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Original Article

Formulation and evaluation of gastro retentive tablets of clarithromycin prepared by using novel polymer blend

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ABSTRACT

Clarithromycin is a semi synthetic macrolide antibiotic that is proved to be extremely effective mono therapy in treating *H. pylori* infection. One of the various reasons reported for partial eradication of *H. pylori* infection is that the short dwelling time of antimicrobial agents in the stomach. Hence the principal object of the present work was to design and develop floating and swellable gastro retentive tablet of clarithromycin to obtain its prolonged release in the stomach. HPMC K 100LV was blended in the present study with the Gel isolated from the seeds of *Ocimum basilicum* to overcome the drawback of time dependent erosion of former. This novel polymer blend was investigated and exploited as a matrix material for the development of gastro retentive tablets of clarithromycin as drug delivery system. Hydrogen bonding between the Glucomannan – a component of the Gel and HPMC K100LV was envisaged and further confirmed by ATR-FTIR. Tablets of clarithromycin prepared by using the polymer blend of Gel and HPMC K100LV exhibited fast swelling with almost instantaneous buoyancy followed by prolonged release of drug from the swollen, floating dosage form. The retention of the optimized tablet formulation of clarithromycin in the stomach was confirmed by γ scintigraphy.

1. Introduction

Clarithromycin is a semi synthetic macrolide antibiotic that is proved to be extremely effective in treating *H. pylori* infection. *H. pylori* are pathogenic bacteria and colonize deep inside the gastric mucosa. Clarithromycin penetrates bacteria cell wall and reversibly binds to domain V of the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome thereby blocking translocation of aminoacyl transfer-RNA and polypeptide synthesis. Therefore the high concentration of clarithromycin in stomach is essential to ensure effective eradication of *H. pylori* irrespective of its rapid absorption throughout gastrointestinal tract. Otherwise conventional oral treatment of clarithromycin may lead to resistance to clarithromycin (MIC in such resistant cases > 1 mg/L). Therefore the object of the present study was to design and develop gastro retentive tablets of clarithromycin [1–4]. Hydroxypropyl methylcellulose (HPMC) is the most common excipient that is being used in the design of floating swellable gastro retentive tablets. The effect of viscosity grade of HPMC used in the tablets on floating characteristics of tablets is well researched and documented. Inclusion of low viscosity grade HPMC (e.g. HPMC K100LV) in floating swellable drug delivery systems was reported to exhibit better floating properties but limited by insufficient retention in the stomach and time dependent drug and matrix release (i.e. matrix erosion) [5–10]. To ensure gastric retention of floating swellable tablet as a dosage form it should float on the stomach content achieving full swelling in less than 20 min and should retain the dimension greater than the diameter of pyloric sphincter i.e. greater than 15 mm for the predetermined time period [11].

In the present study HPMC K100LV was blended with hydrogel isolated from the seeds of *Ocimum basilicum* (Gel) to take the advantage of buoyancy characteristics of the former and swelling characteristics of the later [12]. The composition of the Gel is reported to be acid stable glucomannan having the ratio glucose: mannose as 10:2 (43%) and a 1 → 4 linked xylan (24.29%) [13]. Glucomannan interactions with other polymers had been extensively studied to exploit its versatility in the design and development of drug delivery systems [14]. The complexation through hydrogen bonding between HPMC K100LV and Glucomannan content of the Gel was envisaged and studied in the

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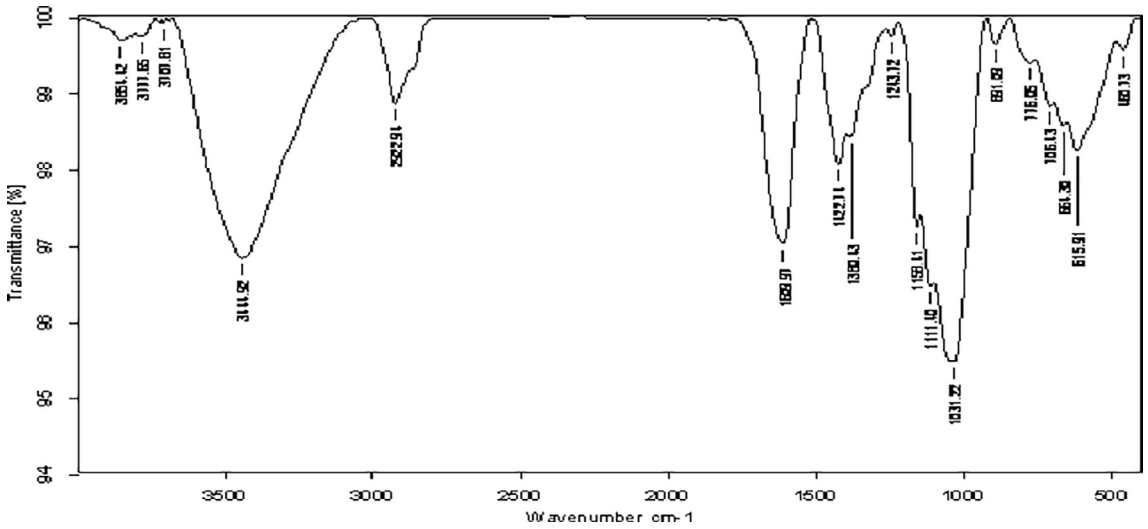

Fig. 1A. ATR-FTIR of DM (Dried Gel).

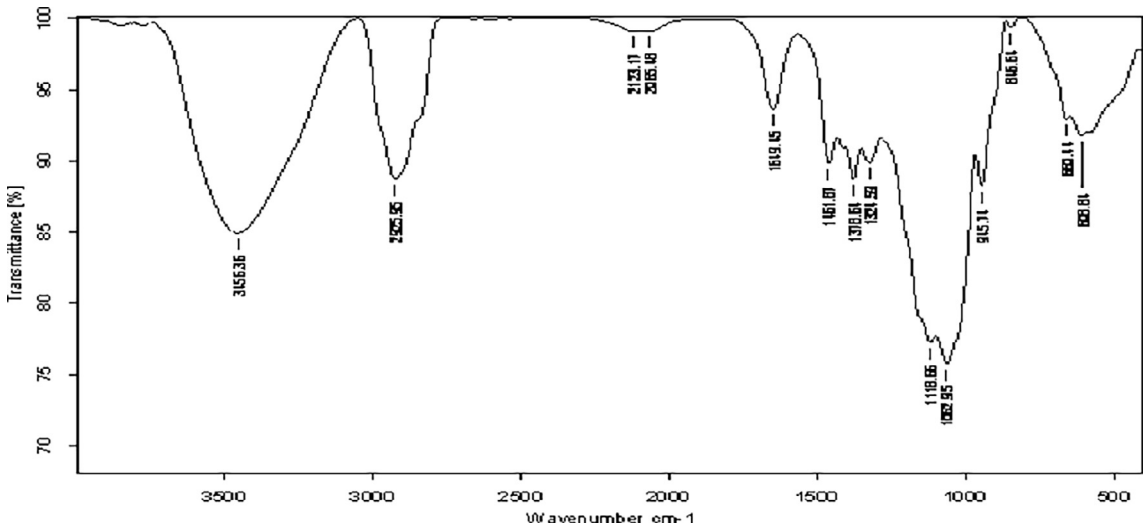

Fig. 1B. ATR-FTIR of HPMC K100LV.

present work [15,16]. The functionality of this novel polymer blend was investigated by designing and evaluating floating swellable tablet of clarithromycin as a drug delivery system.

2. Materials and methods

2.1. Materials

Low molecular-weight Hydroxy propyl methylcellulose (HPMC K100LV) was received as a gift sample from Colorcon Asia Pvt. Ltd., Goa, sample of Clarithromycin was received from Cipla Ltd., Kurkumbh and sample of sucralfate was received from Lupin Research Park, Pune. The Gel was isolated in the laboratory from the seeds of *Ocimum basilicum* collected from regional sources. The plant was authenticated by CSIR-National Botanical Institute (authentication number-LWG-46) and deposited in National Repository, Lucknow, India. All other chemicals used in the analysis were of analytical grade and others were at least of pharmaceutical grade and used without further purification.

2.2. Methods

2.2.1. Preparation and characterization of polymer blend

Gel was isolated from whole seeds of *Ocimum basilicum* by the method reported earlier (Hardikar et al, 2009). Sufficient volume (calculated from its specific gravity) of Gel was mixed with low viscosity grade hydroxyl propyl methylcellulose (HPMCK100LV) in 1:1 proportion by weight. This mixture was dried in microwave oven at level 5 (350 W) for 30 min to obtain polymer blend.

2.2.2. Fourier transform infrared spectroscopy

Dried mucilage (DM) was the material obtained by drying the Gel (isolated mucilage) in microwave at level 5 (350 W) for 30 min. ATR-FTIR of the Dried Gel was recorded to confirm the presence of Glucomannan as a major component of the Gel. ATR- FTIR of DM (Fig. 1A) and overlay of ATR-FTIR spectra of DM, polymer blend prepared by method reported earlier (in 2.1), physical mixture of DM and HPMC K100LV in proportion 1:1 by weight and HPMC K100LV alone is shown in Fig. 1B. Since hydrogen bonding was an important form of

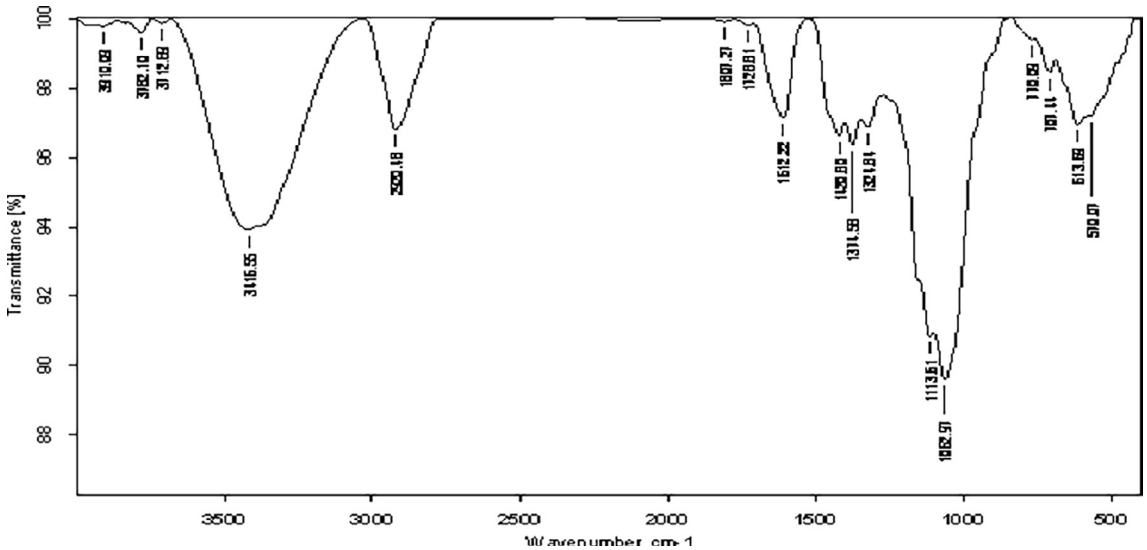

Fig. 1C. ATR-FTIR of Novel polymer blend.

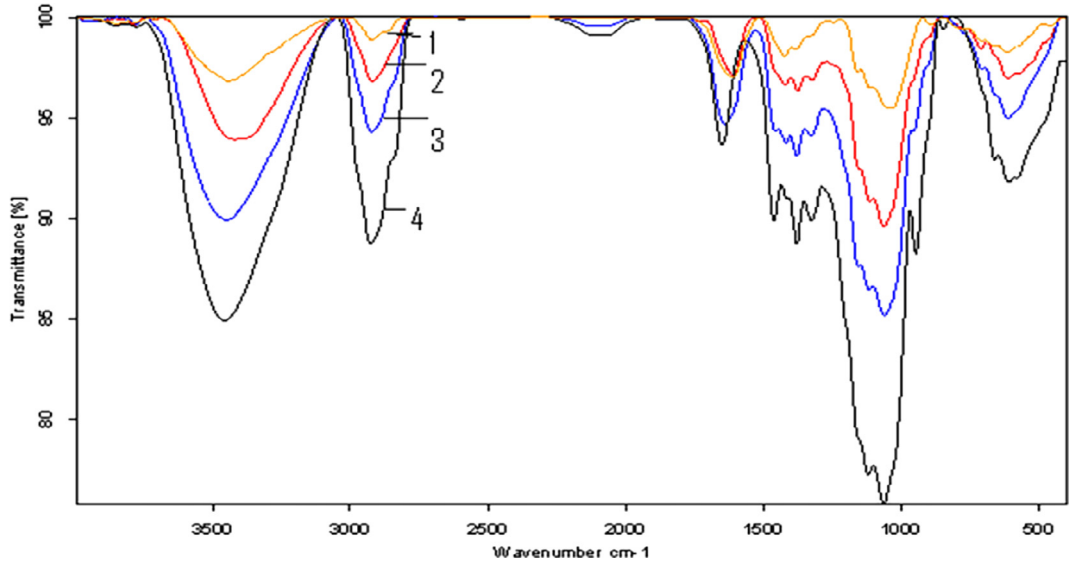

Fig. 1D. Overlay of ATR-FTIR of (1) DM (Dried Gel), (2) Polymer blend, (3) Physical mixture and (4) HPMC K100LV.

polymeric association expected in this study; FTIR spectra were recorded using an ATR stage.

2.2.3. Scanning electron microscopy (SEM) studies

Scanning electron microscopy (SEM) was performed to study the morphology of the polymer blend. SEM images of physical mixture of DM and HPMC K100LV and polymer blend were taken recovered after immersing them in 0.1 N HCl for 10 min. Samples were sputter coated with a thin layer of gold–palladium under argon vacuum prior to analysis. SEM was performed using a 5 kV beam acceleration voltage. The SEM images are shown in Fig. 2.

2.2.4. Swelling study of tablets prepared by using polymer blend as a matrix

Microwave dried polymer blend along with clarithromycin in proportion 1:1by weight (S1), the physical mixture of the DM, HPMC K 100LV and clarithromycin in proportion 0.5:0.5:1 by weight (S2) and the physical mixture of HPMC K 100LV and clarithromycin in proportion 1:1by weight (S3) were compressed on hydraulic press machine at 0.25 ton compression pressure. The swelling study of these tablets (each of 500 mg) was carried out in triplicate as per the method reported by Sally AE et al., 2014 [17]. The swelling indices of the tablets were determined by transferring each tablet in the basket of USP dissolution apparatus II containing 250 mL 0.1 N HCl at rotation speed of 50 rpm. The medium was maintained at 37 ± 0.5 °C throughout the study. The tablets were withdrawn carefully, at predetermined time intervals, and gently blotted to remove excess water and weighed. Swelling index (S. I.) of each tablet was calculated according to the equation-

$$S = \frac{Ws - Wd}{Wd} \times 100$$

Where S is the swelling index (%), W_s is the weight of the swollen tablet, and W_d is the weight of the dry tablet. The averages of the results of relative swelling characteristics are shown in Fig. 3.

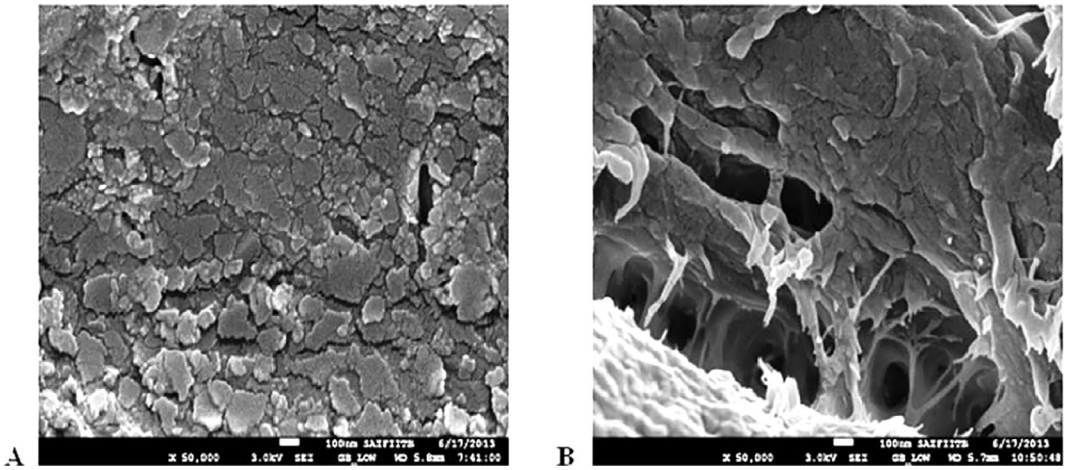

Fig. 2. SEM images of physical mixture of DM and HPMC K100LV (A) and polymer blend of DM and HPMC K100LV (B) recovered after immersing in 0.1 N HCl for 10 min.

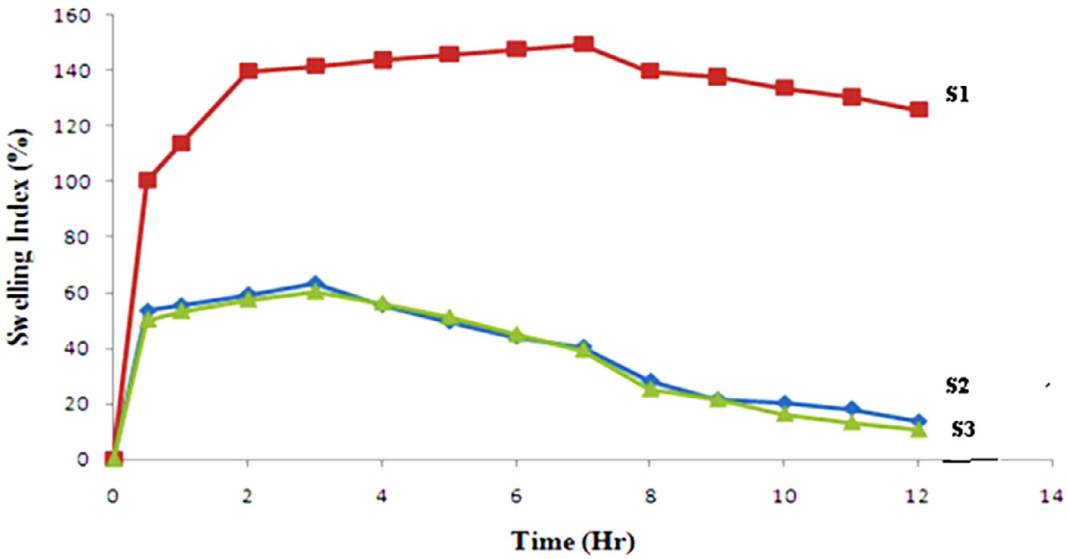

Fig. 3. Relative swelling at 37 °C of S1, S2 and S3 in 250 mL 0.1 N HCl.

2.2.5. Development of drug delivery systems

2.2.5.1. Preparation of solid dispersion of clarithromycin and compatibility study. Solid dispersion of clarithromycin was prepared by adopting cogrinding/comicronization method [18,19]. Gel was isolated from the seeds of *Ocimum basilicum* adopting the procedure described earlier in Section 3.1. Sufficient amount of HPMC K 100LV and Gel were mixed together to attain the proportion 1:1 by weight. Clarithromycin was added to this to achieve drug: polymer blend ratio (on dry basis) as 1:1. The resultant admixture was mixed thoroughly and dried in microwave at 350 mW for 20 min to obtain solid dispersion of clarithromycin.

Solid dispersion was kept in glass vials previously dried in hot air oven and exposed to 40 °C/75% RH for three months. The samples were withdrawn initially as well as at the end of 3 months duration; evaluated for appearance and FTIR to confirm the presence of principal peaks of clarithromycin. DSC patterns were also recorded periodically i.e. initially, after 1 month, after 2 months and at the end of 3 months duration (Fig. 4).

Uniformity of content of clarithromycin in solid dispersion was determined by RP- HPLC method as reported in the Indian Pharmacopoeia. A solid dispersion equivalent to 0.0625 %w/v solution of clarithromycin in methanol was prepared. Diluted 3 mL of the solution to 10.0 mL with mobile phase (methanol: 0.067 M monobasic potassium phosphate in 65:35 proportions). A mixture of methanol: 0.067 M monobasic potassium phosphate (adjusted to pH 4.0 with orthophosphoric acid) in 65:35 proportion was used as mobile phase with flow rate 1 mL/min. Chromatograms were recorded by injecting 20 µL and recording the absorbance at 205 nm. A mixture of methanol: 0.067 M monobasic potassium phosphate (adjusted to pH 4.0 with orthophosphoric acid) in 65:35 proportion was used as mobile phase with flow rate 1 mL/min. Chromatograms were recorded by injecting 20 µL and recording the absorbance at 205 nm. Calibration was done by using 62.5 µg/mL to 250 µg/mL [20].

2.2.5.2. Formulation development and evaluation of gastro retentive tablets of clarithromycin. The composition of powder blend for preparation of preliminary batches (P1 to P6) of gastro retentive clarithromycin tablets is reported in Table 1. All the formulations were carefully observed for buoyancy time (floating lag time) and duration of floating.

2.2.5.3. Optimization of gastro retentive tablets of clarithromycin. A 2^2 factorial design was implemented for optimization of gastro retentive tablet formulation of clarithromycin [21]. According to the model it contained 2 independent variables at 2 levels, $+1, -1$. The different independent variables were compression pressure (X1) and presence or absence of polymer blend (X2). The levels of factor were chosen based on the observations and evaluation results of preliminary

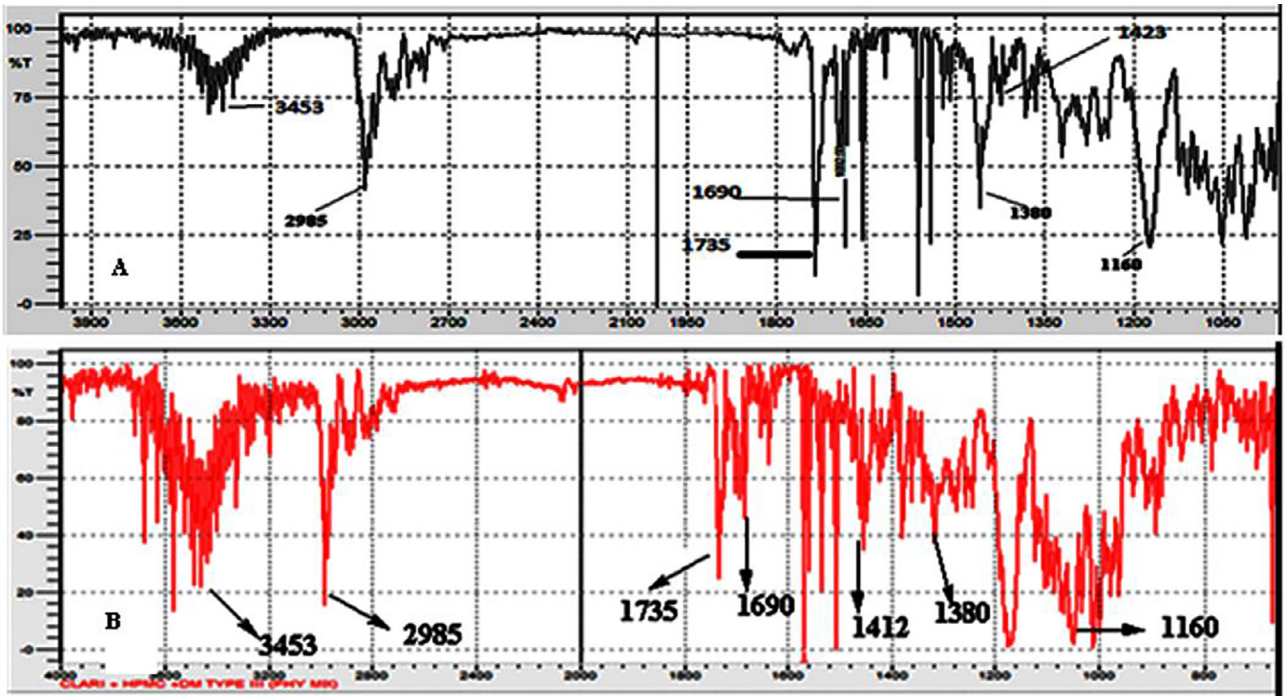

Fig. 4. FTIR spectra of solid dispersion of clarithromycin initially (A) and after 3 months compatibility studies (B).

Table 1
Compositions of gastro retentive tablet formulations of clarithromycin.

Formulation Code	Ingredients (mg/tab)				
	Solid dispersion equivalent to 250 mg of clarithromycin	Sodium Bi -carbonate	Polymer blend	Sucralfate	Total weight of tablet
P1*	500	100	–	–	600
P2**	500	100	–	–	600
P3**	500	–	–	100	600
P4**	500	–	–	200	700
P5*	500	–	100	100	700
P6**	500	–	100	100	700

* Prepared at low compression pressure (0.25 ton).
** Prepared at high compression pressure (at 0.5 ton).

batches P5 and P6 (Tables 2 and 3). According to model total four formulations are possible; the compositions of different formulations are shown in Table 4. Dependent factors included buoyancy time and % swelling index at 6 h. The tablets of factorial batches were also evaluated for weight variation, friability, uniformity of content and in vitro drug dissolution studies. All the observations are reported in Tables 5, 6 and 7.

The significant response polynomial equations generated by Design Expert version 8.0.7.1. Response surface plots were generated to visualize simultaneous effect of each variable on response parameters (Figs. 5 and 6).

2.3. In vivo (Gamma scintigraphy) study

Gamma scintigraphy was performed to confirm the gastric retention time of the tablets of optimized formulation F3. The protocol for conduct of γ scintigraphy study was approved by Ethical Committee of Sumtibai Shah Ayurved Mahavidyalay, Hadapsar, Pune. Radiolabeled charcoal was prepared by mixing ^{99m}Tc-DTPA to charcoal along with sufficient amount of water and then evaporating to dryness using a hot air oven as per procedure reported by Ghimire et al, 2010. Radio

Table 2
The design of the Factorial batches.

Formulation code	Variable Level In Coded Form	
	X1	X2
F_1	−1	−1
F_2	+1	−1
F_3	−1	+1
F_4	+1	+1

Table 3
Coded Values translated in Actual Unit.

Variable level	Low (−)	High (+)
X1 = Compression pressure	0.25 ton	0.5 ton
X2 = Polymer blend	00 mg	100 mg

Table 4
Composition of factorial batches.

Formulation Code	Ingredients (mg/tab)			
	CLA SD equivalent to 250 mg of CLA	Polymer blend	Sucralfate	Total weight of tablet
F1*	500	–	100	600
F2**	500	–	100	600
F3*	500	100	100	700
F4**	500	100	100	700

* Prepared at low compression pressure (0.25 ton).
** Prepared at high compression pressure (at 0.5 ton).

labeled tablets of composition Formulation F3 were prepared by adding 100 mg of radiolabeled charcoal per tablet just before dosing. Radioactivity of each tablet containing radio labeled charcoal labeled with ^{99m}Tc-DTPA at a time of dosing was determined and was found to be 2 mCi. The radio imaging was done periodically and shown in

Table 5
Response data of the Factorial batches.

Formulation code	Response	
	Buoyancy time* (min)	Swelling index* %
F1	12.33 ± 2.51	126.56 ± 4.85
F2	39.00 ± 5.29	114.83 ± 5.29
F3	0.194 ± 0.048	139.89 ± 3.02
F4	0.58 ± 0.38	151.66 ± 6.43

* All values indicate mean ± SD.

Figs. 7A,B (radio images of two volunteers are shown and stomach outline is provided for visualization of the tablet location).

2.4. Stability studies

Gastro retentive tablets of clarithromycin of optimized formulation F3 were kept in glass vials and exposed to 40 °C/75%RH for three months in stability chamber according to the ICH guidelines [22].

3. Results and discussion

3.1. Preparation and characterization of polymer blend

Hot air oven drying was also tried in preliminary studies to obtain polymer blend but the physical properties of the blend were not suitable for further processing. Hence only microwave drying was adopted in present study.

3.1.1. Fourier transform infrared spectroscopy

In ATR FTIR spectrum of the Dried Gel the broad peak at 3444 cm^{-1} resulted from the stretching vibration of O—H groups which is a moderately strong hydrogen bonding group. The peaks at 2923 cm^{-1} (reference value ~2900 cm^{-1}), 1380 cm^{-1} (reference value ~1370 cm^{-1}) and 1031 cm^{-1} reference value ~1034 cm^{-1}) are assigned to $-CH_2$ stretching vibration, C—H bending modes and α –glucan respectively. The linear and branched (14)-β- xylan show the main band maximum at about 1047 cm^{-1}. Since xylan units influence the frequency of IR band maximum and band shape is influenced by the glucomannan from the side chain; a prominent peak at 1031 cm-1 was observed. The peak at 1158 cm^{-1} (reference value ~1150 cm^{-1}) is usually cited as C—O—C (C—O—C—O—C) stretching modes from ether groups in the pyranose ring. β-Glucosidic and β-mannosidic linkages are observed at 800–900 cm^{-1}. These peaks are clear and intense in ATR-FTIR spectrum and revealed presence of Glucomannan and xylan as major components of the Gel (Fig. 1A) [23,24].

Glucomannan and HPMC are oxygenated compounds. The infrared absorption of oxygenated compounds offers the most powerful means of elucidating structures of molecules and intermolecular interactions as well; hydrogen bonding in particular[25]. Glucomannan represents hydroxyl groups in abundance and Hydroxypropylmethylcellulose (HPMC) also contains hydroxyl groups. The important band in infrared spectrum of hydroxyl compounds arises from the O—H stretching vibrations. The hydroxyl group is highly polar and also forms hydrogen bonds with other molecules containing polar groups. Frequency shift due to hydrogen bonding in polymer blends is well documented. Frequency shift from 3444 cm^{-1} (in ATR-FTIR belonging to DM-Fig. 1A) and from 3456 cm^{-1} (in ATR-FTIR belonging to HPMC K100LV-Fig. 1B) to lower frequency i. e. at 3416 cm^{-1} (in FTIR belonging to polymer blend; Fig. 1C and D) indicated hydrogen bonding between Glucomannan present in DM and HPMC K100LV.

3.1.2. Scanning electron microscopy (SEM) studies

Scanning electron microscopy (SEM) was done to study morphology of the swollen polymer blend. The polymer blend exhibited formation of porous channels. Such materials have wide applications in dosage form designing particularly in designing of gastro retentive dosage forms. Thus the tablets were prepared by using this novel combination of polymers and investigated for swelling study to confirm the potential of polymer blend as a matrix material in design of gastro retentive tablet.

3.1.3. Swelling study

In preliminary study the tablet prepared of polymer blend of HPMC K100 LV and Dried mucilage in1:1 w/w proportion exhibited fast swelling and least erosion. Hence polymer blend of HPMC K100 LV and Dried mucilage in proportion 1:1 by weight was taken in further study as swellable matrix. The swelling index of the polymer/polymer blend reveals its ability to absorb water and swell. The results reported in Fig. 3 indicated that the tablet of composition S1 (i.e. polymer blend and clarithromycin in1:1 proportion) exhibited fast swelling and least erosion. This was because of formation of porous channels (Fig. 2) that enabled polymer blend to absorb more amount of water than tablet of composition S2 or composition S3 [26]. Integrity of polymer blend was upheld for prolonged period as a consequence of hydrogen bonding between HPMC K100 LV and Dried mucilage (DM). It is reported that xylan mixed with other hydrophilic polymers like resulted in increased porosity and improved mechanical properties. Results obtained in this work are in agreement with earlier reports. Xylan component of the dried mucilage had been contributed to the integrity of the tablet matrix in addition to the improved porosity along with HPMC L100LV in present study [27].

Polymer blending is the most promising and convenient strategy to develop new polymeric material with performance advantages superior to that of individual polymer component. Polymers blends are formed due to formation of inter associated hydrogen bonds between component polymers. Though the energy of the single hydrogen bond is low, however when there is a simultaneous formation of inter polymeric hydrogen bonds; the strength of such interaction is significant. Hydrogen bonded polymer blends exhibit distinctive physicochemical properties, which can be explored for development of novel dosage forms [15]. The functionality of the polymer blend as matrix material to design gastro retentive tablet was strategically explored in the further study.

3.2. Development of drug delivery systems

3.2.1. Preparation of solid dispersion of clarithromycin and compatibility study-

The compatibility studies of clarithromycin with polymer blend was performed with an aim to develop a stable and robust formulation.

Table 6
Data of evaluation of the tablets.

Formulation code	Parameter			
	Average Weight* (mg) (n = 20)	Friability * (%) (n = 20)	Drug content* (%) (n = 5)	Buoyancy time* (min) (n = 6)
P5	675.52 ± 19.91	1.23	99.27 ± 1.02	0.194 ± 0.048
P6	702.52 ± 16.83	1.52	99.61 ± 0.73	0.58 ± 0.38

* All values indicate mean ± SD.

Table 7
In vitro drug release data.

Time (h)	0	1	2	3	4	5	6	7	8	9	10	11	12
	Percent drug release*												
P5	0	13.05 ± 0.05	18.40 ± 0.07	24.10 ± 1.20	31.14 ± 3.24	36.34 ± 0.37	44.09 ± 0.18	53.11 ± 0.21	59.11 ± 0.22	68.38 ± 0.27	77.42 ± 0.47	86.15 ± 1.30	94.40 ± 0.26
P6	0	8.30 ± 0.83	18.94 ± 1.60	23.51 ± 1.31	29.30 ± 0.78	36.03 ± 0.25	41.56 ± 0.57	49.88 ± 0.98	62.29 ± 0.89	67.73 ± 0.77	75.17 ± 1.02	82.63 ± 0.88	89.00 ± 1.40

* All values indicate mean ± SD. (n = 3).

There was no change in the appearance of the solid dispersion during stability studies. All the characteristic peaks of clarithromycin were retained in the FTIR spectrum of solid dispersion of clarithromycin at the end of stability studies indicated compatibility of clarithromycin with polymer blend (Fig. 4). The peaks observed were at 1690 cm^{-1} due to C═O stretching vibration from ketone group (ketone carbonyl) in a lactone ring, at 1735 cm^{-1} from O—C—O stretching (lactone carbonyl) vibration in a lactone ring, at 1423 cm^{-1} from N—CH_3 stretching vibration, at 2985 $cm^{-1}$from alkane stretching, at 3453 cm^{-1} due to hydrogen bond between OH groups, at 1160 $cm^{-1}$from —C—O—C stretch and at 1380 cm^{-1} due to CH_2 group. DSC curve of clarithromycin showed one endothermic peak of fusion having a peak maximum of 227.10 °C. A single sharp melting endotherm was observed with an onset temperature 225.65 °C [28]. This endotherm was also observed in the solid dispersion of clarithromycin at the end of stability studies without any additional endothermic peak (Fig. 5). Uniformity of the content of clarithromycin in its solid dispersion was found to be 98.5% ± 2.13.

3.2.2. Formulation development and evaluation of gastro retentive tablets of clarithromycin.

The ultimate goal of design and development of gastro retentive tablets of clarithromycin was to prepare and optimise the formulation which would remain buoyant on dissolution medium (in vitro studies) releasing the drug for prolonged period (preferentially up to 12 h). Hence preliminary batches (P1 to P6) were designed and prepared successively considering buoyancy characteristics of each formulation. The preliminary formulations P1 and P2 were prepared by using sodium bi carbonate; exhibited instantaneous buoyancy but did not retain the shape of the swollen tablet. Tablet material formed gel like mass that remained buoyant at latter phase of dissolution studies. Formulation P2 showed more signs of erosion even in the initial phase of buoyancy studies. In these formulations sodium bi carbonate was added expecting that it would assist instantaneous buoyancy of the formulations. It performed as disintegrating agent in addition to contributing to buoyancy characteristics of the tablet. Hence in next preliminary batches (P3 and P4) sodium carbonate was replaced with sucralfate.

In formulations P3 and P4 sucralfate was added for two reasons- to increase the viscosity of the swollen formulation (as gel forming agent) and to improve the stability of clarithromycin due to ingress of dissolution medium of acidic pH < 2 in the swollen dosage form [2]. The formulation containing more amount of sucralfate (P4) exhibited delayed buoyancy (41 min; though retained the shape of swollen tablet throughout the study period) as compared to formulation containing less amount of sucralfate i.e. P3 (only 11 min). This might be due to gelling ability of sucralfate which was more in the composition of formulation P4. Since sucralfate in formulations P3 and P4 found to delay buoyancy, some amount of polymer blend as such was added in further batches (P5 and P6) expecting reduction in lag time. The tablet formulations P5 and P6 exhibited buoyancy lag time less than a minute.

Preliminary formulations P5 and P6 demonstrated satisfactory buoyancy characteristics and tablets of these batches were evaluated for tableting properties and in vitro drug release studies. The results of evaluation of tablets of formulations P5 and P6 are reported in Tables 5 and 6. All the tablets were round and flat faced with diameter of 12 mm and height of 0.51 cm–0.53 cm. Uniformity of the content was within the limits for all the formulations. Compression pressure is one of the important process parameters that affects the porosity and buoyancy of tablet dosage form and hence was intentionally varied. Dissolution or rate of release of the drug was slightly affected by compression pressure and the presence of polymer blend. Tablet formulations P5 were compressed at low compression pressure (0.25 ton) released more drug up to 12 h (94.4%) than the tablet formulations P6 (89.00%) prepared by applying high pressure (0.5 ton). This might be because of lesser porosity of the tablet belonging to batch P6 resulting in decreased ingress

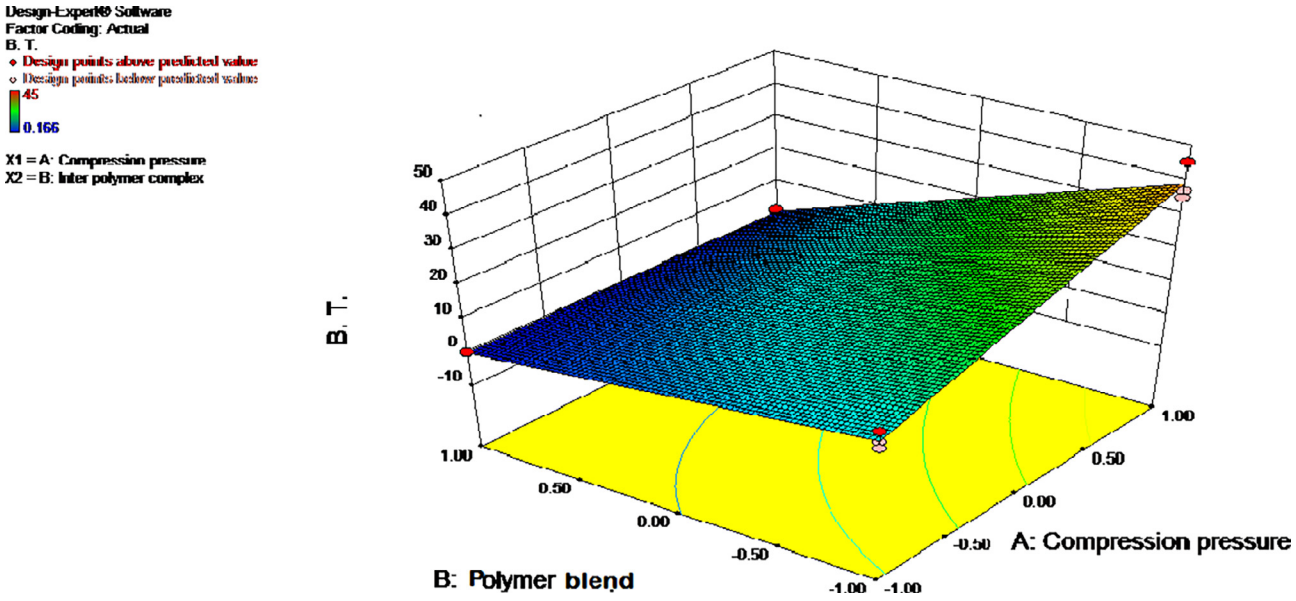

Fig. 5. The response surface plot showing the effect of formulation variables on buoyancy time.

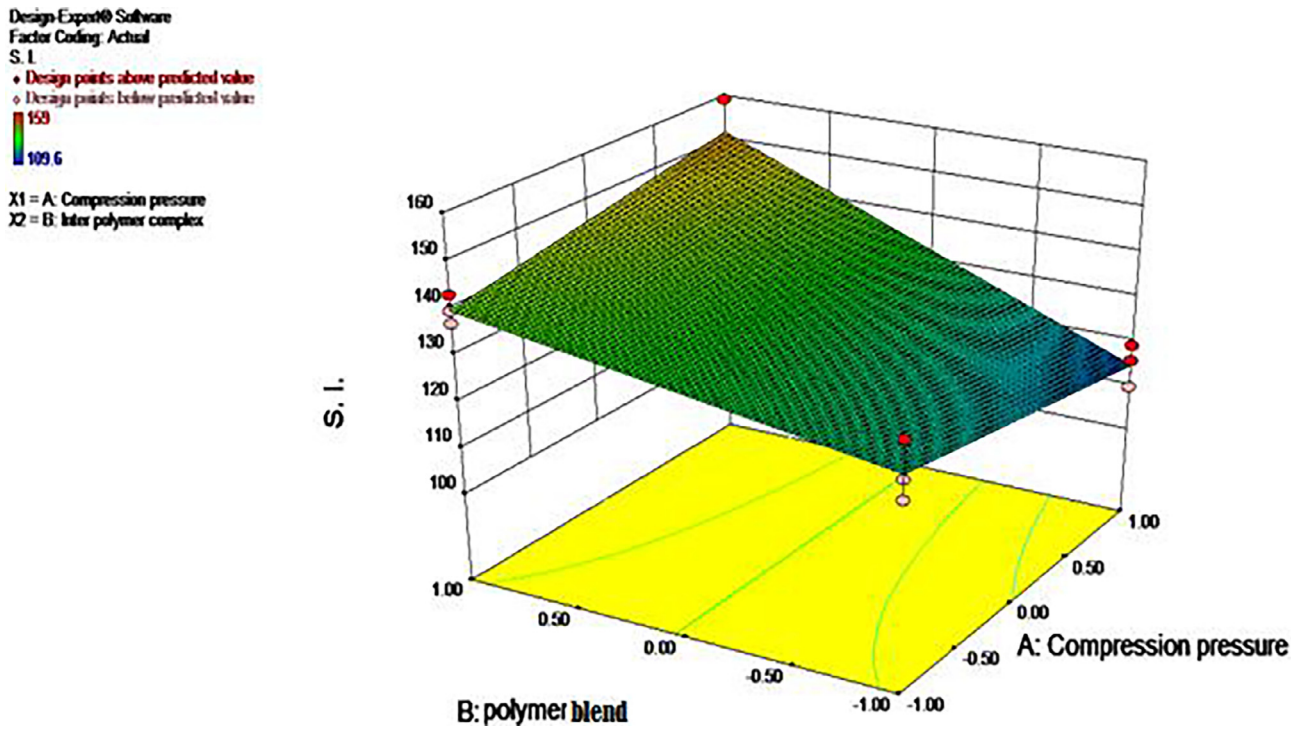

Fig. 6. The response surface plot showing the effect of formulation variables on swelling index.

of dissolution medium; due to application of more compression pressure. Since formulation P5 exhibited maximum drug release with minimum buoyancy lag time; this composition was systematically modified to optimize the formulation.

3.2.3. Optimization of gastro retentive tablets of clarithromycin.

The design was evaluated by quadratic model to describe the response surface curvature, which produced polynomial equations as Buoyancy Time (Y_1) = 13.03 + 6.76X1 − 12.64X2 − 6.57X1X2 and Swelling index at 6 h (Y_2) = 133.24 + 0.001X1 − 12.54X2 + 5.88X1X2. Regression analysis suggested that; buoyancy time increased as compression pressure applied was increased as indicated by positive coefficient of X1. As the percentage of inter polymer complex increased in the formulation the buoyancy time decreased as indicated by negative coefficient of X2. The interaction between the factor X1 and X2 was considerable and both were found to negate the effect of each other. It was obvious by negative coefficient of X1X2. Also There was no influence of compression pressure on swelling index at 6 h as indicated by very low (which can be neglected) positive coefficient of X1. As the percentage of inter polymer complex increased in the formulation the swelling index at 6 h decreased as indicated by negative coefficient of X2. The interaction between the factor X1 and X2 was considerable and both were found to add the effect of each other and was evident by positive coefficient of X1X2.

The tablets of factorial batches were round and flat faced with diameter of 12 mm and height of 0.51 cm–0.53 cm. Uniformity of the

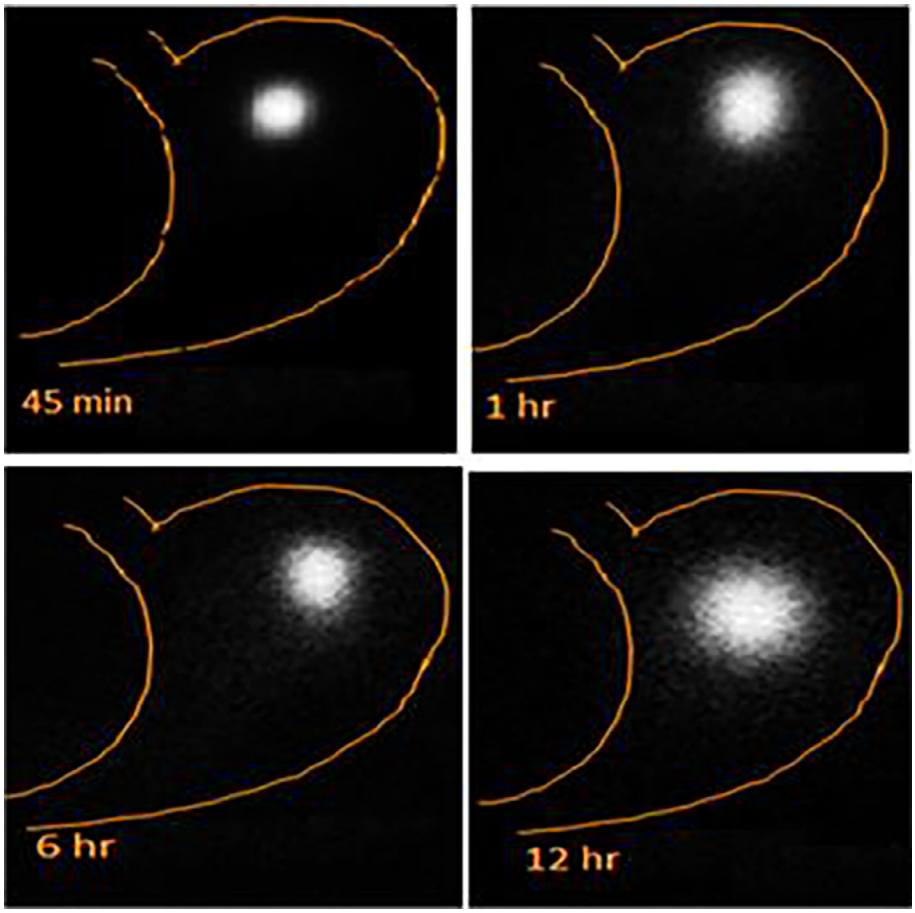

Fig. 7A. Gamma scintigraphy images of Volunteer 1 exhibiting retention of the tablet in the stomach at 12 h.

content was within the limits for all the formulations. Friability of formulations F3 and F4 were found more due to inclusion of polymer blend as such. Polymer blend being porous in nature might erode from the tablet surface easily making tablets more friable. Since formulation F3 exhibited maximum drug release with minimum buoyancy time it was selected as optimized batch and kept for stability studies.

3.3. In vivo (Gamma scintigraphy) study to confirm gastric retention of tablets

γ scintigraphy has been used as non-invasive technique for the quantitative determination of *in vivo* dissolution or erosion of matrix tablets. It was employed in the present work to confirm gastric retention time of the tablet F3. The origin of HPMC is cellulose which is not soluble in water. Degree of substitution to cellulose moiety plays a role in the solubility and also in the swelling rate. It is reported that tablets prepared by using low viscosity grade HPMC K100LV swells faster with proportionately high erosion rates as compared to tablets prepared by using high viscosity grades [6]. Thus, if these grades are used to prepare gastro retentive dosage forms they exhibit good buoyancy but there are higher chances of their early evacuation from the stomach. Gel has high swelling index and hence was selected and tried in the present study to form the polymer blend with HPMC L100LV; to overcome time dependant fast erosion of HPMC K100LV. This was expected in this study as a consequence of formation of integrated structure of polymer blend owing to hydrogen bonding between HPMC K100LV and Glucomannan which is confirmed by ATR-FTIR. *In vivo* γ scintigraphy study confirmed gastric retention of tablet up to twelve hours (Fig. 7A) in one volunteer whereas tablet was evacuated from the stomach in second volunteer (Fig. 7B) at the same time. The average retention time of the tablet in stomach of volunteers included in the study was observed to be between 8 and 12 h.

3.4. Stability studies of gastro retentive tablet of clarithromycin

The stability testing was performed for optimized batch F3. The tablets after 3 months stability testing study were observed carefully. It was noted that the tablets became more friable particularly the surface; which contained more amount of plain inter polymer complex that might had eroded from the surface of the tablet due to absorption of moisture during stability studies. Uniformity of content of the drug in the formulation was found to be 99.2 ± 3.1 even at the end of stability studies. The results of uniformity of content of the formulation clearly indicated that the drug was stable in the formulation F3. Dissolution studies when carried out in triplicate after 3 months of stability testing showed dissolution pattern similar to the initial dissolution pattern of the tablets of batch F3. The dissolution or release of drug from tablets after stability testing was found rapid for initial phase of study (up to 2 h). This might be because the tablets became of shedding of surface material which contributed to initial rapid release and dissolution of drug.

4. Conclusion

The hydrogen bonded polymer blend of Gel containing Glucomannan and HPMC K100LV was prepared and investigated as a

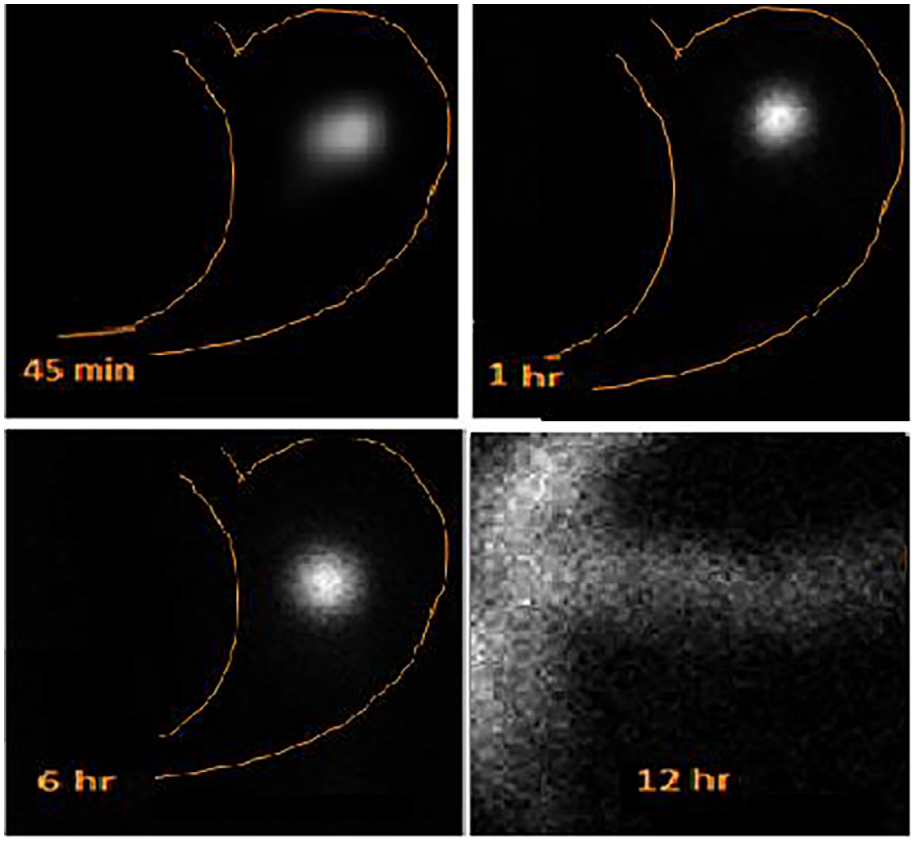

Fig. 7B. Gamma scintigraphy images of Volunteer 2 exhibiting evacuation of the tablet from the stomach at 12 h.

matrix material to develop gastro-retentive tablets of clarithromycin. Hydrogen bonding between the components of polymer blend was confirmed by ATR-FTIR studies. The formulation of gastro retentive tablets of clarithromycin was optimized by adopting 2^2 full factorial design. The gastric retention of the tablets of optimized formulation of clarithromycin was confirmed by γ scintigraphy. The tablets of optimized formulation were found stable when stability studies were conducted as per ICH guidelines.

5. Conflict of interest

Authors declare no conflict of interest.

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