaluated for swelling and floating properties also, the batches containing combination of Carbopol with natural polymers Guar and Xanthan Gum shows good swelling properties since natural gums swells rapidly and efficiently in water. The *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer concentration and the polymer used. The sustained drug release with better floating was achieved with natural polymers. The developed floating tablet of Domperidone used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient compliance. . All the batches showed Mixed Matrix and Peppas best fitted model for release kinetics, which showed that,the release of the drug from the prepared tablets is sustained by swelling, followed by drug diffusion and slow erosion of the polymer.
Key words : Domperidone, Floating tablets, Carbopol, Natural polymers, Release kinetics.

Introduction

Prolonged gastric retention improves bioavailability, reduces drug waste and improves solubility for drugs that are less soluble in a high pH environment. Floating drug delivery system provides better bioavailability for the drugs that are unstable in intestinal or colonic environment[1].Floating systems or Hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time[2-3]. The Gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability[4].

Natural polymers remain attractive primarily because they are inexpensive, readily available, be capable of chemical modifications, non-carcinogenicity, mucoadhesivity, biodegradable, biocompatible, high drug holding capacity and high thermal stability and easy of compression

Natural gums are biodegradable and non toxic, which hydrate and swell on contact with aqueous media and these have been used for the preparation of dosage form[5],Carbopol are crosslinked, acrylic acid-based high molecular weight, water swellable polymer which forms hydrogels in aqueous solutions[6] Xanthan gum is a linear, high molecular weight extracellular heteropolysaccharide, produced commercially by viscous fermentation of gram negative bacterium *Xanthomonas campesteris.* It has been also used as effective

excipients for sustained release formulation; it not only retards drug release, but also provides time independent release kinetics[7]. Guar gum is used primarily for preparation of hydrophilic matrix tablets because of its unique properties such as swelling, gel formation, non toxicity and biodegradability[8-9].Domperidone is a synthetic benzimidazole compound used as a prokinetic agent for treatment of upper gastrointestinal motility disorders antiemetic and gastroprokinetic properties[10].It has poor aqueous solubility and the oral bioavailability of Domperidone has been reported at the range of 13- 17%.The poor aqueous solubility may be one possible reason for its low bioavailability. In order to increase the bioavailability of Domperidone, a controlled release dosage form has been prepared to increase the solubility of Domperidone[11].

The aim of the current study was to develop gastric floating matrix tablet of domperidone using combination of carbopal with xathan gum and guar gum to improve bioavailability, therapeutic efficacy and patient compliance.

Materials and Method:

Materials:

Domperidone was obtained as gift sample from Dr Reddy's Laboratories Ltd, Hyderabad , India. Carbopol, Xanthan gum and guar gum were purchased from Himedia, Mumbai, India. All other ingredients used were of Analytical grades.

Methods:

Drug polymer compatibility studies

FT-IR studies:

The FTIR spectra of pure domperidone and its physical mixtures (1:1) with carbopol 934, xanthan gum and guar were carried out using FT-IR (Shimadzu 8400 S, CE).

DSC studies:

Thermal analysis of drug and polymer was carried out using Differential Scanning Calorimetry (Mettlor Toledo DSC 822).

Formulation of floating tablets of Domperidone:

Floating matrix tablet of Domperidone were prepared by conventional wet granulation method according to the formula given in Table 1. Ingredients except glidants and lubricant were thoroughly mixed and passed through sieve no. 60. Granulation was done using isopropyl alcohol as granulating agent. The wet mass was passed through sieve no. 12 and dried at 50 °C for 2 h. The dried granules were lubricated with magnesium stearate and talc. Tablet compression was carried out in rotary compression machine using 5 mm concave punches. Compression force was kept constant throughout the study. Tablet weight was adjusted to 100 mg.

Table 1: Composition of Floating Matrix tablets of Domperidone

Ingredients(mg)	Formulation Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Domperidone	30	30	30	30	30	30	30		
Carbopol 934	30	-		20	15	10	20	15	10
Guar gum	-	30		10	15	20			
Xanthan gum			30				10	15	20
Sodium bicarbonate	10	10	10	10	10	10	10	10	10
Magnessium state	2	2	2	2	2	2	2	2	2
PEG 400	5	5	5	5	5	5	5	5	5
Lactose	23	23	23	23	23	23	23	23	23
Total	100	100	100	100	100	100	100	100	100

Evaluation of granules:

The granules were evaluated for their flow properties. Angle of repose of granules was determined by the funnel method.Loose bulk density (LBD) and tapped bulk densities (TBD) were determined, according to the method reported by Raghuram et al.[12],The Carr index (compressibility index) and Hausner ratio determined from the LBD and TBD[13].

Evaluation of tablet:

Prepared tablet were evaluated for quality control tests like weight variation test, hardness test, friability test and content uniformity study[14-15].

Swelling Study[16]:

The tablets were weighed individually W1) and placed separately in glass beaker containing 200 mL of 0.1 N HCl maintained at 37°C±1°C. At regular 1-h time intervals until 24 h, tablets were removed from beaker, and the excess surface liquid was removed carefully using the paper. The swollen tablets were then re-weighed (W2) and swelling index (SI) was calculated using the following formula.

$$SI = (W2-W1)/ (W1)$$

Floating property[17]:

Buoancy lag time (BLT)is the time required for tablet to rise to the surface of dissolution medium and total floating time (TFT) is the time the tablet constantly float on the water surface were evaluated in a dissolution vessel (dissolution apparatus, Lab India) filled with 900 ml of 0.1M HCL (pH 1.2) set at 37±0.5^{O}C with paddle rotation at 50 rpm.

***In vitro* drug release study:**

The *in vitro* drug release study was performed using USP type II (Electrolab Tablet Dissolution tester – USP, Model No. TDT – 06P) at 50 rpm in 900 mL of 0.1M HCl (pH 1.2) maintained at 37±0.5°C. The samples were withdrawn at predetermined time intervals for period of 12 hr and replaced with the fresh medium. The samples were filtered through 0.45 μm membrane filter, suitably diluted and analysed at 286 nm using double beam UV-VIS spectrophotometer (Mode No. UV 2300, Techcomp). The content of drug was calculated using equation generated from calibration curve. The test was performed in triplicate and the mean value was used to construct the release profile.

Determination of release kinetics and release mechanism[18-19]:

The release data obtained were treated according to zero-order, first-order, Higuchi and Korsmeyer-Peppas equation models.

Results and Discussion:

Drug polymer compatibility studies

The FT-IR specra of pure drug and its physical mixture with polymers carbopol934, eudragit RSPO, Guar gum, Xanthan gum revealed no considerable changes in IR peaks of Domperidone indicating absence of interaction between drug and polymer used. The results of DSC studies also confirmed that there was no appreciable change in the melting endotherm which further supports the IR spectroscopy results. . These results clearly indicate the usefulness of the utilized materials for preparation of Gastro retentive Floating Tablets.

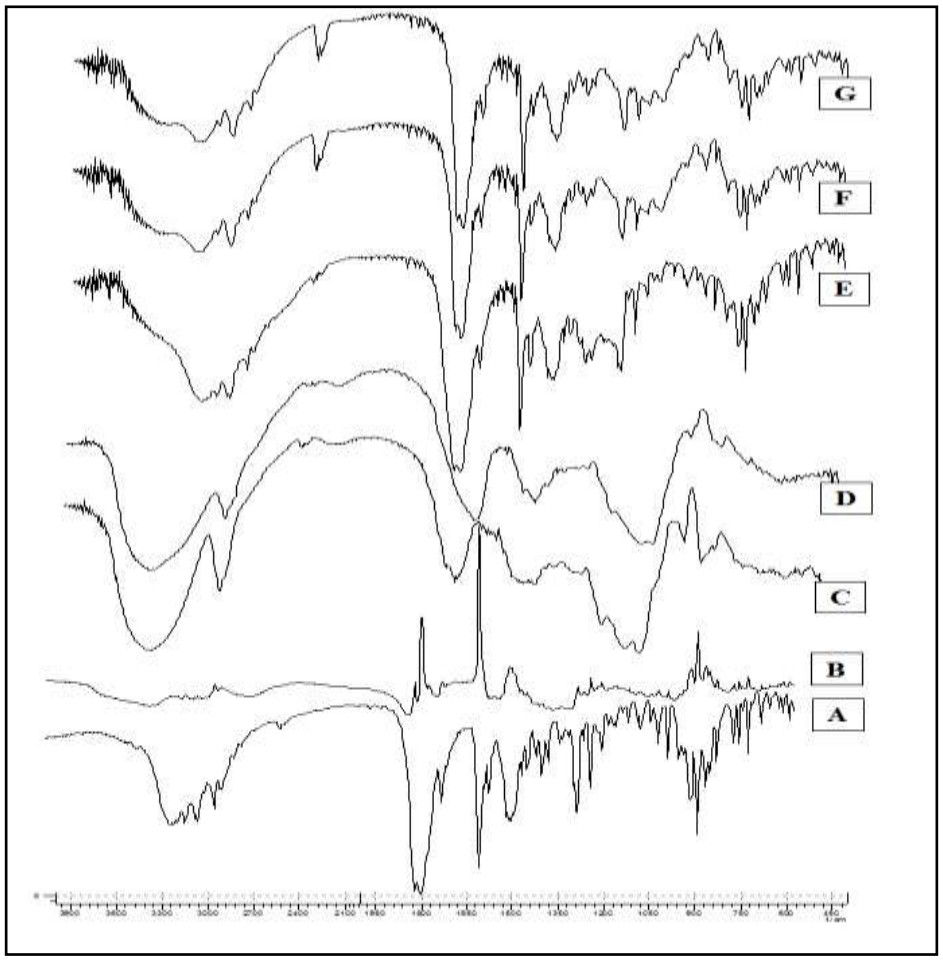

Figure 1: FTIR Spectra of pure drug and polymers.(A) Domperidone, (B) Carbopole 934 (C) Guar Gum, (D) Xanthan Gum,(E)Domperidone and Carbopol,(F) Domperidone and Guar Gum,(G) Domperidone and XanthanGum

Evaluation of granules

Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. All the batches of granules showed good flow properties since all batches had angle of repose of between 25°-35° which indicate good flow of granules. All batches had compressibility index between of between 12-15% and hausner ratio between 1.12-1.17 which indicates good flow character of granules. The results are as depicted in table 2.

Table 2: Pre compression properties of granules:

B. No.	Bulk density (g/mL)	Tapped density (g/mL)	Angle of Repose (°)	% Compressibility	Hausner ratio
F1	0.517	0.566	35.78	14.51	1.16
F2	0.439	0.505	27.35	12.96	1.14
F3	0.317	0.364	26.20	12.94	1.14
F4	0.405	0.468	26.95	13.46	1.15
F5	0.422	0.482	26.77	12.50	1.14
F6	0.330	0.380	25.30	13.16	1.15
F7	0.476	0.557	26.18	14.54	1.17
F8	0.474	0.550	26.00	13.72	1.15
F9	0.393	0.458	25.82	14.06	1.16

Evaluation of tablet:

The hardness of all the compression coated tablets was found to be within 6-7 kg/cm^2. The percent weight loss in the friability test was less than 1% in all the batches. All the batches contained drug within 100±5% of labeled amount. All the other physical parameters for core tablet formulation were within the limits as shown in table3.

Table 3: Post-compression assessment of domperidone floating tablets:

B. No.	Friability	Hardness	Thickness	% Weight variation#	% Content*
F1	0.166	7.3±0.23	3.96 ± 0.092	101 ± 2.9	97.34±0.4
F2	0.166	6.8±0.38	3.96 ± 0.083	101±2.3	97.24±0.5
F3	0.222	6.6±.82	3.98 ± 0.03	102 ± 3.9	96.32±0.9
F4	0.116	6.5±0.71	3.97 ± 0.03	100 ± 3.9	98.45±0.7
F5	0.421	6.5±1.43	3.92 ± 0.023	98 ± 3.4	96.38±0.2
F6	0.166	7±2.83	3.91 ± 0.041	102 ± 2.8	95.79±0.9
F7	0.642	6.5±0.51	3.69 ± 0.026	100± 2.0	96.31±1.1
F8	0.166	6.5±0.93	3.82 ± 0.10	101 ± 3.01	92.18±1.1
F9	0.112	6±0.32	3.82 ± 0.011	101 ± 3.1	95.41±1.2

Swelling study:

Swelling is an important factor to ensure floating and drug dissolution. Swelling study was performed on all the batches for 7 hrs. The rate and extent of swelling increased with an increasing concentration of polymer in the formulation. The swelling index of Batch F1-F9 formulations was in the range of 72.82±0.13to 80.72±0.22%.The results of swelling index were depicted in Figure: 2

The maximum swelling index was observed in formulations containing Guar gum with their increasing concentration in formulation. Carbopol 934 increases swelling index with their increases concentration. Carbopol934 when given in combination with Guar gum and xanthan gum showed more swelling. From the results, it was concluded that swelling increases as the time passes because the polymer gradually absorb water due to hydrophilicity of polymer.

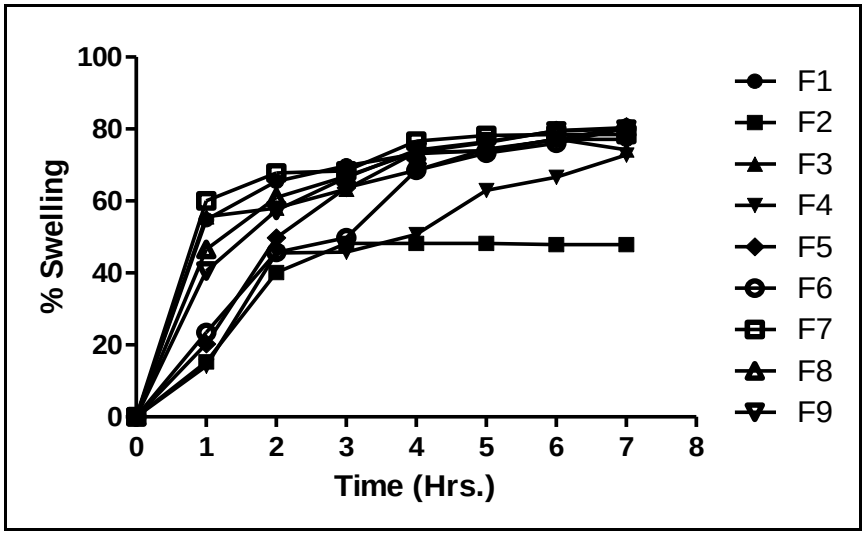

Figure 2: Swelling Study of Batch F1-F9

Floating Behaviors of Tablet:

The tablets were floated and remained buoyant without disintegration thus it, maintains its dimensional stability during floating. The formulation F1,F2 and F3 containing Carbopol, Guar and Xanthan Gum Showed BLT 8, 8 and 6 minutes and TFT 12, 6 and 7 respectively. Batch F4-F9 batches showed BLT within the range of 11-14minutes and TFT from 11-14 hrs respectively shown in the Table 4. The total buoyancy/floating time of batch containing plain carbopol934 and natural gums shows good floating behavior. When carbopol934 used with natural polymers it shows better floating behavior. Increased in concentration of natural polymer Xanthan and guar gum with carbopol934 increases floating time as shown in table 4.

Table 4: Floating behavior of tablets

B. No	BLT(min)	TFT (hr)
F1	8	12
F2	8	6
F3	6	7
F4	6	11
F5	10	13
F6	12	13
F7	10	14
F8	10	13
F9	15	14

***In vitro* drug release study:**

The percentage of the drug released from the formulations F1, F2 and F3 was found to be 77.6 ± 0.63 %, 91.15 ± 0.75 % and 94.582 ± 0.12 %, respectively. The percentage of thedrug released from the formulations F4, F5, and F6 was found to be 78.7 ± 0.24 %, 77.63 ± 0.48, and 71.41 ± 0.37 % respectively. The percentage of the drug released from the formulations F7, F8 and F9 was found to be 96.2 ± 0.29 %, 94.3 ± 0.33 and 94.3 ± 0.34 %, respectively as depicted in figure 2.

It was also observed that as the amount of polymer increases in the formulation there was decrease in drug release rate, which may be due to the drug entrapped in hydro gel by forming hydrophilic polymers. Xanthan gum and guar gum systems showed rapid drug release in first 6 h, so these systems cannot provide extended drug delivery over prolonged period of time, probably due to rapid partial tablet disintegration and slower swelling of these polymers resulting in a lack of contribution to hydrogel formation[20].Combination of carbopol934 with guar gum shows good sustained release properties than with Xanthan gum.

ANOVA was carried out using Bonfferroni post test between the drug release data of formulation, F1-F3 of plain polymer batches and combination of polymers batches F4 to F9, with their respective combinations are analyzed,***p*** values were less than 0.001 indicating statistical significant difference existing between release profile of tablets containing different polymer-polymer combinations and different combination ratio.

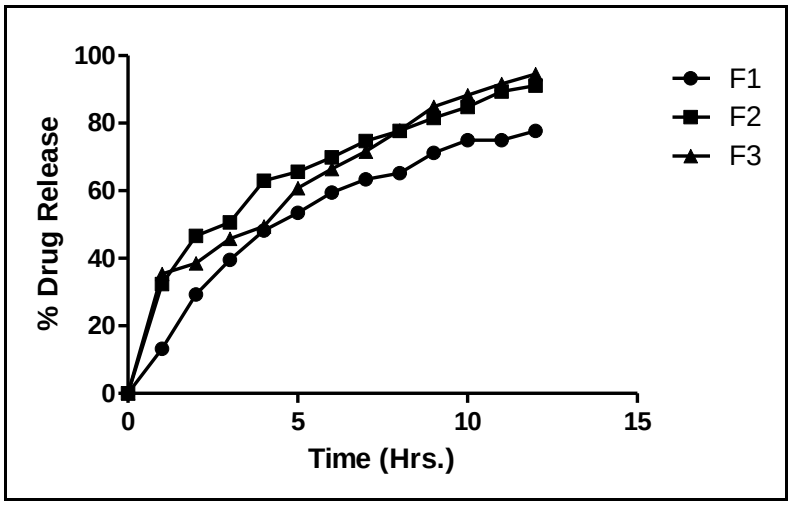

Figure 3: Drug Release profile of Batch F1-F3

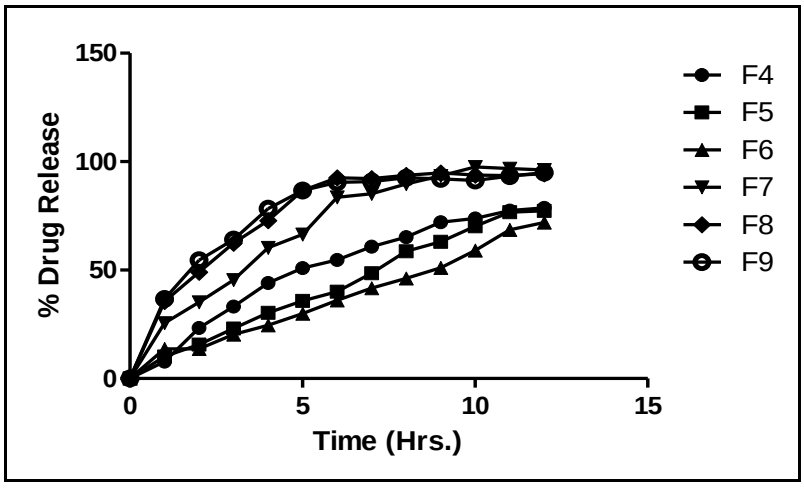

Figure 4: Drug Release profile of Batch F4-F9

Determination of release kinetics and release mechanism

The best fitting model for all formulation was calculated. The plain polymer batches F1, F2 and F3, the best fitted models was found to be Higuchi and Korsmeyer peppas release. The batch F4 followed Higuchi, F5 First order and all other batches followed Korsmeyer peppas model as shown in Table5. The values of *n* as estimated by linear regression of log (M_∞ / M_t) vs. log (*t*) of formulations indicated a non-Fickian release behavior, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. Thus, the release of the drug from the prepared tablets is sustained by swelling of the polymer; followed by drug diffusion through the swelled polymer, slow erosion of the polymer

Table 5: Determination of release kinetics and release mechanism

Batch	Zero order		1st order		Matrix		Hix.Crow		Peppas	Exponent of Korsmeyer -Peppas Eq	Constant of Korsmeyer-Peppas Eq.
	R	k	R	k	R	k	R	K	R	N	K
F1	0.8840	7.8765	0.9857	-0.1354	0.9897	23.1437	0.9646	-0.0371	0.9646	0.6656	16.7896
F2	0.8979	2.3471	0.9348	-0.0269	0.9859	7.3986	0.9240	-0.0086	0.9854	0.5206	7.0418
F3	0.8618	9.3251	0.9798	-0.2133	0.9938	27.4423	0.9868	-0.0515	0.9763	0.5466	30.2693
F4	0.9454	7.7606	0.9975	-0.1344	0.9777	22.5505	0.9903	-0.0367	0.9713	0.8620	11.0037
F5	0.9952	6.9266	0.9764	-0.1148	0.9427	19.7317	0.9901	-0.0318	0.9967	0.8632	9.2388
F6	0.9818	6.5306	0.9860	-0.1016	0.9640	18.7787	0.9921	-0.0289	0.9927	0.6988	12.3370
F7	0.8693	10.2431	0.9726	-0.2982	0.9851	30.1336	0.9833	-0.0642	0.9862	0.5862	25.4084
F8	0.5317	10.7101	0.9132	-0.3006	0.9419	32.2134	0.8487	-0.0667	0.9564	0.5047	39.3545
F9	0.4180	10.6302	0.9152	-0.2856	0.9296	32.0739	0.8266	-0.0647	0.9530	0.3690	42.0859

Conclusion:

The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. The work was carried out using individual polymersand the combination of Carbopol and natural polymersXanthan and Guar gum in the different concentration. FTIR and DSC studies proved that no chemical interaction in Domperidone and polymers.. The developed floating tablet of Domperidone used to prolong drug release for more than 12 hrs, thereby improving bioavailability and better patient complianceThe *in-vitro* drug release studies revealed the drug release from the formulation depended upon the polymer concentration and the polymer used. The sustained drug release with better floating was achieved with natural polymers.

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