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Research Article

Formulation and Evaluation of Gastroretentive Dosage Forms of Clarithromycin

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Abstract. The purpose of this research was to develop the hydrodynamically balanced delivery system of Clarithromycin (CLA) which, after oral administration should have the ability to prolong gastric residence time with the desired *in vitro* release profile for the localized action in the stomach, in the treatment of *Helicobacter pylori* (H.pylori) mediated peptic ulcer. By applying wet granulation technique floating tablets of Clarithromycin were prepared. The proportion of sodium bicarbonate was varied to get the least possible lag time, also the polymer part varied to get the desired release. *In vivo* radiographic studies were performed with Barium sulphate loaded formulation to justify the increased gastric residence time of the dosage form in the stomach, based on the floating principle. The formulation developed using 66.2% Clarithromycin, 12% HPMC K4M polymer, 8% sodium bicarbonate gave floating lag time less than 3 min with a floating time of 12 h, and an *in vitro* release profile very near to the desired release. X-ray studies showed the enhanced gastric residence time of the tablet to 220± 30 min. The mechanism of release of Clarithromycin from the floating tablets is anomalous diffusion transport and follows zero order kinetics. *In vivo* radiographic studies suggest that the tablet has increased gastric residence time for the effective localized action of the antibiotic (Clarithromycin) in the treatment of H.pylori mediated peptic ulcer.

KEYWORDS: clarithromycin; floating; HPMC; H.pylori; peptic ulcer.

INTRODUCTION

Clarithromycin (CLA) is a macrolide antibiotic widely prescribed in H.pylori mediated peptic ulcers, Upper Respiratory Tract Infections (1). The recommended adult oral dosage of clarithromycin is 500 mg twice daily for the effective treatment of H.pylori caused peptic ulcer. As the drug is effective when the plasma fluctuations are minimized, sustained release dosage form of clarithromycin is desirable. The short biological half life of drug (~3–5 h) (2) also favors development of sustained release formulation.

A traditional oral sustained release formulation of clarithromycin may not be useful in the eradication of H. pylori, because the organism lives deep inside the gastric mucosa, also the oral bioavailability of clarithromycin is 55%. Thus it is a logical way to improve the therapeutic efficacy of the antibiotic if the gastric residence time of the dosage form is increased in the ecological niche of bacterium. The high concentrations of clarithromycin in the stomach will ensure effective localized treatment for the pathogen (3). This makes the necessity for the development of gastroretentive dosage forms of clarithromycin. Several approaches are currently used to prolong gastric retention time. These include floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, polymeric bioadhesive systems, modified-shape systems, high density systems and other delayed gastric emptying devices (4). The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

In context of the above principles, a strong need was recognized for the development of a dosage form to deliver CLA in the stomach and to increase the efficiency of the drug, providing sustained action. The present investigation applied a systematic approach to the development of gastroretentive CLA dosage forms.

MATERIALS AND METHODS

Materials

Clarithromycin, HPMC K4M were received as gift sample from Cadila Pharma, Ahmedabad, India. Avicel ph-101, from Danmed Pharma, Hyderabad, India. Sodium bicarbonate, Sodium carbonate, Aerosil and Magnesium Stearate, Folin-ciocalteu's phenol reagent were purchased from S.D. fine chemicals Pvt Ltd, Mumbai, India. Hydrochloric acid was purchased from Merck specialties Pvt Ltd, Mumbai, India. All other ingredients were of laboratory grade.

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Table I. Lag time Optimization Trials

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8
Xanthan gum	15	–	15	20	–	–	–	–
Carbopol 934P	–	15	–	–	–	–	–	–
HPC LF	–	–	–	–	15	–	–	–
HPMC K4M	–	–			–	15	18	18
$NaHCO_3$	15	15	10	10	15	15	14	10
Filler	2.25	2.25	7.25	–	2.25	2.25	–	4.25

All the formulations contain 1% of Aerosol, 0.5% of Magnesium stearate. Two percent PVP-k30 in Isopropanol was used as binder. All the numerical values were expressed in their % *w*/*w* to the total tablet wt. All the formulations contain 500 mg of Clarithromycin U.S.P.

Methods

Preparation of Clarithromycin Floating Tablets

CLA 500 mg was mixed with required quantities of HPMC K4 M, Avicel ph-101 for 3–5 minutes, the blend was granulated mechanically by hand, using 2% PVP K-30 in Isopropanol as binder, the wet coherent mass was dried in hot air oven at 40°C and passed through sieve # 20, the granules were mixed with sodium bicarbonate, followed by lubrication for 4–5 min with 1% Aerosil and 0.5% Magnesium stearate. Mixing was done manually using polyethylene bag. The granules were compressed on 16 station rotary tablet press (Cadmach, Ahmedabad, India) using 16.4 X 8 caplet punches. The applied batch size was 100.

The tablets were capsule shaped with an average length of 16.3±0.1 mm and average thickness of 6.64±0.1 mm. The formulations of the all batches are shown in Tables I and II.

Evaluation of Floating Tablets

The prepared tablets were evaluated for quality control tests like weight variation, hardness, thickness, friability and content uniformity.

Weight Variation

Twenty tablets were selected at random and average weight was determined. Then individual tablets were compared with the average weight.

Hardness and Friability

Hardness of tablet was determined by Monsanto hardness tester. Friability test was done by Roche friabilator. Ten tablets were weighed and were subjected to the combined effect of attrition and shock by utilizing a plastic chamber that revolve at 25 rpm dropping the tablets at distance of 6 in. with each revolution. Operated for 100 revolutions, the tablets were de dusted and reweighed. The percentage friability was calculated.

Thickness

The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

Drug Content Uniformity

Ten tablets were selected, crushed in a mortar and pestle, 755 mg of the powdered mass (equivalent to ~500 mg of CLA) was accurately weighed and dissolved in 250 ml of 0.1 N HCl taken in a volumetric flask. The drug was allowed to dissolve in the solvent and filtered. One milliliter of filtrate was taken in 10 ml volumetric flask and diluted using 2 ml Folin–Ciocalteu's phenol reagent (diluted to 1:2 with distilled water) and 2 ml of 20% sodium carbonate solution. The volume of each volumetric flask was adjusted to 10 ml with distilled water. After thoroughly mixing, the volumetric flask were set aside for 10 min for the reaction to complete. The absorbance of solution in each volumetric tube was measured at 760 nm against reagent blank. The concentration of Clarithromycin in milligram per milliliter was obtained by using standard calibration curve of the drug. Claimed drug content was 500 mg per tablet (5).

In Vitro Buoyancy Studies

The *in vitro* buoyancy was determined by floating lag time, per the method described by Rosa *et al*. The tablets were placed in a 100-ml beaker containing 0.1 N HCl. The

Table II. Formulations of Clarithromycin 500 mg Floating Tablets

F. Code	HPMC K4M	Sodium Alginate	$NaHCO_3$	Avicel ph-101
F9	20	–	8	4.27
F10	18	–	8	6.27
F11	16	–	8	8.27
F12	14	–	8	10.27
F13	12	–	8	12.27
F25	–	20	8	4.27
F26	–	18	8	6.27
F27	–	16	8	8.27
F28	–	14	8	10.27
F29	–	12	8	12.27
F30	–	10	8	14.27
F31	–	8	8	16.27
F32	–	6	8	18.27
F33	–	4	8	20.27

All the formulations contain 1% of Aerosol, 0.5% of Magnesium stearate. Two percent PVP-k30 in Isopropanol was used as binder. All the numerical values were expressed in their % *w*/*w* to the total tablet wt

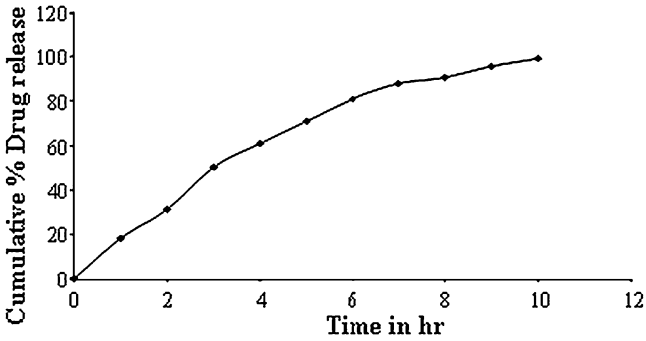

Fig. 1. Cumulative Percent Drug Release of Marketed Product (CRIXAN OD 500 mg)

time required for the tablet to rise to the surface and float was determined as Floating Lag Time (FLT) and the time period up to which the tablet remained buoyant is determined as Total Floating Time (TFT) (6).

In Vitro Dissolution Studies

The release rate of CLA from floating tablets (n=3) was determined using *United States Pharmacopoeia (USP)* 24 Dissolution Testing Apparatus 2 (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5°C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 h, the samples were replaced with fresh dissolution medium. The filtered samples were diluted to a suitable concentration with 0.1 N HCl. Absorbance of these solutions was measured at 760 nm (7) using an Elico UV–Vis double-beam spectrophotometer (Hyd, India). Cumulative percentage drug release was calculated using an equation obtained from a standard curve. The time for 50% drug release was calculated based on the Korsemeyer and Peppas model (8).

Kinetic Modeling of Drug Release

The dissolution profile of all the batches was fitted to Zero order, first-order, Higuchi, Hixon-Crowell, Korsemeyer and Peppas to ascertain the kinetic modeling of drug release.

t-Test. *t*-Test was performed to the best formulation and marketed product using Graph Pad Prism 4 software.

Table III. Dissolution Studies of Marketed Product (CRIXAN OD 500)

Sampling Time (h)	Cumulative % Drug Release
1	18.1±1
2	31.3±1
3	50.2±1
4	61.2±1
5	71.2±1
6	81.3±1
7	88.6±1
8	90.7±1
9	95.8±2
10	99.3±1
11	99.3±1
12	99.1±1

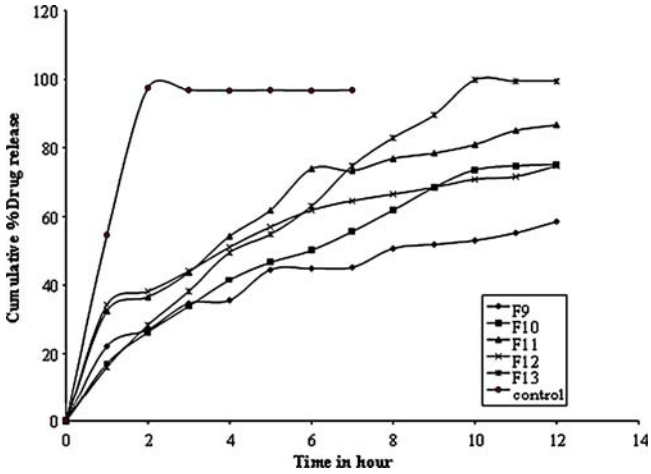

Fig. 2. Plot of cumulative % drug release *vs* time in hours (HPMC K4M as polymer)

***In vivo* Radiographic studies**

Four healthy male volunteers in the age group of 20–23 weighing between 55–70 kg were selected for the study, they were made clear about the usage and adverse effects of the drug. The tablets loaded with Barium Sulfate were administered orally. During the study they were fed with light meal, water was allowed to take. The X-ray photographs were taken at different periods of time to find the total residence time of the tablet in the stomach. The Institutional Human Ethical Committee approved the protocol for this study.

RESULTS AND DISCUSSION

Clarithromycin has more stability in acidic medium. When orally ingested, about 55% of the normal dose can be absorbed, so it fulfills the required criteria for selection of drug for floating dosage form.

The objective of the Preliminary studies was the optimization of lag time i.e. the time required for the dosage form for its buoyancy. The least possible lag time was optimized by varying the ratio of sodium bicarbonate to the polymer, if the SBC is much more higher than polymer concentration in a formulation, rapid erosion of tablet occurs

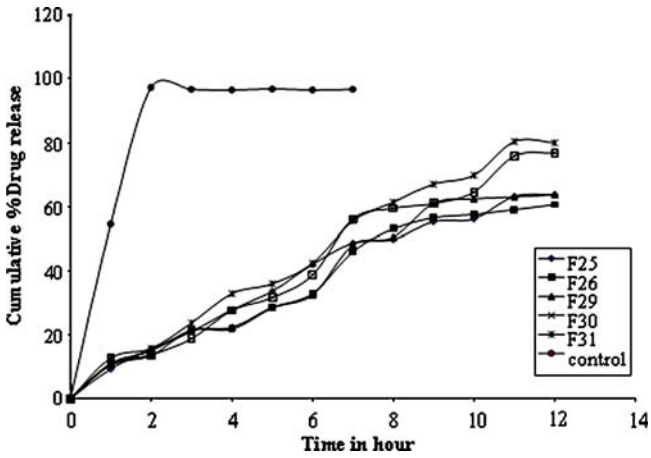

Fig. 3. Plot of cumulative% drug release *vs* time in hours (sodium alginate as polymer)

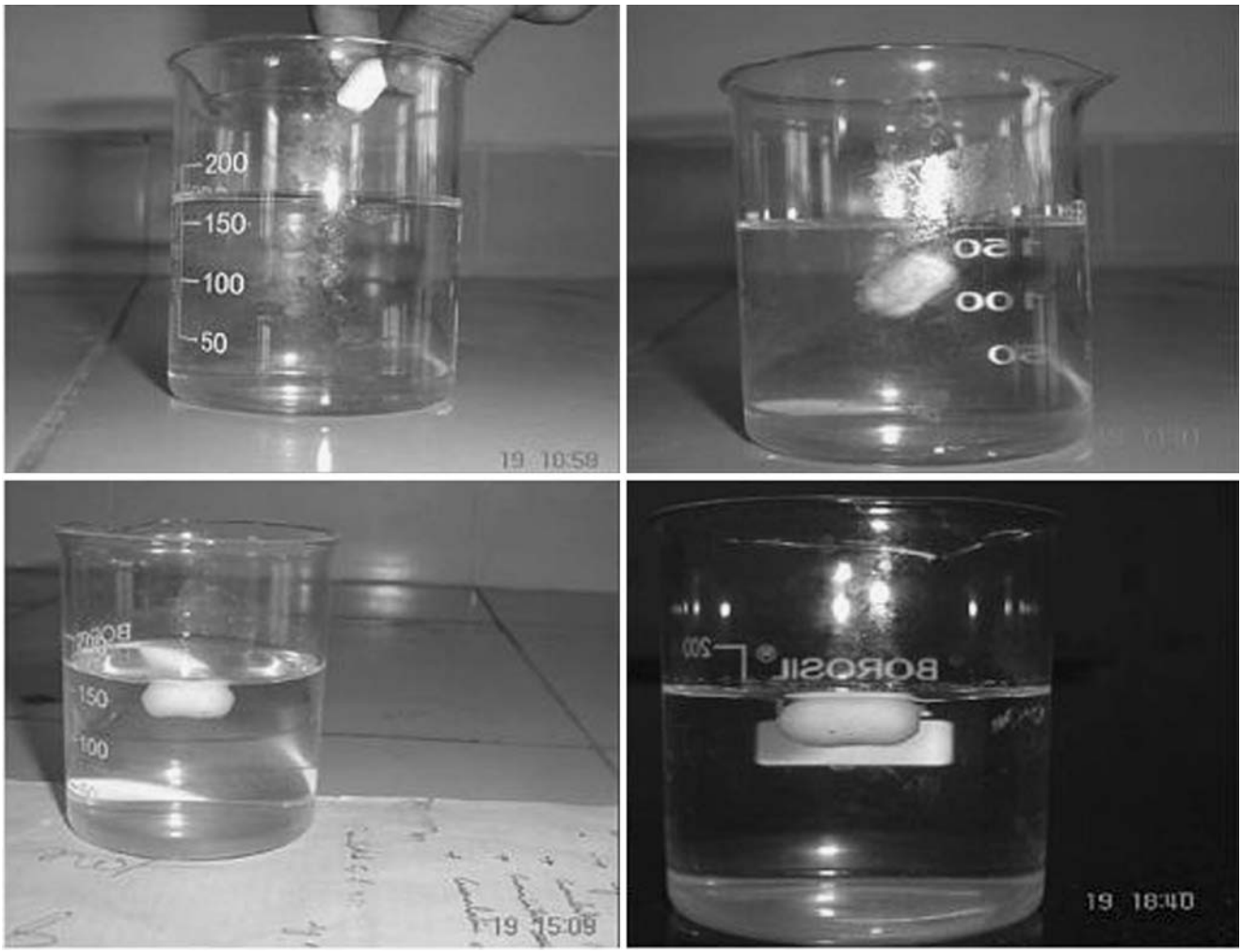

Fig. 4. Floating properties

as the released Carbon dioxide will tend to escape faster and if the polymer is in sufficient concentrations the evolved gas will get entrapped in the polymer network leading to the floating of the tablet, thus it indicates that lower polymer levels with higher levels of SBC in a formulation causes erosion rather than floating. Similarly, if the polymer concentration is higher than that of SBC the desired drug release profile may not be achieved as the higher polymer portions can delay the drug release, thus the ratio of polymer to the SBC concentrations were altered to get least possible lag time achieving the desired drug release.

Also the gel forming capacity, extent of swelling of different polymers like Carbopol 934P, HPMC K4M, Xanthan gum, HPC LF and sodium alginate were observed during the study.

Table IV. Cumulative Percent Drug Releases of Formulations with HPMC K4M

Sampling Time(h)	F9	F10	F11	F12	F13
1	22.1±1.8	17.0±1.7	34.2±2.3	32.4±2.8	16.0±2.4
2	27.0±1.5	26.2±1.5	38.1±1.5	36.5±2.4	28.3±2.6
3	34.6±1.8	33.8±2.1	44.0±2.2	43.6±2.3	38.1±1.5
4	35.6±1.5	41.4±0.7	51.0±2.6	54.2±2.7	49.5±1.8
5	44.4±2.1	46.5±2.6	56.9±2.3	61.8±2.1	54.7±2.8
6	44.8±1.4	50.0±1.8	61.8±1.9	73.9±2.0	63.0±2.2
7	45.1±2.8	55.5±1.6	64.5±2.6	73.3±2.6	74.7±2.3
8	50.6±2.7	61.8±2.2	66.5±2.2	76.9±2.0	82.9±1.5
9	51.8± 1.4	68.4±2.7	68.4±2.7	78.4±1.5	89.2.±2.8
10	53.0± 2.1	73.5±2.4	70.8±2.2	81.0±2.2	99.7±2.8
11	55.1±2.7	74.7±2.1	71. ±1.6	85.0±1.9	99.9±2.1
12	58.5±2.2	75.1±1.9	74.7±2.3	86.7±2.7	99.3±2.9

n=3 for all the dissolution studies

Table V. Cumulative Percent Drug Releases of Formulations with Sodium Alginate

Sampling Time(h)	F25	F26	F29	F30	F31
1	9.1±2.2	10.3±1.8	10.9±1.2	10.7±1.3	12.7±2.4
2	15.4±3.4	13.5±0.9	14.8±2.3	13.6±2.1	15.6±1.2
3	20.9±1.9	21.3±1.4	21.3±0.8	18.7±1.8	23.6±1.8
4	27.7±2.3	21.7±0.7	22.3±1.3	27.5±2.1	32.8±2.2
5	33.6±1.8	28.3±2.2	28.5±2.7	31.6±2.4	36.0±1.4
6	42.0±2.4	32.8±2.6	32.4±1.8	38.7±3.1	42.4±0.8
7	48.7±1.6	45.9±3.2	48.1±2.6	56.1±2.0	55.5±1.2
8	49.8±1.1	53.0±1.4	50.4±1.4	59.4±1.4	61.4±2.4
9	55.3±0.8	56.5±1.6	61.0±2.2	61.0±1.7	67.1±0.8
10	56.1±0.5	57.5±2.8	62.4±0.6	64.5±0.9	69.8±1.1
11	63.1±1.8	59.0±1.1	63.0±0.8	75.9±1.2	80.4±0.8
12	63.7±0.9	60.6±0.8	63.7±.4	76.8±0.8	80.0±1.4

n=3 for all the dissolution studies

With the Xanthan gum least possible lag time (35 s) was obtained for the formulation (F3), but the tablet integrity was poor. Further attempts were made to improve the structural integrity by increasing the polymer percentage, but were unable to show the desired integrity within the highest possible concentration of the polymer, may be due to low viscosity grade of the polymer.

Carbopol 934P was employed in the trial F5, but was discarded, as the least possible lag time was found to be 16.5 min with the highest possible effervescent portion

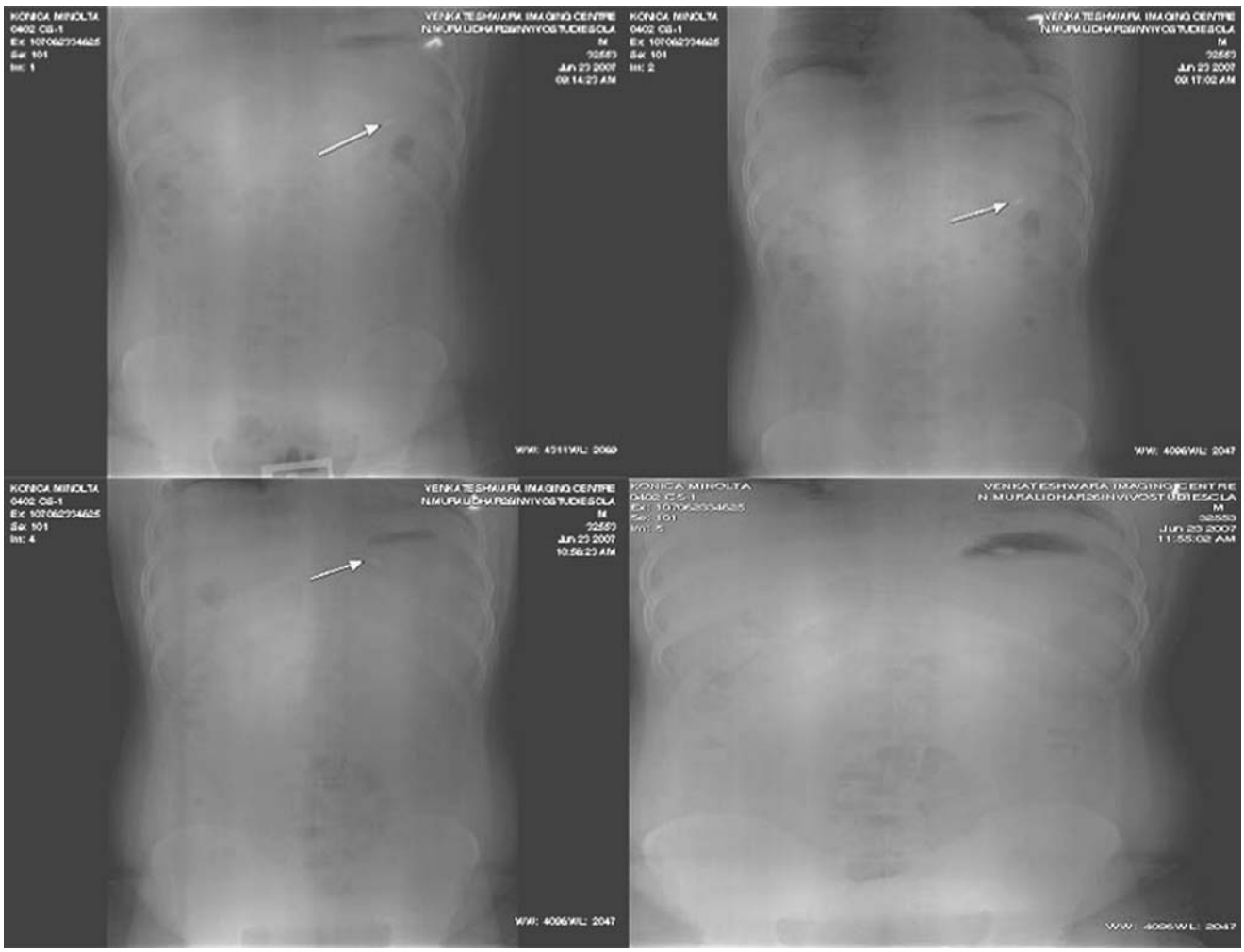

Fig. 5. A representative radiographic images showing the presence of $BaSO_4$ loaded floating tablet in the stomach at different time periods (tablet is pointed by an *arrow*)

(15% *w*/*w*). Further the integrity of the tablet was lost in 2 h.

Hydroxy Propyl Cellulose (HPC LF) was considered in the trial F4. The polymer was unable to show the desired floating characteristics, further tablet started early erosion rather than floating.

Thus polymers Xanthan gum, Carbopol 934P, HPC LF were found to be unsuitable for the formulation of matrix tablets of Clarithromycin with desired floating characteristics. In further trials, Hydroxy Propyl Methyl Cellulose K4M was considered.

Further, Hydroxy Propyl Methyl Cellulose (HPMC) K4M was evaluated varying the sodium bicarbonate portion. Finally, lag time was fixed at less than 3 min optimizing the sodium bicarbonate portion at 8% *w*/*w* to the total tablet weight. Also the tablet integrity, swelling characteristics were found satisfactory.

In the next step, the extended release marketed product (CRIXAN OD 500 mg) was evaluated for its drug release profile and all other physical evaluation parameters (Fig. 1; Table III)

Subsequent formulations were made with HPMC K4M to match the drug release profile of commercial product (Fig. 2).

However, the physical evaluation parameters were also tested. Average weight of the tablet was fixed at 755 mg and the weight variation for every batch was tested and was found within the limits as per United States Pharmacopoeia/ National Formulary (U.S.P./N.F.).

Hardness of the tablet was fixed between 8–9 kg/cm^2 and was maintained for all the batches in order to minimize the effect of hardness on the drug release because, the effect of polymer concentration is the only area of interest (Fig. 3). Friability test of all the formulations was found satisfactory showing enough resistance to the mechanical shock and abrasion. Drug content uniformity in all formulations was calculated and was found satisfactory.

Floating characteristics like lag time, total floating time for all the formulations were studied and found satisfactory (Fig. 4).

A formulation without sodium bicarbonate and polymer was made as a "control" and justified that the tablet without sodium bicarbonate was unable to float and unable to retard the drug release for the desired period of time.

The *in vitro* dissolution testing was performed and compared to the commercial product and the results of best formulations were expressed (Tables IV and V).

Formulations F11, F13 with HPMC K4M were showing F2 values of 52.26, 53.2 respectively.

The formulations containing sodium alginate did not show promising results, however least lag time was optimized, but the drug release was poor, this is due to the conversion of sodium alginate to alginic acid in the acidic medium (pH 1.2) producing a tough and rubbery texture to the tablet. The drug release was further inhibited by sodium bicarbonate in the alginate matrices. The results obtained with the alginate matrices were also supported by the literature (9).

The mechanism of release for the above formulations was determined by finding the R^2 value for each kinetic model viz. Zero-order, First-order, Higuchi, and Korsmeyer–Peppas corresponding to the release data of each formulation. For most of the formulations the R^2 value of Korsmeyer–Peppas and zero-order model is very near to 1 than the R^2 values of other kinetic models. Thus it can be said that the drug release follows Korsmeyer–Peppas and zero-order model mechanism.

The *n* values of Korsmeyer–Peppas model of the best formulations are in between 0.55 and 0.85. Therefore the most probable mechanism that the release patterns of the formulations followed was non-Fickian diffusion or anomalous diffusion (10).

From this, best formulation was found to be 13 containing 12% of HPMC K4M. *t*-Test was performed to the best formulation and marketed product using Graph Pad Prism 4 software. And the *P* value was 0.4758 indicating no variances significantly different.

In-vivo studies were conducted on healthy human volunteers to find the gastric residence time of the tablet. The studies were based on X-ray radiography. Images were taken at different time points to find the location of the tablet, changes in the tablet locations indicates tablet did not adhere to the gastric mucosa and the gastric residence time was 220± 30 min (n=4) (Fig. 5).

CONCLUSIONS

Formulation F13 gave better controlled drug release and floating properties in comparison to the other formulations.

The most probable mechanism that the release patterns of the formulations followed was non-Fickian diffusion or anomalous diffusion.

In vivo radiographic studies indicated that tablets remained in the stomach for 220±30 min, indicating that GRT was increased by floating principle, which was considered for the localized action in the treatment of Peptic ulcer caused due to H.pylori.

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