Research Article

FORMULATION, OPTIMIZATION AND COMPARATIVE EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF CINNARIZINE AND DOMPERIDONE MALEATE FLOATING TABLET

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ABSTRACT

The drug therapeutic indices could be maximized while indices of adverse reactions or side effects could be minimized by regulating the drug release in body in a well-defined controlled manner. Domperidone maleate (Antidopamine) and Cinnarizine (Antihistamine) contribute to the overall efficacy of an agent as an antiemetic. Both drugs have solubility in acidic environment. Half lifes of Domperidone maleate and Cinnarizine are 4-7 hrs and 3-6 hrs respectively. Hence to improve patient compliance and to minimize the frequency of dosage administration, the controlled release floating tablet of drug combination was formulated. This system is also known as hydro dynamically balanced system (HBS/FDDS). Here the density lower than gastric fluid, i.e. their density is less than 1gm/cm^3 and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. Here a formulation of a drug (CIN + DOM) and gel forming hydrocolloids (Hydroxy Propyl Methyl Cellulose and Sodium alginate) meant to remain buoyant on stomach contents. This not only prolongs GI residence time but also maximize the area at which the drug reaching its absorption site in solution and hence ready for absorption while the system is floating on the gastric contents. In the present study Methocel polymers of different viscosity (Methocel K4M, Methocel K15M) were selected as polymer because of their independence from pH or ionic content of the dissolution medium. The tablets were prepared containing various concentrations (20% - 50%) of Methocel polymers. The floating behavior and drug release study was done in 900 ml of dissolution medium (0.1N HCl) at 37±0.5°C at a rotation speed of 50 rpm which conferred the formulation D3 as suitable for dissolution studies as it offered a proper lag time of 10-15 sec and floating time of 12 hours. Sodium bicarbonate (15 mg) and sodium alginate (18 mg) as gas generating agents were essential to achieve *in vitro* buoyancy of 12 hours so that the formulation is on the gastric surface by 10-15 sec after administration.

Keywords: Domperidone maleate (DOM), Cinnarizine (CIN), hydro dynamically balanced system, hydroxy propyl methyl cellulose, sodium alginate, Methocel K4M, Methocel K15M.

INTRODUCTION

Gastroretentive Drug Delivery Systems can remain in gastric region for several hours and hence, significantly prolong gastric residence time of the drug. Prolonged gastric retention improves bioavailability, reduce drug waste and improve solubility for drugs that are less soluble in a high pH environment. Oral controlled drug delivery system should be primarily aimed at achieving more predictable and increased bioavailability of drugs. In present study the GET of 12 hours is achieved and GRT of 12 hours in floating state is achieved in D3.

The real issue in the development of oral controlled release dosage form is not just to prolong the delivery of drugs for more than 12 hrs but also to prolong the presence of dosage forms in the stomach or somewhere in the upper small intestine. Dosage forms with prolonged gastric residence time (GRT), i.e. gastro remaining or gastro retentive dosage form (GRDF), will bring about new and important therapeutic options. For instance, these will significantly extend the period of time over which drugs may be released, and thus prolong dosing intervals and increase patient compliance beyond the compliance level of existing controlled release dosage forms.

In present study floating System (Low Density Approach) is opted to achieve sustained and steady state drug blood levels. These systems are also known as hydro dynamically balanced system (HBS/FDDS). They have a bulk density lower than gastric fluid, i.e. their bulk density is less than 1. The specific gravity of gastric fluid is approximately 1.004–1.010 g/cm^3 and thus the FDDS remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time.. This not only prolongs GI residence time but also maximize absorption while the system is floating on the gastric contents. The floating system here is obtained by inducing effervescent effect. A drug delivery system was made to float in the stomach by incorporating a floating chamber, which was filled with inert gas. The gas in floating chamber was introduced by effervescent reaction between organic acids and bicarbonate salts (sodium alginate and sodium bicarbonate). These effervescent components liberate carbon dioxide by the acidity of gastric contents and entrapped in the gelified hydrocolloid this produces an upward motion of dosage form and maintains its buoyancy. These buoyant delivery systems utilize effervescent reaction between carbonate/ bicarbonate salts and citric/tartaric acid to liberate CO_2 which gets entrapped in the jellified hydrochloride layer

of the system, thus decreasing its specific gravity and making it float over chyme.

In present study Domperidone an antidopaminergic and Cinnarizine an antihistaminic have been used in combination. Domperidone works primarily by blocking dopamine receptors which are found in an area of the brain known as the chemoreceptor trigger zone (CTZ). The CTZ is activated by nerve messages from the stomach when an irritant is present. It is also activated directly by agents circulating in the blood, for example anti-cancer medicines. CTZ once activated, it sends messages to another area of the brain that is the vomiting centre, which in turn sends messages to the gut, causing the vomiting reflex. Blocking the dopamine receptors in the CTZ in the brain prevents nausea messages from being sent to the vomiting centre. This reduces the sensation of nausea and prevents the action of vomiting.

Cinnarizine has antihistaminic, anti-emetics and antivertigo activity by blocking the histamine H_1 receptors. It also shows weak antimuscarinic and local anesthetic activity. Cinnarizine inhibits stimulation of the vestibular system.

MATERIALS AND METHODS

Cinnarizine I.P, Domperidone Maleate B.P., HPMC-K4M, HPMC-K15M were gift samples from Johnson and Johnson Pvt.Ltd, FDC Pvt. Limited, Mumbai and Colorcon Asia Pvt.Ltd., Goa respectively. Also Sodium Bicarbonate, Sodium alginate, Magnesium stearate, Talc were purchased from SD Fine Chem, Boisar, Maharashtra. All other chemicals used were of analytical reagent grade.

Experimental[4-6]

1) Preparation of granules

All the polymers and drugs were passed through stainless steel sieve (mesh no. 60) to break the lumps and aggregates. Lactose, sodium bicarbonate and sodium alginate were accurately weighed and blended thoroughly using glass mortar and pestle manually with isopropyl alcohol in geometric proportion. The powder blends were passed through sieve (mesh no.12) then dried at room temperature for 15 minutes, Talc and magnesium stearate were added in to granules. Granules were prepared by wet granulation method and compressed on Labpress single rotator 8 station compression machine. Table No.3 depicts the formulae for the preparation of granules of Domperidone maleate and cinnarizine tablets.

2) In Vitro Characterization of GFDDS[3-5]

Evaluation of post compression parameter of floating tablets

Thickness: The thickness of the tablet was determined using a Vernier Calliper. Three tablets from each type of formulations were used and average values were calculated.

Tablet Hardness: The resistance of tablets to breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 3 tablets were determined using the monsanto hardness tester. The value at this point was noted in kg/cm^2.

Weight variation test: For weight variation 20 tablets of each formulation were weighed individually using an electronic balance, average weight was calculated and individual tablet weight was then compared with average value to find the deviation in weight.

Specifications as per Indian Pharmacopoeia

Average weight of tablet	% Deviation
80 mg or less	10
More than 80 mg but less that 250 mg	7.5
250 mg or more	5

Density of tablets: Density of tablets was calculated by the formula,

Density= Mass/Volume

Density = $Mass/\Pi r^2 h$.

Where, Π=Circular constant

r = Radius of tablet, h = Thickness of tablet.

Floating Behaviour: The *in-vitro* buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1N HCl. The time required for the tablet to rise to the surface and to float was determined as floating lag time. The duration for which the tablet remains to float on surface of solution is known as floating time.

Table 1: Formulae for the preparation of granules of Domperidone maleate and Cinnarizine tablets containing 20%w/w to 50% w/w concentration of Methocel

Batch Code	Drug (mg) DM	Drug (mg) CIN	Polymers (mg)		$NaHCO_3$ (mg)	Sodium Alginate (mg)	Lactose (mg)
			Methocel K15M	Methocel K4 M			
D1	15	20	60	-	15	18	166
D2	15	20	90	-	15	18	136
D3	15	20	120	-	15	18	106
D4	15	20	150	-	15	18	76
D5	15	20	-	60	15	18	166
D6	15	20	-	90	15	18	136
D7	15	20	-	120	15	18	106
D8	15	20	-	150	15	18	76

***** Total weight of tablet kept constant = 300 mg.

***** Each Tablet formulation contains 1% w/w of magnesium stearate and talc.

Table 2: Evaluation of Domperidone Maleate (DM) and cinnarizine (CIN) floating tablets

Batch code	Weight Variation**	Average* Thickness (mm)	Hardness* (kg/cm^2)	Friability (%)	Percentage Drug Content of DM	Percentage Drug Content of CIN
D1	299±0.5	3.28±0.02	2.5±0.55	0.33	99.07±0.48	98.01±0.21
D2	298±0.6	3.30±0.03	3.0±0.5	0.16	99.01±0.51	97.20±1.18
D3	300±0.1	3.29±0.02	3.0±0.40	0.33	99.00±0.54	98.15±1.15
D4	299±0.5	3.28±0.05	2.4±0.65	0.34	98.01±0.58	99.25±0.85
D5	298±0.6	3.29±0.09	2.5±0.60	0.50	99.12±0.20	98.35±0.35
D6	300±0.1	3.30±0.01	2.5±0.45	0.33	98.17±0.18	97.50±1.31
D7	298±0.6	3.28±0.06	3.0±0.50	0.50	99.12±0.41	98.12±0.55
D8	300±0.1	3.30±0.07	2.5±0.40	0.45	98.17±0.08	97.15±1.30

*n = 3,**n=20.

Drug Content of cinnarizine and domperidone maleate from combination tablets: From each batch two tablets were weighed and powdered each containing 20 mg of cinnarizine and 15 mg of domperidone maleate. A quantity of powder equivalent to 10 mg of Cinnarizine and domperidone maleate was accurately weighed and transferred to 50 ml of volumetric flask. Sufficient quantity of Methanol was added with shaking and volume was made up to the mark and filtered through whatman filter paper no. 41. Further dilutions were made in triplicate and the absorbance of domperidone maleate and cinnarizine was recorded at 286.5 nm and 254 nm respectively using multicomponent mode analysis.

1) *In Vitro* Dissolution studie[6-9]

The study was carried out using dissolution apparatus USP Type II (Paddle)

Dissolution medium : 0.1 N HCl.

Speed of paddle : 50 rpm.

Temperature of medium : 37 ± 0.5°C

The release rate of domperidone maleate and cinnarizine from floating tablets was determined using USP Dissolution Testing Apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and speed of 50 rpm. Aliquot (5 ml) of the solution was collected from the dissolution apparatus hourly for 12 hours and were replaced with fresh dissolution medium. The aliquots were filtered through whatmann filter paper no. 41. Absorbance of these solutions was recorded at 284.5 nm (Domperidone maleate) and 254 nm (Cinnarizine) in photometric mode for single drug and in multicomponent mode analysis for combined drugs. Aliquots were withdrawn at one hour interval from a zone midway between the surface of dissolution medium and the top of rotating paddle not less than 1 cm apart from the vessel wall. Drug content in dissolution sample was determined by software (PCP disso v3) version.

2) Differential Scanning Calorimetry of optimized formulation

The differential calorimetric scanning of optimized formulation was carried out using Differential Scanning Calorimeter

3) *In vivo* study of experimental floating tablets[28,29]

In vivo Study was carried out using X-Ray photography and was performed on healthy male New Zealand white strain rabbits weighing from 2.0 - 2.5 kg. After fasting for 24 hrs, rabbits were allowed to access water for 12 hrs just before start of study. The protocol according to Form B was approved by Committee for the purpose of control and supervision of Experiments on animals (CPCSEA) and Institutional Animal Ethics Committee (IAEC).

The placebo floating tablets were prepared for the rabbits. The placebo floating tablets was given to the rabbits. 35 mg of barium sulphate was added in each tablets. The tablet was administered to the rabbit through oral route. The lateral view of rabbit stomach was taken by using Digital X-Ray machine (Semens, make-200 MA).

4) Stability study[31,32]

Preparation of stability study batch

Tablets obtained from optimized batch i.e. **batch D3** were subjected to the stability testing. The tablets were packed in 40 cc high density polyethylene bottle (HDPE) and exposed to 40°C/75% RH in stability chambers (Neutronics) for three months. During the stability storage period the tablets were evaluated for physical characteristics, *in vitro* drug release and drug content (UV assay) at the end of 30 days, 60 days and 90 days of storage period. The tablets were evaluated for various parameters like physical appearance, weight variation, % Drug content, buoyancy lag time, total buoyancy time and *in vitro* dissolution study.

RESULTS AND DISCUSSION

Evaluation of Domperidone maleate and cinnarizine tablets

Table 2 and 3 shows the data for the tablet were evaluated for the properties such as appearance, weight variation, hardness, thickness, density, percent drug content and floating behaviour.

Appearance: The tablets were observed visually size, shape, colour, odour, marking and did not show any defect such as capping, chipping and lamination.

Weight Variation: When the average mass of the tablet is 250 mg or more than 250 mg, the pharmacopoeial limit for percentage deviation is ± 5%. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation.

Thickness of tablets: The thickness of tablets was measured using digital vernier calliper. The thickness of tablets was between 3.28 mm to 3.30 mm.

Test for friability: Friability testing was performed using Roche friabilator. 20 tablets of each formulation were carefully dedusted and accurately weighed. These tablets were placed in the rotating drum of the friabilator. Drum was operated for the 100 revolutions at the speed of 25rpm/min. The tablets were removed and dedusted and reweighed. Percentage weight loss was calculated using following formula.

% F = Loss in weight /Initial weight ×100

Hardness of tablets: The hardness of tablets was determined using Monsanto hardness tester. It was found in the range of 2.4 to 3.0 kg/cm^2. Hardness values were satisfactory and indicated good mechanical strength of tablets.

Drug Content: Drug content of all the tablets was found within 95% -105%.

In the evaluation it was found that the density of all the tablets was found to be less than 1, therefore it floats on gastric surface. The floating lag time for all the formulations was tested in dissolution vessel containing 900 ml of 0.1N HCl solution. All the tablets showed floating lag time of 10-15 second. The floating time for all the formulations tested in dissolution vessel containing 900 ml of 0.1N HCl solution. All the tablets showed floating time of more than 11 hrs, except the tablets (D1, D2, D6, D7, D8) less than 11 hrs.

Table 3: Evaluation of floating properties of domperidone maleate (DM) and cinnarizine (CIN) tablets

Batch code	Density	Floating Lag Time (sec)	Floating Time (hr)
D1	0.997	10-15	<11
D2	0.998	10-15	<11
D3	0.997	10-15	>11
D4	0.999	10-15	>11
D5	0.998	10-15	>11
D6	0.998	10-15	<11
D7	0.999	10-15	<11
D8	0.997	10-15	<11

Dissolution Profile

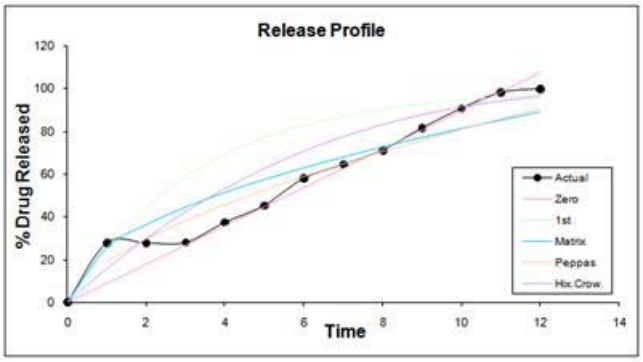
The dissolution data for tablets D1 to D8 was fitted to various drug release kinetic models like Zero order, First order, Higuchi Matrix and Korsemeyer Peppas model. Release exponent (n) values obtained in Korsemeyer Peppas model are also given in table 4. The model that gives maximum 'R' value is considered as the best fit model for the release data. It was found that Zero order as best fit model for all the formulations tested, except D5 to D8. For formulation D5 to D8 best fit model was matrix type. It indicates that the drug release from tablets shifted from non-fickian to zero order transport as the concentration of polymer increased. Graphical representation of best fit model of Domperidone maleate in D3 depicted in figure 1. Graphical representation of best fit model of Cinnarizine in D3 depicted in figure 2.

Table 4: Values of rate constants (K) and correlation coefficients (R) for release of Domperidone Maleate (DM) from tablets

Batch Code	Zero Order		First Order		Matrix		Korsmeyer Peppas		
	(K)	(R)	(K)	(R)	(K)	(R)	(n)	(K)	(R)
D1	9.1477	0.9667	-0.1732	0.9347	24.09	0.9490	0.5751	20.17	0.9185
D2	9.2427	0.9694	-0.1787	0.9231	24.34	0.9492	0.5773	20.30	0.9176
D3	8.9681	0.9768	-0.2949	0.7838	25.74	0.9516	0.6194	19.47	0.9361
D4	7.8718	0.9666	-0.1547	0.9309	22.61	0.9433	0.5556	19.34	0.9091
D5	11.8349	0.9322	-0.1782	0.9457	25.14	0.8951	0.4707	25.14	0.8951
D6	9.3026	0.8559	0.1291	0.9377	21.23	0.9768	0.3739	25.32	0.9308
D7	9.0881	0.8972	-0.1345	0.9585	21.93	0.9741	0.4227	24.41	0.9308
D8	8.766	0.9109	-0.1360	0.9711	22.32	0.9765	0.4503	23.86	0.939

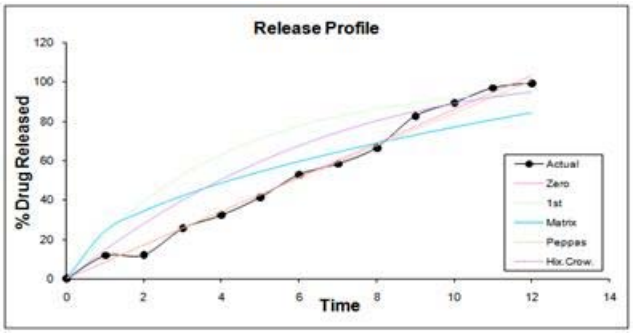
Table 5: Values of rate constants (K) and correlation coefficients (R) for release of cinnarizine (CINN) from tablets

Batch Code	Zero Order		First Order		Matrix		Korsemeyer Peppas		
	(K)	(R)	(K)	(R)	(K)	(R)	(n)	(K)	(R)
D1	7.564	0.8996	-0.1515	0.8146	18.81	0.7579	1.0031	5.82	0.8116
D2	8.862	0.9607	-0.2083	0.8311	22.39	0.8356	1.0802	6.72	0.9216
D3	8.621	0.9960	-0.2503	0.8287	24.34	0.9183	0.9769	8.87	0.9811
D4	8.349	0.9949	-0.1814	0.9376	23.76	0.9394	0.8646	11.05	0.9951
D5	13.75	0.9322	-0.4276	0.7124	27.47	0.8238	0.8670	14.73	0.8638
D6	11.67	0.9092	-0.4156	0.6843	24.53	0.7723	1.1672	7.25	0.8772
D7	10.83	0.9268	-0.2915	0.7923	24.33	0.7915	1.1765	6.57	0.8776
D8	8.044	0.9556	-0.1450	0.8165	19.37	0.8349	0.9826	7.40	0.9202



Time in hour

Figure 1: Best fit model for DM in formulation D3



Time in hour

Figure 2: Best fit model for CIN in formulation D3

From the n values of all formulations it can be concluded that as the concentration (20% to 50%) and viscosity of polymer was increased the value of diffusion exponent also increases. By using PCP Disso v3 Software one can predict *in vitro* release of domperidone maleate and cinnarizine for 12 hrs. It will be 99.87 % and 99.40% from D3 tablet. *In vitro* release study for formulations D3 (Methocel K4M - 40%) indicated consistent floating characteristics as well as controlled release kinetics and both followed zero order release kinetics. Therefore formulation (D3) was selected for *in vivo* studies. Dissolution of Optimized batch (D3) was shown in figure 3.

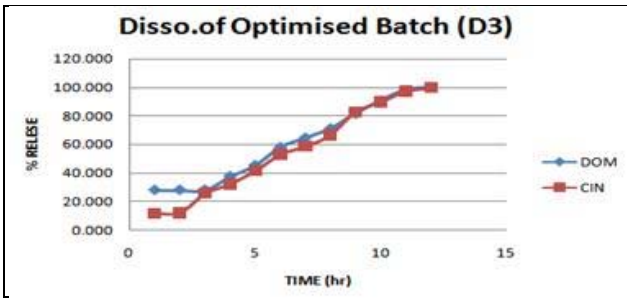


Figure 3: Dissolution of Optimized batch D3

Differential Scanning Calorimetry

Thermograms of Domperidone maleate, Cinnarizine and Optimized formulation (CD1) were obtained using a Mettler - Toledo DSC 821^{e} instrument. The powder samples were hermatically sealed in an aluminium pan and heated at constant rate 10^{o}C/min, over a temperature range of 0^{o}C to 300^{o}C.

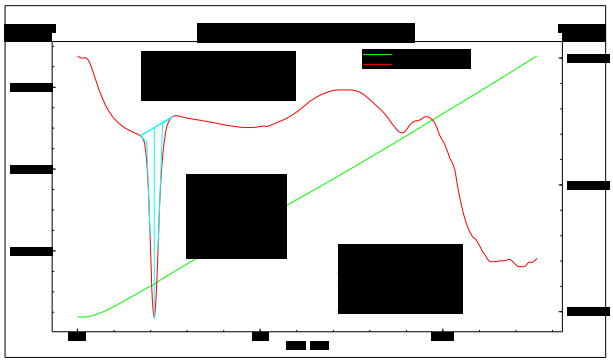


Figure 4: DSC Thermograph of optimized batch D3 formulation.

Figure 4 reports the DSC curves of Formulation (D3), which contains domperidone maleate and cinnarizine mixed with Methocel K4M polymer, the thermogram indicates characteristic peaks for melting of cinnarizine (121.73°C) and domperidone Maleate (242.20°C). Endothermic peak at (125.94°C) may be due to the melting of Methocel K4M. This indicates absence of drug - drug and drug - polymer interactions.

Floating behavior of experimental floating tablet

Figure 5 Shows photograph of floating tablet (D3) in dissolution vessel.

Figure 5: Floating behavior of experimental floating tablet (CD1).

***In Vivo* study of floating behaviour of experimental optimized tablet**

The optimized tablet (D3) was selected for *in vivo* evaluation. The *in vivo* study was carried out using X-ray technique in healthy rabbits weighing 2 kg to 2.5 kg. The data for in vivo evaluation is given in following X ray photos.

The X-Ray photos of floating tablet (Barium sulphate containing tablet similar to CD1) are shown in photo no 1 to 4 from 3 hr to 12 hr respectively.

Figure 6, 7, 8 and 9 shows the X-ray photograph of floating tablet in rabbit stomach.

From these experiments it is shown that floating tablet remains in stomach for at least 12 hrs.

All the physical parameters were in the acceptable limits which showed that formulation was stable over the period of 90 days.

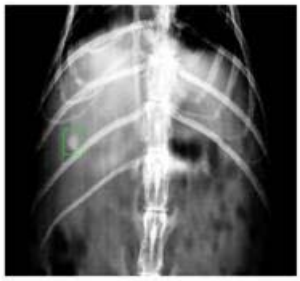


Figure 6: After 3 hr.

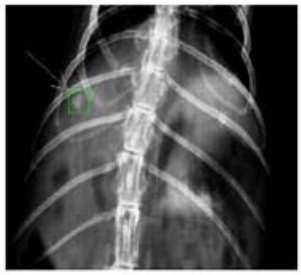


Figure 7: After 6 hr.

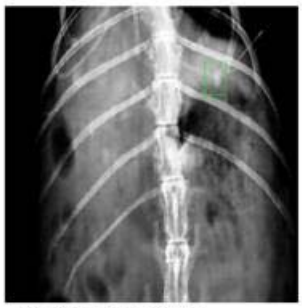


Figure 8: After 9 hr.

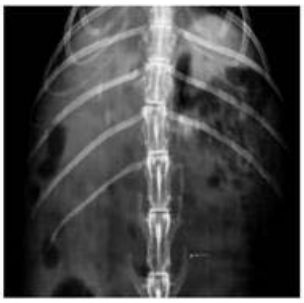


Figure 9: After 12 hr.

The stability studies of the optimized formulation (D3) of floating tablets revealed that there were no significant changes in the physical parameters when stored at accelerated temperature and humidity conditions. No significant reduction in the content of the active drug was observed over a period of three months; hence no special storage conditions are required. The optimized formulation did not show any significant change in floating parameters and drug release profile. Hence we can conclude that optimized batch is stable at various storage and humidity conditions.

CONCLUSION

Controlled drug delivery systems have acquired a center stage in the arena of pharmaceuticals as such systems offer predictable control over the release of drug. Oral controlled drug delivery systems represent the most popular form of controlled drug delivery systems for the obvious advantages of oral route of drug administration. Such systems release the drug with constant or variable release rates. As there are many parallel pathway involved in process of emesis. The pathogenesis of nausea and vomiting is complex, multifactorial and the symptoms are influenced by the origin of emetic response, hence this drugs are used in combination in the treatment of nausea and vomiting as they differ in their efficacy depending on primary cause of emesis. Domperidone maleate (Antidopamine) and Cinnarizine (Antihistamine) contribute to the overall efficacy of an agent as an antiemetic. Both drugs have solubility in acidic environment. Half lifes of Domperidone maleate and Cinnarizine are 4-7 hrs and 3-6 hrs respectively. Hence to improve patient compliance and to minimize the frequency of dosage administration, the controlled release floating tablet of drug combination was formulated.

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