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Characterization and evaluation of Clarithromycin Hydrophilic floating matrix tablets

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ABSTRACT

Present investigation describes the preparation of Clarithromycin hydrophilic matrix tablets by direct compression technique followed by in vitro floating characterization statistically. The floating hydrophilic matrix tablets prepared by using different grades of polymer (HPMC) of varying concentrations, different concentration of sodium bicarbonate and varying ratios of MCC. Floating properties such as FLT, TFT, and Swelling index. Tablet hardness had found to be affecting on floating behavior. Hydrophilic matrix floating tablets of Clarithromycin were developed to increase the gastric residence time which leads to increased bioavailability by giving sufficient time to release the drug in GI tract.

Key Words: Clarithromycin, Hydrophilic Matrix, Floating Tablet, HPMC

INTRODUCTION

A drug can be delivered to its target area at a rate and concentration that both minimize side effects and maximizes the therapeutic effects, the drug will not be maximally beneficial to the patient and the extreme, and an otherwise useful drug may be discarded. The most convenient method of controlled delivery of drug is undoubtedly oral, but oral controlled release of the drug for an extended period of time that exhibits more absorption in stomach and upper small intestine, has not been successful with conventional approaches. Consequently, most research efforts have been focused on platforms to extend gastric residence time (GRT) of these drugs.

The underlying principle of gastric retentive system is to prolong the release of the drug in the stomach¹.

Since the discovery of *Helicobacter pylori* by Marshall and Warren (1983-1984), *H. Pylori* are believed as a main microorganism causing gastric or peptic ulcer (Peterson, 1991). Therefore, eradication of *H. pylori* is prerequisite for curing a gastric or peptic ulcer and for preventing its recurrence (Labenze, 2001). The eradication rate of *H. pylori* can be to enhance by extending the resistance time of the antibiotic agents in the stomach. The extended release of the drug can maintain a higher concentration of the antibiotic in the gastric region where *H. pylori* exist and there by can improve its therapeutic efficacy².

From the formulation and technological point of view, the floating drug delivery system (FDDS) is considerably an easy and logical approach in the development of gastroretentive dosage forms. Hence in the present study, the formulation of GRDFs is done by floating drug delivery system.

MATERIALS AND METHODS

Materials

Clarithromycin was procured as a gift sample from Alembic limited, Baddi (H.P.) Batch No: AL/HP/STR/0057. Methocel K15M and Methocel K100M premium USP/EP is the brand name of HPMC procured as a gift sample from Colorcon Asia Pvt.Ltd., Goa. Batch No: SE16012N11 (K15M) and TA15012N31 (K100M). Avicel PH102, brand name of MCC supplied by FMC Biopolymer, USA. Avicel PH102 procured as a gift sample from signet chemical company, Mumbai. Batch No: 7532C. Magnesium stearate was procured from S D Fine Chemicals Ltd., Mumbai. Lactose DC and Talc was procured from Loba Chemicals. Pvt. Ltd., Mumbai. Sodium bicarbonate was procured from Ranbaxy Fine chemicals Ltd. New Delhi.

All other chemicals used in the study were procured from local market and used as received without further purification.

Method

Clarithromycin Floating hydrophilic matrix tablets prepared by direct compression technique³ using different grades of polymer of varying concentrations as well as different concentration of sodium bicarbonate and varying ratios of MCC. All the ingredients except magnesium stearate and talc were blended in glass mortar pestle uniformly. After sufficient mixing of the drug as well as other components, magnesium stearate and talc was added and further mixed for additional 2-3 minutes. The

Tablets were compressed using 19.9×9 punch on a 16 station rotary tablet punching machine. The weight of tablets was kept constant for tablets of all formulation, which were 804 mg for formulation F1 to formulation F9. The compositions of all the formulations are tabulated in **Table 1**.

Table 1, Formulation Design for Clarithromycin Tablet

Ingredients (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin	402	402	402	402	402	402	402	402	402
HPMC K15M	134	--	134	134	134	--	134	90	--
HPMC K100M	-	134	--	--	--	134	--	44	--
Sodium bicarbonate	-	--	50	100	200	100	100	100	100
Avicel 102 pH	250	250	200	150	50	150	--	150	150
Lactose DC	-	--	--	--	--	--	150	--	--
Magnrsium Stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Silicon dioxide	3	3	3	3	3	3	3	3	3
Total (mg)	804	804	804	804	804	804	804	804	804

RESULT**Evaluation of floating tablets****Hardness⁴**

Hardness of prepared tablets measured using – Monsanto type hardness tester. For each formulation three tablets were tested and the values are shown in **Table 3**.

Table 2, % Deviation Limit for Weight variation test as per IP 1996 Specification

Percentage deviation allowed under weight variation test	
Avg. Weight of Tablets	% Deviation Limit
$X \leq 80$ mg	10
$80 < X < 250$ mg	7.5
$X \geq 250$ mg	5

Table 3, Physical properties for tablets of each formulation

Formulation code	Evaluation Parameters				
	Average weight of tablets (mg) ±SD n=20	Hardness (kg/cm ²) ±SD n=5	% Friability	FLT (sec)	TFT (hr)
F1	804 ± 1.86	6.0 ± 0.61	0.53	--	--
F2	805 ± 1.50	6.2 ± 0.27	0.59	--	--
F3	805 ± 1.07	6.6 ± 0.42	0.59	240	>12
F4	803 ± 1.37	6.4 ± 0.42	0.56	50	>12
F5	806 ± 1.12	6.3 ± 0.27	0.53	30	>12
F6	808 ± 1.23	6.5 ± 0.35	0.53	65	>12
F7	803 ± 1.74	6.6 ± 0.22	0.57	45	>12
F8	808 ± 1.24	6.3 ± 0.27	0.55	60	>12
F9	804 ± 1.49	6.6 ± 0.42	0.57	50	6.5

Friability⁴

Twenty tablets weighed and placed in the Electrolab friabilator. The apparatus was rotated at 25rpm for 4mins. After 4 minutes the tablets were dedusted and weighed again. The percentage friability was measured using the formula,

$$\%F = \{1 - (W/W_0)\} \times 100$$

Where, % F = Friability in percentage
 W_0 = Initial weight of tablets
W = Final Weight of tablets after 4 minutes.

The results of measured percentage friability are shown in **Table 3**.

Weight Variation (WV)⁵

Twenty tablets were randomly selected from each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes WV test if not more than two of the individual tablet weight deviate from the average weight by more than the percentage shown in **Table 2** and none deviate by more than twice the percentage shown. The values of average weight and standard deviation of the tablets of each formulation are given in **Table 3**.

Floating Lag Time (FLT)

The time taken for dosage form to emerge on to the surface of medium is called floating lag time (FLT).

Total Floating Time (TFT)

Total duration of time by which the dosage form constantly emerges on surface of medium is called Total Floating Time (TFT).

Procedure

One tablet from each formulation was placed in USP type II dissolution apparatus containing 900 ml of 0.1 N HCL (pH 1.2) using paddle at a rotational speed of 100 rpm. The temperature of medium and the duration of time by which the tablet constantly remains on the surface of the medium were noted. The Floating lag time and Total Floating Time of tablet of each formulation is shown in **Table 3**.

Swelling Index^{6,7}

Swelling of tablet excipients particles involves the absorption of a liquid resulting in an increase in weight and volume. Liquid uptake by the particle may be due to saturation of capillary spaces within the particles or hydration of macromolecule. The liquid enters the particles through pores and bind to large molecule; breaking the hydrogen bond and resulting in the swelling of particle. The extent of swelling can be measured in terms of percentage weight gain by the tablet.

Swelling of hydrophilic polymers such as HPMC greatly depends upon the contents of the stomach and the osmolarity of the medium. These eventually also influence the release slowing action and the residence time.

Table 4 Swelling Index of Clarithromycin Floating Tablets

Time (hr)	Formulation code						
	F3	F4	F5	F6	F7	F8	F9
1	82	80	83	78	83	98	69
2	126	122	118	130	128	123	74
3	156	150	147	166	152	162	70
4	178	176	171	194	180	165	64
5	194	190	189	210	194	176	49
6	214	208	206	232	202	193	46
7	230	225	220	248	211	195	43
8	240	238	231	267	226	20	16

For each formulation, one tablet was weighed and placed in a breaker containing 200ml of distilled water. After each hour the tablet was removed from breaker and weighed again up to 8hours. The swelling study was not performed for batch F1 and F2 as the tablet of these batches did not float in floating property study. The percentage weight gain by the tablet was calculated by the formula.

Swelling Index (S.I)

$$= \{(W_t - W_o) / W_o\} \times 100$$

Where, S.I. = Swelling index

 W_o = Weight of tablet before immersion W_t = Weight of tablet at time t

The swelling index of tablets was given in **Table 4** and the plot of swelling index vs Time (hr) depicted as **Figure 1**.

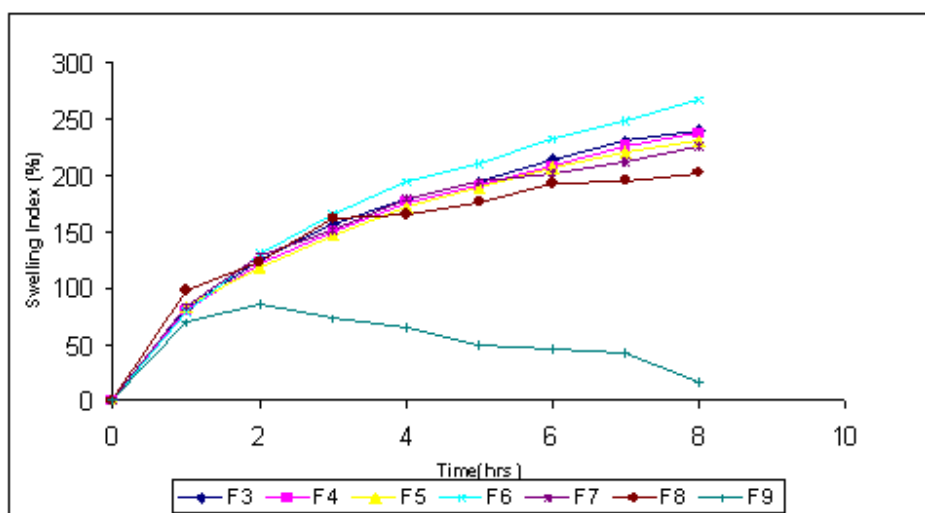
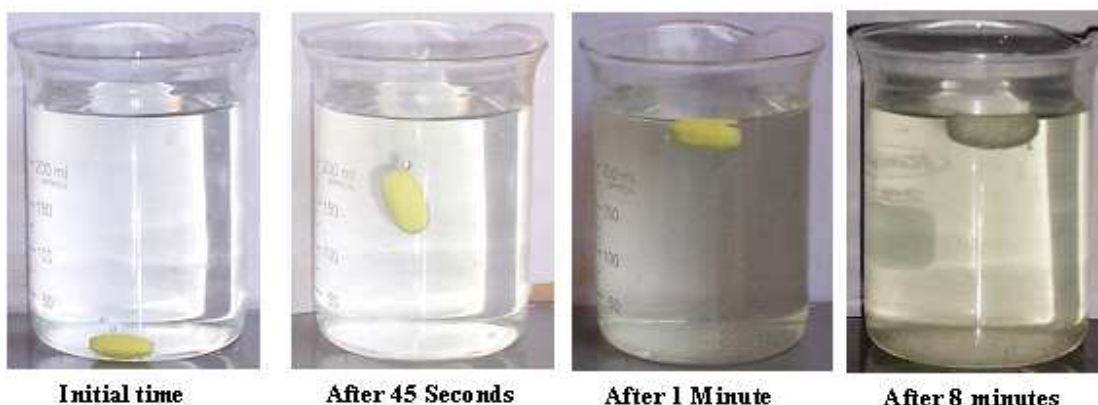


Figure 1. Swelling study of Clarithromycin floating tablets.

In Vitro Buoyancy Study⁸

The result of the in vitro buoyancy study of selected formulation F4 are shown in **Figure 4**. The figure 4 clearly indicates the floating lag time (45 seconds) of the Clarithromycin tablets and the floating and swelling tendency of the formulation. The tablet swelled radially and axially. The average length after 8 hours was 23.6 mm, while the thickness was 16.2 mm. The figure also indicates that tablet remained buoyant for 8 hours, but the tablet actually floated throughout the entire study of 10 hrs.

Figure 4. In Vitro buoyancy study



Effect Of Hardness On Floating Lag Time

The tablets of selected formulation F4 compressed by using three different compression pressures to get hardness of 5kg, 7kg, 10kg and 15kg. The tablets were evaluated for floating lag time. The result of floating lag time was 30sec, 50sec, 160 sec and 945 sec with the hardness respectively. The plot of floating lag time (sec) vs hardness (Kg.) depicted as **Figure 5**.

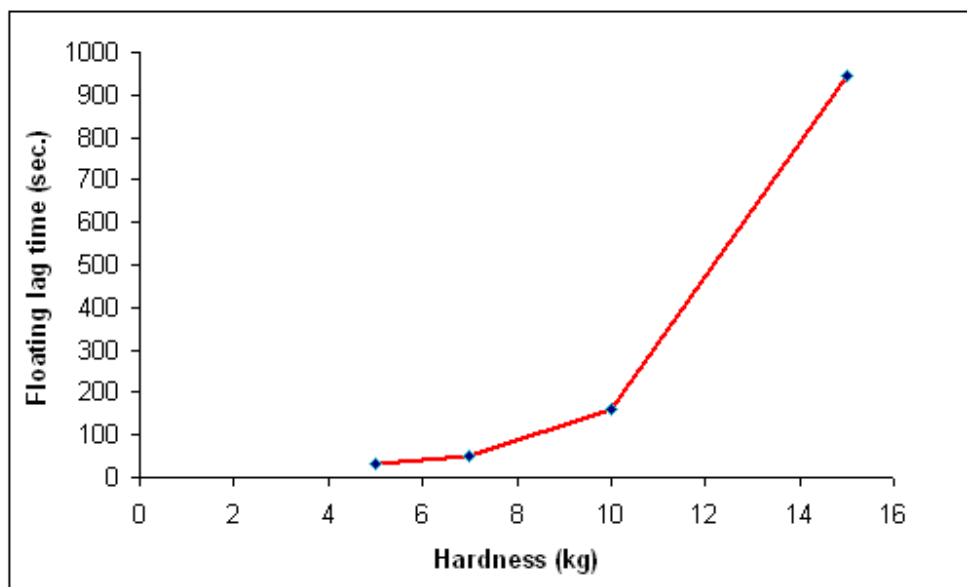


Figure 5 : Effect of hardness on floating lag time.

Assay**Mobile Phase:**

A mixture of 0.067M Potassium di-hydrogen phosphate (KH_2PO_4) solution containing Acetonitrile and Methanol in a ratio of 40:30:30 was prepared; 1mg per ml of n-Hexane sulphonic acid sodium salt was added, filtered and degassed.

Standard preparation:

100 mg Clarithromycin RS was weighed accurately and transferred it into dry 100ml volumetric flask, 50ml of methanol was added, sonicated it to dissolve. The resulting solution was diluted up to 100ml with methanol.

Assay preparation:

Accurately counted number of Tablets was finely powder, equivalent to about 2000mg of Clarithromycin; quantitatively transferred the powder to 500 ml volumetric flask, 250ml methanol was added and sonicated for 30 minutes. The resulting solution was diluted with methanol to 500ml, and insoluble matter was allowed to settle. The resulting solution was diluted to get a concentration about 1 mg/ml. A portion of this solution was passed through a filter having a porosity of 0.5 μm

Chromatographic system

Column	L1 (Hypersil, 250mm \times 4.6 mm, 5 μm)
Column temperature	Room temperature

Detector	UV100
Pump	P 100; Isocratic
Wavelength	210 nm
Flow rate	2 ml/min
Retention time	4 – 5 mins.

Procedure

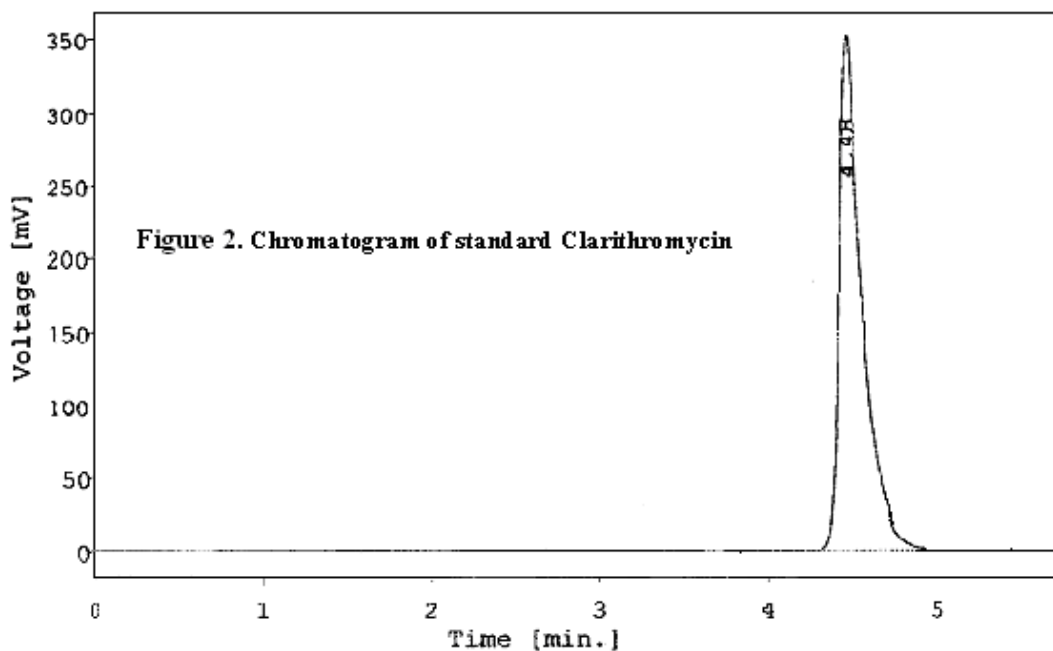
20 μ l of the standard preparation and assay preparation were injected into the chromatogram, chromatograph was recorded and response of the major peak was measured. The amount of Clarithromycin was calculated by the formulation.

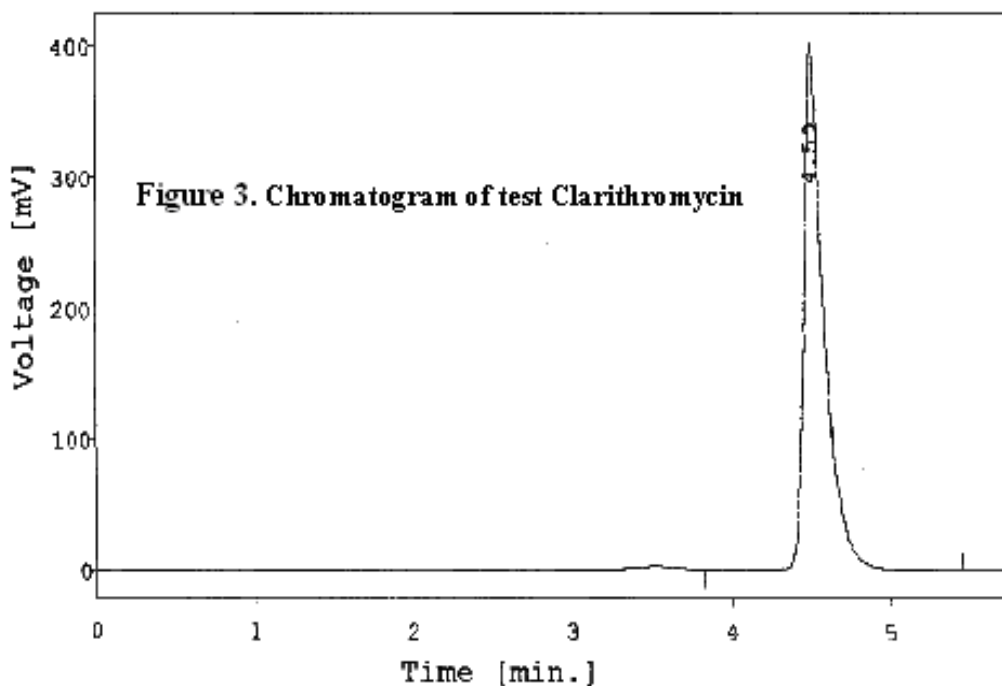
$$\text{Percentage purity} = (R_u/R_s) \times (W_s/W_u) \times (W_a/W_d) \times S_p$$

Where, R_u and R_s are the peak response obtained from the assay preparation and standard preparation respectively, W_s and W_u are the weights of standard and assay sample respectively, W_u and W_d are the average weight of clarithromycin floating tablet and labeled amount of Clarithromycin in mg in each tablet and S_p is the percentage purity of the standard drug.

Observation:

The result of assay of optimized formulation was 98.15%, which complied the official limit given by the USP 24. The chromatograms were shown in **Figure 2** and **Figure 3**.





DISCUSSION

The tablets were compressed using 19.9×9 mm punch on a 16 station rotary tablet punching machine. The weight of tablets was kept constant for all formulation, which were 804 mg for formulation F1 to formulation F9.

All the prepared formulation has got good physical properties but the studies on floating property of tablets, it was found that except formulation F1 and formulation F2 all the formulation had good floating properties (**Tablet 3**), which might be due to absence of sodium bicarbonate in the formulations. The finding was also supported by the study of Baumgartner *et al.*⁹ who reported that incorporation of sodium bicarbonate helps to improve floating properties by reacting with gastric fluid when the dosage form comes in contact and produce carbon dioxide gas which when entrapped inside the hydrophilic matrices leads to increase in volume of dosage form resulting in lowering of density and that the dosage form starts to float.

The effect of sodium bicarbonate concentration on Floating Lag Time (FLT) was studied for formulation F3, F4 and F5. The results, shown in (**Table 3**), demonstrated that as the amount of sodium bicarbonate increases, the floating lag time decreases. The study also supported by Dave B. S. *et al.*⁸

Total Floating Time (TFT), found to be good except tablets of formulation F9. In that higher viscosity grade of HPMC absent, it's having good sustain properties for all formulation. The tablets of formulation F9 dissolved in 6.5 hours which might be due to low viscosity of polymer used in the formulation which was supported by Li and co-workers¹⁰ who reported that higher viscosity grade generally exhibited greater floating capability. From the swelling study it was concluded that swelling index increases as the time passes because the polymer gradually

absorbed water due to its hydrophilic nature and swelling power. In case of formulation F9, the swelling index increases with time up to 2 hours that might be due to the low viscosity of polymer (100 cp) and after that the polymer chain relaxation was a dominating phenomenon as swelling reaches thresholds resulting in lowering of swelling index shown in **Figure 1**.

Thus, the viscosity of polymer had major influence on swelling process, matrix integrity and floating capability. The higher swelling index was found for tablets of formulation F6, which contain HPMC K100 M having nominal viscosity of 1,00,000 cp. Thus it was concluded that there might be a linear relationship between the swelling process and the viscosity of polymer. The finding was also supported by Parakh *et al.*¹¹ who studied water absorption rate of swellable matrices and reported that the water absorption rate increases as the viscosity of the polymer increases and, at the end of the experiment polymer of the higher viscosity showed the maximum absorption.

The effect of filler was found to be little effect on swelling behaviors as the ratio of microcrystalline cellulose: lactose changed from 100:0 to 0:100 the swelling index after reaching certain threshold started to decline as the lactose content was increased as lactose is a water soluble filler leached from the tablets when comes in contact with water. From the study of swelling process, it was observed that the tablet of batch F3 to F7 had good swelling properties and ultimately matrix integrity.

The results of the swelling study indicated the importance of the use of higher viscosity polymer (formulation F4 vs F8), as after 8 hours swelling layer remains intact as well as swelling index increases with time of formulation F4 than formulation F8. Hence the formulation F4 was selected as the optimum formulation among all the formulation and was taken for further study.

In vitro buoyancy study of selected formulation F4 are shown in **Figure 4** that clearly indicates the floating lag time (45 seconds) of the Clarithromycin tablets and swelling tendency of the formulation. The tablet swelled radially and axially. The average length after 8 hours was 23.6 mm, while the thickness was 16.2 mm. The figure also indicates that tablet remained buoyant for 8 hours, In fact the tablet actually floated throughout the entire study of 10 hrs. Buoyancy of the tablet was governed¹² by the swelling of the hydrocolloid particle on surface when it comes in contact with gastric fluids, which results an increase in the bulk volume and the presence of internal void space in the dry center of the tablet (porosity).

The hardness gives great impact on the floating behavior shown in **Figure 5**. It suggested that by increasing the hardness of tablets for selected formulation F₄ from 5 kg to 15 Kg, drastically increased floating lag time which might be due to high compression resulting in reduction of porosity of the tablets and moreover, the compacted surface of the hydrocolloid particles on the surface of the tablet can not hydrate rapidly when the tablets contacts the gastric fluids and as a result of this, the capability of the tablet to float is significantly reduced.^{13, 12}

CONCLUSION

Review of literature indicates that gastroretentive drug delivery systems can be used to increase the gastric residence time of dosage form, which leads to increased bioavailability of the various drug substances.

The present investigation was made to deliver Clarithromycin via floating drug delivery system to the vicinity of absorption site by prolonging the gastric residence time of the dosage form. For the formulation of floating drug delivery system hydroxy propyl methyl cellulose was used as the hydrophilic matrix-forming polymer. Floating tablets were prepared using different grades of HPMC and varying concentrations of sodium bicarbonate, a gas-generating agent along with varying ratios of microcrystalline cellulose and lactose as filler.

Tablets were subject to various evaluation parameters such as hardness, weight variation, friability, floating property studies, swelling studies. It was revealed that tablets of all batches had acceptable physical parameters. Tablets of formulation F4 had good floating properties along with good swelling behaviors. Tablet of formulation F4 was selected as an optimum formulation and was evaluated for the effect of hardness on floating lag time.

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