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Original Article

DEVELOPMENT, FORMULATION AND EVALUATION OF A BILAYER GASTRIC RETENTIVE FLOATING TABLETS OF RANITIDINE HCL AND CLARITHROMYCIN USING NATURAL POLYMERS

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ABSTRACT

Objective: Bilayer gastric retentive floating tablets (BGRFT) with ranitidine HCl and clarithromycin using natural gums have been developed to prolong the gastric residence time and increase drug bioavailability. Literature review revealed no published studies on the present study.

Methods: Immediate release (IR) layer prepared by using different diluents and super disintegrants like sodium starch glycolate, crosscarmellose sodium and crospovidone. Controlled released (CR) layer prepared by using neem gum, damar gum and copal gum. Prepared tablets were evaluated for *in vivo* and *in vitro* buoyancy, *in vitro* dissolution studies and fourier transformation-infrared spectroscopy (FTIR). Drug release was evaluated with zero and first order for release kinetics, Higuchi, Hixson-Crowell erosion models for release mechanism.

Results: Prepared IR layer followed first order rate kinetics and CR layer followed zero order rate kinetics with non-Fickian diffusion mechanism. BGRFT also showed similar results as that of the individual layer. Optimized formulations were characterized by FTIR studies and found no interactions between drug and polymer.

Conclusion: The results demonstrate the feasibility of the model in the development of BGRFT. BGRFT enhanced the drug release and finally the bioavailability of clarithromycin when compared with commercial tablet (Biomycin 250). The present study could establish the suitability of neem gum as CR polymer in the design of BGRFT.

Keywords: Ranitidine HCl, Clarithromycin, Super disintegrants, Neem gum, Damar gum, copal gum, Gastric retention, Immediate release, Controlled release, Bilayer floating tablet

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INTRODUCTION

Gastric retention systems are such systems, which increase the gastric retention time of the dosage form at the stomach and upper parts of the small intestine and suitable for the drugs having site specific absorption from the above sites. The controlled release of the drug from these systems at the preferred absorption site optimizes delivery of the drug, maximizing its therapeutic benefits and reduces side effects by permitting a large portion of the drug to be absorbed before passing through the lower gastro intestinal tract. Many attempts like floating drug delivery systems, swelling and expanding systems, polymeric bioadhesive systems, modified shape systems, high density systems and other delayed gastric emptying devices have been made in recent years to provide a dosage form with a longer gastric retention time and therefore more efficient absorption [1].

Compared to these approaches, the gastric floating drug delivery system (GFDDS) developed has provided several advantages, as shown by the encouraging results reported earlier. Furthermore, the buoyancy action provided by the GFDDS seems to offer a greater safety for clinical uses than some of the above mentioned approaches. In fact, no adverse effects due to floating devices have been reported to date. GFDDS are also appropriate for drugs which are locally active to the gastric mucosa in the stomach, in particular case of antibiotic administration for *Helicobacter pylori* (*H. Pylori*) eradication in the treatment of peptic ulcer disease [2].

In the present investigation ranitidine HCl and clarithromycin were selected as model drugs for the development of bilayer gastro retentive floating tablets (BGRFT). Ranitidine HCl is used to reduce the acid secretion in the stomach, which in turn helps in stabilizing and enhancing the concentration of clarithromycin. Hence, the combination of ranitidine HCl and clarithromycin was selected. Ranitidine HCl is a non selective beta-adrenergic receptor blocking agent prepared as an immediate release layer using lactose as a diluent and sodium starch glycolate as disintegrant. Clarithromycin is a macrolide antibiotic which is used in the treatment of *H. Pylori* infection. Clarithromycin controlled release tablets were prepared using natural polymers (neem gum, gum copal and gum damar) as release retarding polymers in the present investigation.

Based on previously published literature, applications of gastro retentive drug delivery system (GRDDS) may be suitable for the drugs insoluble in intestinal fluids. As discussed earlier, clarithromycin degrades in acid secretion, but its absorption window is in stomach and in presence of ranitidine HCl the bioavailability of clarithromycin is increased, which makes it suitable for BGRFT. Till now there were no reports found on neem gum used as a release retarding polymer [3-11]. Through this present investigation we have developed a BGRFT of ranitidine HCl and clarithromycin. In this study the applicability of neem gum, gum copal and gum damar as a release retarding agents for controlled release layer was seen.

MATERIALS AND METHODS

Materials

Ranitidine HCl and clarithromycin were provided by Dr Reddy's Laboratories Ltd (Hyderabad, India). Neem, copal and damar gum procured from Palaniappa Chettian Traders. (Chennia, India). All other reagents and chemicals were of analytical grade.

Preparation of ranitidine HCl immediate release tablets

All the ingredients sufficient for a batch of 100 tablets according to the formulae shown in table 1 and 2 were passed through sieve #40 (425 µm). All the ingredients were geometrically mixed to obtain a

homogenous blend. Magnesium stearate and Aerosil, passed through sieve #60 (250 µm) were mixed with the powder blend for 3 min in poly bag. The flow properties of the final blend were found to be good so final blend was directly compressed into tablets on a 12-station rotary punching machine (M/s. Karnavati Engineering Ltd. India) using 9 mm round flat punches.

Table 1: Formulae of ranitidine HCl immediate release tablets with diluents

Ingredients (mg)	FR1	FR2	FR3	FR4	FR5	FR6	FR7	FR8
Ranitidine HCl	150	150	150	150	150	150	150	150
MCC 101	40	-	-	-	-	-	-	-
MCC 102	-	40	-	-	-	-	-	-
Lactose	-	-	40	-	-	-	-	-
Ac-di-sol	-	-	-	40	-	-	-	-
Spray dried lactose	-	-	-	-	40	-	-	-
SSG Primogel	-	-	-	-	-	40	-	-
Di calcium phosphate	-	-	-	-	-	-	40	-
Lycatab	-	-	-	-	-	-	-	40
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	5	5	5	5	5	5	5	5
Total weight (mg)	200	200	200	200	200	200	200	200

Table 2: Formulae of ranitidine HCl immediate release tablets with different super disintegrants ratios

Ingredients(mg)	FR9	FR10	FR11	FR12	FR13	FR14	FR15	FR16	FR17
Ranitidine HCl	150	150	150	150	150	150	150	150	150
Sodium starch glycolate	4	6	8	-	-	-	-	-	-
Cross carmellose sodium	-	-	-	4	6	8	-	-	-
Crospovidone	-	-	-	-	-	-	4	6	8
Lactose	38	36	34	38	36	34	38	36	34
Magnesium stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

Preparation of gastric retentive floating tablets of clarithromycin

All the formulations containing clarithromycin 250 mg were prepared by direct compression using different proportions of drug-polymer ratio as given in table 3 to 5. The respective powders, clarithromycin, release retarding polymers, a gas forming agent and diluent were passed separately through sieve #40 (425 µm). The batches were prepared according to the formulae, mixing of powders was carried out by passing through the sieve #40. Blend was lubricated with magnesium stearate passed through sieve #60 (250 µm) for 3 min in poly bag. The lubricated blend was evaluated for flow characteristics as described in the previous section. The final blend was directly compressed into tablets on a 12-station rotary punching machine (M/s. Karnavati Engineering Ltd. India) using 12 mm round flat punches.

Table 3: Formulae of clarithromycin controlled release tablets of gastroretentive floating tablets with neem gum

Ingredients (mg)	NG01	NG02	NG03	NG04	NG05	NG06	NG07	NG08
Clarithromycin	250	250	250	250	250	250	250	250
Neem gum	100	125	150	175	200	150	175	200
Sodium bicarbonate	-	-	-	-	-	62.4	62.4	62.4
MCC 102	105	80	55	30	5	52.6	27.6	2.6
Magnesium stearate	5	5	5	5	5	5	5	5
Total weight (mg)	460	460	460	460	460	520	520	520

Table 4: Formulae of clarithromycin controlled release tablets and gastroretentive floating tablets with damar gum

Ingredients (mg)	DM01	DM02	DM03	DM04	DM05	DM06	DM07	DM08
Clarithromycin	250	250	250	250	250	250	250	250
Damar gum	100	125	150	175	200	200	225	250
Sodium bicarbonate	-	-	-	-	-	74.4	74.4	74.4
Povidone K 30	-	-	-	-	-	31	31	31
MCC 102	105	80	55	30	5	58.6	33.6	8.6
Magnesium stearate	5	5	5	5	5	6	6	6
Total weight (mg)	460	460	460	460	460	620	620	620

Table 5: Formulae of clarithromycin controlled release tablets and gastroretentive floating tablets with copal gum

Ingredients (mg)	CP01	CP02	CP03	CP04	CP05	CP06	CP07	CP08
Clarithromycin	250	250	250	250	250	250	250	250
Copal gum	100	125	150	175	200	200	225	250
Sodium bicarbonate	-	-	-	-	-	74.4	74.4	74.4
Povidone K 30	-	-	-	-	-	31	31	31
MCC 102	105	80	55	30	5	58.6	33.6	8.6
Magnesium stearate	5	5	5	5	5	6	6	6
Total weight (mg)	460	460	460	460	460	620	620	620

Preparations of bilayer gastric retentive floating tablets

Bilayer gastric retentive floating tablets (BGRFT) of ranitidine HCl (IR layer containing 150 mg) and clarithromycin (CR layer containing 250 mg) were prepared from the optimised formulations of each layer (optimised in immediate release and controlled release layer). The components of the individual layers of the BGRFT are given in table 6**.** The two layers were compressed as a single tablet by direct compression technique. Initially the gastric floating layer part of clarithromycin was compressed with a total weight of 520 mg with low compression force to attain hardness of 3-4 kg/cm^2 and then the immediate release portion of the ranitidine HCl was added (200 mg) and bilayer gastric retentive floating tablets was compressed to attain a hardness of 4-6 kg/cm^2.

The tablets were compressed on a 12-station rotary punching machine (M/s. Karnavati Engineering Ltd. India) using 12 mm round flat punches. The total weight of the prepared BGRFT was 720 mg.

Table.6: Formula of bilayer gastric retentive floating tablets

Ingredients (mg)	Ranitidine HCl immediate release layer	Clarithromycin controlled release layer
Clarithromycin	-	250
Neem gum	-	175
Sodium bicarbonate	-	62.4
MCC 102	-	27.6
Ranitidine HCl	150	-
Sodium starch glycolate	6	-
Lactose	34	-
Magnesium stearate	5	5
Talc	5	-
Total weight (mg)	200	520

Evaluation of tablets

***In vitro* dissolution studies of ranitidine HCl immediate release tablets**

In vitro release of ranitidine HCl from the prepared immediate release tablets were studied using USP dissolution test apparatus (LABINDIA, Disso 2000) employing the paddle stirrer (Apparatus-II). 900 ml of 0.1 N HCl was used as dissolution medium maintained at a temperature of 37±0.5 °C and the paddle was rotated at 50 rpm [12]. Aliquots samples (5 ml each) were withdrawn at predetermined time intervals by means of a syringe fitted with 0.45 µm prefilter and immediately replaced with 5 ml of fresh medium maintained at 37±0.5 °C. Samples were filtered through 0.45 µm millipore membrane filter and were suitably diluted with the dissolution medium wherever necessary and the absorbance of the samples was measured spectrophotometrically at 315 nm as per the UV method i.e. 50 mg of ranitidine HCl was dissolved in sufficient amount of 0.1 N HCl in a 50 ml volumetric flask and the solution was made up to the mark with 0.1N HCl to prepare the stock solution [13]. From the stock solution, a series of dilutions were prepared to get 50, 75, 100, 150, 200 and 250 µg/ml by using 0.1 N HCl. The absorbance of these solutions was measured against 0.1N HCl as blank in UV spectrophotometer (Model AX120, M/s. Shimadzu Corporation, Japan) at 315 nm. All the estimations were done in triplicate and average values are reported.

***In vitro* buoyancy studies**

The floating characteristics of all the prepared gastroretentive floating tablets of clarithromycin was determined by floating lag time (FLT) and total floating time (TFT).

Floating lag time

FLT of all the prepared formulations was measured by placing the tablets in a 250 ml glass beaker containing 200 ml of 0.1 N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time. This FLT was due to the time taken for the reaction between sodium bicarbonate and gastric fluids, which produced effervescence for the floating of the tablet. All the prepared formulations floated immediately after they were placed in the beaker.

Total floating time

TFT of all formulations was more than 24 h. The tablets were placed in a 200 ml glass beaker containing 0.1N HCl and the time was noted until the tablets disintegrate. The time interval between the introduction of the tablet and its floating to the top of dissolution medium was taken as FLT and the duration of system floatation was taken as TFT [14].

***In vitro* dissolution studies of both controlled release and gastric floating tablets of clarithromycin**

In vitro release of clarithromycin from the prepared gastro retentive floating tablets (GFT) was studied using apparatus II (Disso 2000, M/s Lab India, Mumbai). The dissolution studies were conducted at a 50 rpm speed, using 500 ml of 0.1N HCl solution as dissolution medium [15, 16]. A sample of 5 ml was withdrawn by means of a syringe fitted with a prefilter at appropriate time intervals and immediately replaced with 5 ml of fresh medium maintained at 37±0.5 °C so as to maintain constant volume. Samples were filtered through 0.45 µm millipore membrane filter and analysed spectrophotometrically at 271 nm as per the UV method i.e. 50 mg of clarithromycin was dissolved in sufficient amount of 0.1 N HCl in a 50 ml volumetric flask and the solution was made up to the mark with 0.1N HCl to prepare the stock solution. Serial dilutions were made from the stock solution to get 20, 30, 40, 60, 80 and 100 µg/ml solutions using 0.1N HCl as dilution medium. The absorbance was measured at 271 nm against 0.1 N HCl as blank. All the estimations and dissolution experiments were done in triplicate and average values are reported.

***In vitro* dissolution studies of BGRFT of ranitidine HCl and clarithromycin**

The tableting properties of weight variation, hardness, friability, assay, *in vitro* buoyancy studies, *in vitro* dissolution studies and release rate kinetics of BGRFT were evaluated as described earlier in the previous sections.

Comparison of the dissolution profiles of prepared BGRFT with the commercially available individual tablets of clarithromycin and ranitidine HCl

The main objective of comparing the profiles is to understand the effectiveness of the prepared BGRFT in comparison with the individual marketed tablets of ranitidine HCl (Histac®150) and clarithromycin (Biomycin 250).

Release kinetics

The analysis of drug release is an important mechanism but, complicated process and is practically evident in the case of matrix systems as a model dependent approach. The dissolution data was fitted into zero [17], and first order for establishing drug release kinetics [18, 19], and Higuchi diffusion model [20]**,** Hixson-Crowell erosion model for establishing drug release mechanism [21].

Zero order model describes the systems where the release rate is independent of the concentration of drug, the first order model describes that the release rate from products is dependent on the concentration of the dissolving drug. Higuchi model describes

diffusion mechanism of drug release whereas; Hixson-Crowell model describes erosion mechanism of drug release from the products. Korsmeyer-Peppas model further supports the diffusion model of drug release mechanism for further understanding [22, 23]. The respective equations for these models are shown in table 7. In this regard, the use of *in vitro* drug dissolution data to predict *in vivo* bio-performance can be considered as the rational development of immediate release formulations.

Table 7: Mathematical models for comparison of dissolution profiles

Model		Equation
Zero-order	:	$Q_t = Q_0 + k_0 t$
First-order	:	$\ln Q_t = \ln Q_0 - k_1 t$
Higuchi	:	$Q_t = k_H \sqrt{t}$
Hixson-Crowell	:	$(Q_0^{1/3} - Q_t^{1/3}) = k_s t$
Korsmeyer-Peppas	:	$Q_t/Q_\alpha = k_k t^n$

Where: Q_t: amount of drug released in time t; Q_o: initial amount of drug in the tablet; $Q_t/Q\infty$: fraction of drug released at time t; k_0, k_1, k_H, k_k, k_s: release rate constants; n: the release exponent

According to Korsmeyer-Peppas equation, the release exponent 'n' value is used to characterize different release mechanisms. For a dosage form in cylindrical shape, if the n value is 0.45 or less, the release mechanism follows Fickian diffusion. If 'n' value is 0.45<n>0.89, the mechanism follows non-Fickian (anomalous) diffusion and when 'n' value is 0.89 it will be non-Fickian case II transport and if n>0.89 it will be non-Fickian super case II transport [24].

Drug interaction studies

Fourier transformation-infrared spectroscopy

Fourier transformation-infrared spectroscopy (FTIR) is used to identify the drug excipient interaction. FTIR studies were performed on drugs, polymers and optimized formulations. Samples were analyzed by potassium bromide pellet method in an IR spectrophotometer (Shimadzu, FTIR 8700) in the region between 3500-500 cm^{-1}.

***In vivo* buoyancy studies**

To confirm the spatial and temporal placement of FDDS, a variety of techniques have been used like string technique, endoscopy and gamma scintigraphy [25-29]. Out of these techniques, X-ray technique was used to determine the gastric residence time of the tablets. In the present investigation X-ray studies were conducted for the evaluation of intragastric floating behaviour of the optimized BGRFT of ranitidine HCl and clarithromycin both in fasted and fed states. The *in vivo* X-ray evaluation of floating ability studies were carried out by administering BGRFT of ranitidine HCl and clarithromycin containing barium sulphate ($BaSO_4$) in humans in fasted and fed state. Two healthy male subjects of mean age 25±2 y (ranging from 23 to 28), mean weight 68±10 Kg (ranging from 58 to 78 kg) and a mean height of 170±5 cm (ranging from 165 to 175 cm) participated in this study. Based on the previous medical history, physical examination and routine laboratory tests the volunteers were judged healthy. The study was conducted under the guidance of radiologist and both subjects were presented with full details of the investigation, verbally and in written form, prior to providing written informed consent. The study was approved from an independent Institutional Ethics Committee of Andhra University, Visakhapatnam (India). The optimized BGRFT of ranitidine HCl and clarithromycin was administered to the two volunteers, one under fasted and another one under fed states.

- Fasted state: The subject was fasted overnight and swallowed the BGRFT tablet with 200 ml of water. No food was allowed up to 3 h of dosing. Subject was not allowed to lay down for sleeping. Every one hour a glass of water (200 ml) was given.

- Fed state: The subject was fasted overnight and in the morning given a high calorie-high fat breakfast with a total calorie value of approximately 900 Cal. The BGRFT tablet was administered with 200 ml of water after half an hour of the breakfast. The subject was not allowed to eat anything up to 6 h but given a glass of water (200 ml) every hour.

Preparation of BGRFT for *in vivo* studies

Optimized BGRFT of ranitidine HCl and clarithromycin containing barium sulphate (BGRFT soB) for *in vivo* X-ray evaluation were prepared by direct compression method. The amount of ranitidine HCl and clarithromycin was reduced to 75 and 125 mg for incorporating the barium sulphate (75 and 125 mg) as radio opaque substance to maintain the constant weight of the tablet. Ranitidine HCl and clarithromycin (75 and 125 mg) was geometrically mixed with their respective formulations until a homogeneous blend was achieved. Barium sulphate (75 and 125 mg) and sodium bicarbonate were added to the above blend, mixed and lubricated with magnesium stearate (1%w/w). The final blend was directly compressed into tablets on a 12-Station rotary punching machine (M/s. Karnavati Engineering Ltd. India) using 12 mm round flat punches at hardness of 4-6 kg/cm^2.

RESULTS AND DISCUSSION

***In vitro* dissolution studies of ranitidine HCl immediate release tablets**

The *in vitro* dissolution studies of the prepared ranitidine HCl tablets with different diluents (FR1-FR8) like MCC 101, MCC 102, Ac-di-sol, spray dried lactose, lactose, SSG primogel, DCP, Lycatab and super disintegrants (FR9-FR17) like sodium starch glycolate (SSG), cross carmellose sodium (CCS) and crospovidone (CP) was carried in 0.1N HCl (pH 1.2), for a period of 75 min and results are shown in fig. 1 and 2.

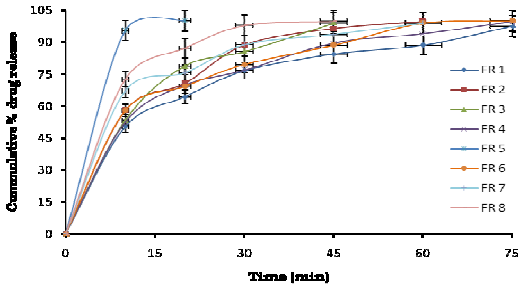


Fig. 1: Dissolution profile of ranitidine HCl immediate release tablets with different diluents with formulation (FR1 to FR8), (Results are expressed as mean, n=3)

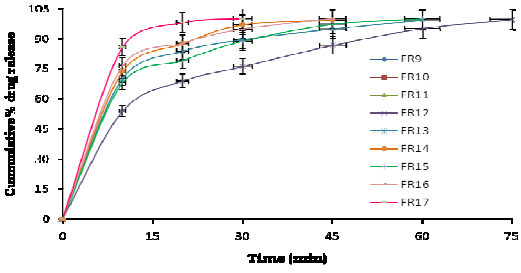


Fig. 2: Dissolution profile of ranitidine HCl immediate release tablets with different super disintegrants with formulation (FR9 to FR17), (Results are expressed as mean, n=3)

All the formulation disintegrated within 10 min. The drug release at 10 min from FR1 to FR8 tablets was 50.26, 57.75, 53.25, 52.18, 81.26, 57.81, 66.99 and 72.47% respectively. It was observed that while with lactose the release was more than 80% of drug within 10 min, the other tablets prepared with remaining diluents released >50% and <73% within 10 min. From the drug release studies and disintegration time, lactose has been selected as optimised diluent for the preparation of immediate release tablets.

From the selected diluent formulation, the super disintegrant and its ratio optimised. The different super disintegrants used in the present study are SSG, CCS and CP. For each disintegrant three ratios (2%, 3% and 4% to the total weight of the tablet) were taken. Super disintegrant based formulations FR9-FR11 containing SSG released more than 95% in 60, 10 and 10 min respectively. CCS based formulations FR12-FR14 released more than 95% in 75 min, 60 and 45 min respectively. Formulations FR15-FR17 containing CP released more than 95% in 60, 45 and 30 min respectively. Drug release property was found to be directly proportional to the concentration of super disintegrant.

From the obtained results, it was found that as the concentration of super disintegrant increases, the disintegration time of the tablet decreases and thereby drug release increases [30]. Therefore SSG containing 3%, CCS containing 4% and CP containing 4% were selected as optimised formulations for the IR tablet of ranitidine HCl. Thus, with less concentration of SSG, maximum drug release was observed within 10 min.

Therefore from all the formulations, FR10 was optimised and 99.99% of drug was released in 20 min. When compared with the other super disintegrants, SSG (3%) showed better release.

The optimised formulation FR10 was compared with the commercial marketed tablets of ranitidine HCl. As the target for complete release of drug is 10 min in the present investigation, comparative study with commercial formulation was conducted. From the drug release data, it was observed that optimised dissolution profile showed better releases when compared to the commercial marketed product Histac® 150 mg tablet.

From the results, it was concluded that the drug release was mainly depended up on concentration of polymer, the drug release varies as the concentration increases the drug release increases (i.e. gives maximum amount of drug release in 10 min).

***In vitro* buoyancy studies**

Initially the concentration of the sodium bicarbonate was optimized for the preparation of the effervescent GFDDS [31]. All the floating tablets were passed physicochemical tests like weight variation, assay and friability. Floating lag times of all the formulations were within the range of 15 to 150 sec, the results are given in table 8. As the concentration of sodium bicarbonate increases, the floating lag time found to be decreased as shown in fig. 3.

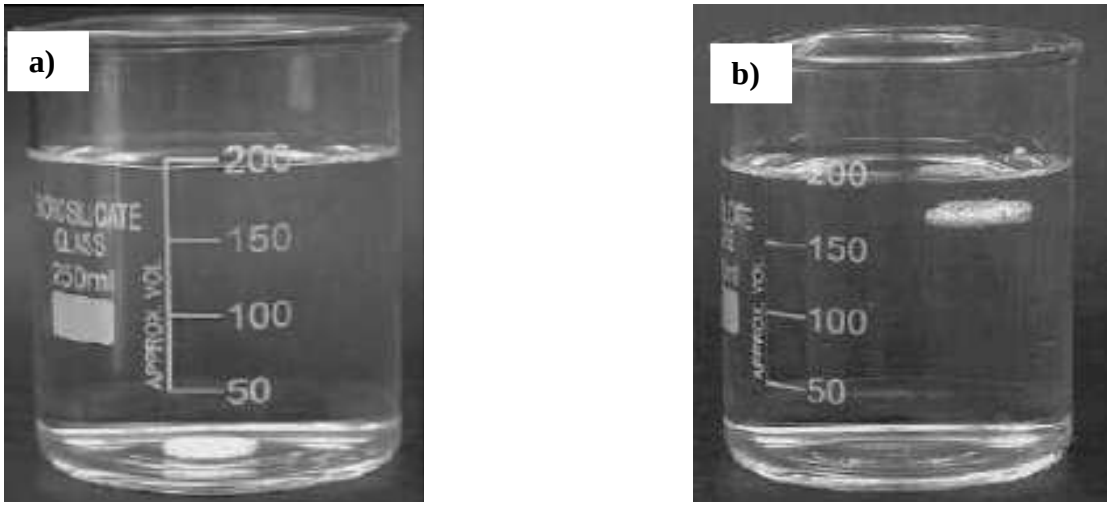


Fig. 3: Floating behaviour of optimised neem gum based formulation (NG07) immediately after placing in the beaker and b) after 30 sec

From the results, it was observed that as the concentration of polymer increased along with concentration of sodium bicarbonate the drug release was retarded. This may be due to increased intensity of air pockets surrounding the jellified surface of the tablet. Increase in the concentration of the sodium bicarbonate at constant polymer concentration also retarded the drug release due to high intensity of the carbon dioxide gas pockets.

Drug retardation was directly proportional to the concentration of polymer, which may be due to the formation of strong compactness between the particles [32].

***In vitro* dissolution studies of clarithromycin both controlled and gastric floating tablets**

The results of the drug release studies of all the prepared formulations are shown in fig. 4 and 5. Since, there are very few reports on the applicability of the selected natural gums as controlled release polymers, natural gum matrix tablets were prepared to evaluate their efficacy in controlling the drug release of clarithromycin [33-37]. Release retarding effect of concentration of gums on drug release was performed on batches containing neem (NG01-05), damar (DM01-05) and copal (CP01-05). From the dissolution studies, it was concluded that as the concentration of gum increased the drug release was retarded.

Clarithromycin controlled release tablets of neem gum based formulation NG01-05 containing drug-polymer ratios 1:0.4, 1:0.5, 1:0.6, 1:0.7 and 1:0.8 released more than 95% of drug in 5, 6, 10, 12 and 14 h respectively. From the above, it can be concluded that the concentration of neem gum is directly proportional to retarding property of the formulation.

Similarly, the controlled release tablets of clarithromycin prepared with hydrophobic gums of damar gum (DM01-05) and copal gum (CP01-05) in different ratios 1:0.4, 1:0.5, 1:0.6, 1:0.7 and 1:0.8 retards the drug release for 3-8 h depending on the drug-polymer ratio. As the natural gums have shown retarding capability, they were used in the formulation of effervescent GFT. The effervescent GFT were prepared with hydrophobic gums of gum damar and gum copal, in 1:0.8, 1:0.9 and 1:1 ratios to evaluate their applicability in designing GFT.

As the controlled release tablets of hydrophobic gums failed to retard the drug release up to 12 h even at 1:0.8 drug-polymers ratio, the GFT were prepared in the above mentioned increasing ratios by using povidone K 30 as binder at 5% concentration to the total weight to improve binding and to retard the drug release.

Table 8: Natural um based formulations with the quantities of gum and tableting characteristics (thickness, floating lag time and total floating time)

Formulation code	Gum quantity (mg)	Sodium bicarbonate (%w/w)	Povidone (%w/w)	Thickness (mm)	Floating lag time (sec)	Total floating time (hrs)
NG01	100	-	-	3.45±0.11	-	-
NG02	125	-	-	3.42±0.12	-	-
NG03	150	-	-	3.26±0.11	-	-
NG04	175	-	-	3.43±0.14	-	-
NG05	200	-	-	3.44±0.11	-	-
NG06	150	62.4	-	3.41±0.13	60	10
NG07	175	62.4	-	3.38±0.12	30	12
NG08	200	62.4	-	3.39±0.11	15	14
DM01	100	-	31	3.36±0.13	-	-
DM02	125	-	31	3.27±0.12	-	-
DM03	150	-	31	3.51±0.11	-	-
DM04	175	-	31	3.28±0.14	-	-
DM05	200	-	31	3.42±0.12	-	-
DM06	200	74.4	31	3.55±0.15	126	10
DM07	225	74.4	31	3.60±0.12	90	12
DM08	250	74.4	31	3.48±0.13	66	14
CP01	100	-	31	3.38±0.13	-	-
CP02	125	-	31	3.41±0.11	-	-
CP03	150	-	31	3.29±0.15	-	-
CP04	175	-	31	3.45±0.09	-	-
CP05	200	-	31	3.37±0.12	-	-
CP06	200	74.4	31	3.52±0.14	150	10
CP07	225	74.4	31	3.51±0.12	78	12
CP08	250	74.4	31	3.56±0.11	60	14

Each value represents mean±SD (n=5) Where n-number of experiments

The effervescent formulations of gum damar (DM06-08) and gum copal (CP06-08) GFT also released more than 98% of the drug in 10, 12 and 14 h respectively. This similarity in drug release may be associated to the fact that both damar and copal gum are gums of hydrophobic nature.

The effervescent GFT prepared with hydrophilic gum i.e. neem gum in 1:0.6, 1:0.7 and 1:0.8 ratios to evaluate the applicability in designing GFT. The formulations of neem gum (NG06-08) retarded the drug release upto 10, 12 and 14 h respectively by increasing the concentration of the polymer.

When compared with the hydrophobic gums, less concentration of polymer is required with hydrophilic gum to achieve the required time period. Hence, neem gum was selected as the suitable polymer for retarding the drug release of clarithromycin controlled release layer with the optimised formulation NG07 released 99.68% of drug at 12 h.

***In vitro* dissolution studies of BGRFT**

The drug release profile of the prepared BGRFT was studied and the results are given in and fig. 6. This BGRFT formulation was prepared to study the effect of immediate release layer (ranitidine HCl) on the absorption rate of the controlled release layer (clarithromycin) and their effect on the *H. pylori* infection [38, 39]. From the dissolution studies it was concluded that the immediate release layer released more than 95% of ranitidine HCl within 10 min and complete release was observed within 30 min.

The controlled release layer of clarithromycin released only 10% of clarithromycin up to 1 hr from controlled release layer and the tablet started floating within 2 min and floating continued upto 12 h. The individual layers of the BGRFT have shown similar results as the optimised FR10 (ranitidine HCl) and NG07 (clarithromycin) optimised earlier. As the clarithromycin drug release was enhances with the effect of ranitidine HCl.

As there are no marketed product of bilayer tablets of ranitidine HCl and clarithromycin, the prepared BGRFT formulation of ranitidine HCl and clarithromycin was compared with the individual marketed products of ranitidine HCl (Histac® 150) and clarithromycin (Biomycin 250). Ranitidine HCl marketed product Histac® 150 released less than 70% within 10 min. and clarithromycin marketed product has released more than 30% within 1 h.

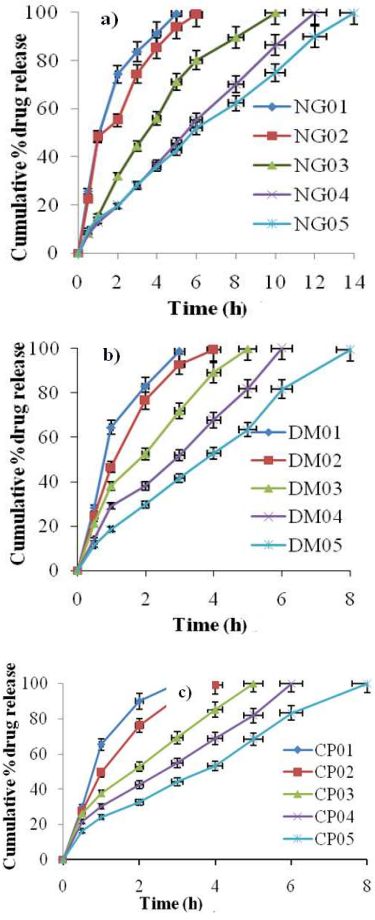


Fig. 4: Dissolution profiles of controlled release tablets of clarithromycin with a) neem gum based formulations (NG01 to NG05), b) damar gum based formulations (DM01 to DM05) and c) copal gum based formulations (CP01 to CP05). (Results are expressed as mean, n=3)

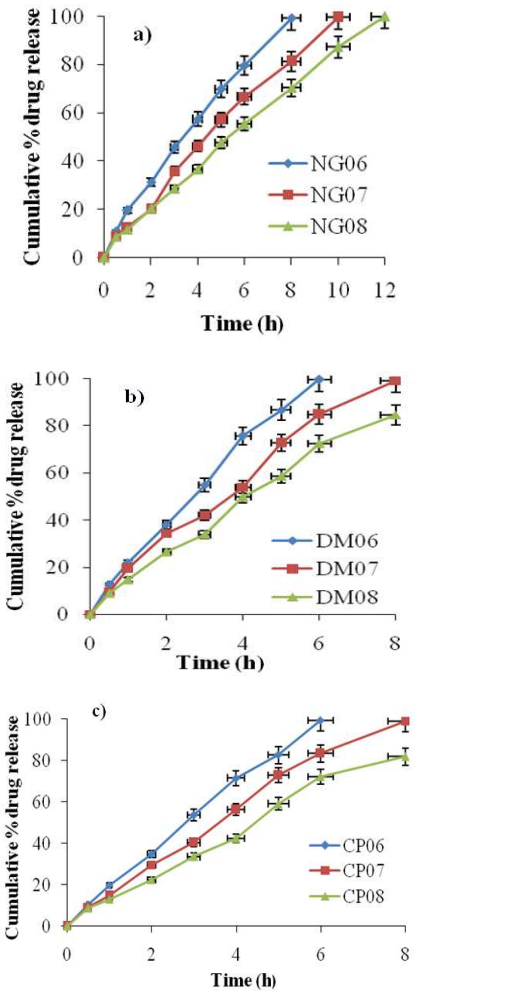


Fig. 5: Dissolution profiles of effervescent gastroretentive floating tablets of clarithromycin using sodium bicarbonate with a) neem gum based formulations (NG06 to NG08), b) damar gum based formulations (DM06 to DM08)and c) copal gum based formulations (CP06 to CP08). (Results are expressed as mean, n=3)

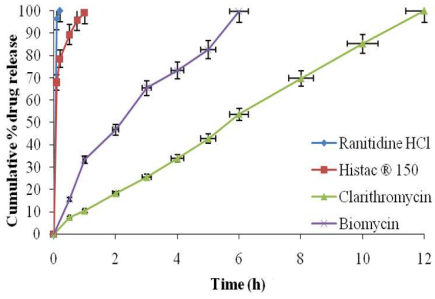


Fig. 6: Dissolution profiles of bilayer retentive gastric floating tablet containing ranitidine HCl and clarithromycin and conventional marketed tablets Histac®150 and Biomycin. (Results are expressed as mean, n=3)

Release kinetics

The dissolution data was fitted to kinetic parameters and the correlation coefficient values ('r') of release kinetics of all the ranitidine HCl formulations are given in table 9. The appropriate correlation coefficient values are highlighted with bold letters indicating the order and release mechanism followed by the respective formulations. The formulations prepared with different diluents FR1 to FR17 followed first order and Fickian diffusion mechanism. The dissolution data of batches FR1 to FR17 was fitted to zero-order, first-order, Higuchi, Hixson-Crowell and Korsmeyer-Peppas models. The drug release data from the ranitidine HCl tablets was best explained by the first order release kinetics. Formulations FR1, FR3 and FR11 followed diffusion mechanism with regression correlation coefficient values 0.9550, 0.9821 and 0.9303. The remaining formulations followed erosion mechanism.

The release kinetics of all the formulations of clarithromycin was given in table 10 and 11. Neem gum based formulations NG01 and NG02 followed first order release rate kinetics with regression values 0.8828 and 0.9115 with non-Fickian mechanism due to low concentration of polymer and rapid disintegration of tablets. Formulations NG03, NG04 and NG05 followed zero order kinetics with non-Fickian diffusion mechanism.

Formulations prepared with damar gum DM01 and DM02 followed first order release rate kinetics with regression values 0.9331 and 0.9324 with erosion mechanism. The formulations DM03, DM04 and DM05 followed zero order kinetics with non-Fickian diffusion mechanism. Copal gum based formulations CP01 and CP02 followed first order release rate kinetics with regression values 0.8930 and 0.9429 with erosion mechanism. Formulations CP03, CP04 and CP05 followed zero order kinetics with non-Fickian diffusion mechanism. Moreover, due to the hydrophobic nature of the damar and copal gums they followed biphasic mechanism for higher concentration formulations.

The effervescent natural gum formulations NG06-08, DM06-08 and CP06-08 followed zero order kinetics with a non-Fickian diffusion mechanism. Drug release from the optimized effervescent GFT NG07 followed zero order kinetics with non-Fickian diffusion mechanism. There was no significant change in release mechanism by altering the concentration of polymers after attaining the achieved time period.

Where BGRFT–bilayer gastric retentive floating tablets

BGRFT release kinetics in comparision with individual marketed products was given in table **12**. The immediate release layer and Histac® 150 followed first order release kinetics and controlled released layer and Biomycin 250 followed zero order kinetics with Fickian diffusion mechanism.

Drug interaction studies

Fourier transformation-infrared spectroscopy

There is always a possibility of drug-excipient interaction in the formulation due to their intimate contact. FTIR studies were used to study the drug-excipient interaction of the optimized formulations and their respective powders. The FTIR spectra of the optimised formulations were compared with the respective spectra of pure drugs and respective polymers. Characteristic spectra of the drugs clarithromycin and ranitidine HCl in the optimized formulation along with each individual excipient layers are shown in fig. 7 to 9.

The FTIR spectrum of pure ranitidine HCl [40-42], showed characteristic O-H dimer stretch at 3256 cm^{-1} and 3191 cm^{-1}, C-H stretch at 3097 $cm^{-1}$and 2974 cm^{-1}, N-H bond in protonated tertiary amine group at 2465 cm^{-1}, a strong primary amine at 1620 cm^{-1} which corresponds to the C=N stretch in an aci-nitro group of nitronic acid, nitro group attached to a saturated carbon atom with a stretch alkanes at 1418 cm^{-1} and amines at 1252 cm^{-1}, C-O stretch at 1006 cm^{-1}, C-Cl stretch at 761 cm^{-1} and C-H alkenes stretch at 701 cm^{-1}.

The FTIR spectra of sodium starch glycolate showed the characteristic O-H alcohols stretch at 3693 cm^{-1}, O-H carboxylic acid stretch at 2885 cm^{-1}, C=O carboxylic acid stretch at 1745 cm^{-1}, C-O carboxylic acid stretch at 1118 cm^{-1} and a C-H alkenes stretch at 917 cm^{-1}.

The optimized formulation FR10 showed all the characteristic peaks of ranitidine HCl with minor shifts in the FTIR spectrum. The spectrum showed O-H dimer stretch at 3257 cm^{-1} and 3191 cm^{-1}, C-H stretch at 3097 $cm^{-1}$and 2974 cm^{-1},N-H bond in

protonated tertiary amine group at 2466 cm^{-1}, a strong primary amine at 1620 cm^{-1} which corresponds to the C=N stretch in an aci-nitro group of nitronic acid, nitro group attached to a saturated carbon atom with a stretch alkanes at 1418 cm^{-1} and amines at 1252 cm^{-1}, C-O stretch at 1006 cm^{-1}, C-Cl stretch at 762 cm^{-1} and a C-H alkenes stretch at 701 cm^{-1}.

The FTIR spectrum of pure clarithromycin [43-46], showed characteristic O–H stretch at 3469 cm^{-1}, C-H aliphatic stretch at 2978 cm^{-1}, C=O ketone stretch at 1726 cm^{-1} and 1691 cm^{-1}, C-H aromatic stretch at 1459 cm^{-1}, C-O tertiary alcohol stretch at 1173 cm^{-1}, C-N stretch aliphatic amines at 1011 cm^{-1} and C-H cis-disubstituted alkenes stretch at 633 cm^{-1}.

Table 9: Correlation coefficient values and release kinetics of ranitidine HCl immediate release tablets

Formulation	Zero order		First order		Higuchi	Hixson-Crowell	Peppas	
	K_0	r	K_1	r	r	R	n	r
FR1	1.0578	0.7562	0.0182	0.9471	0.9550	0.9439	0.3212	0.9871
FR2	1.4499	0.7511	0.0403	0.9504	0.9539	0.9812	0.3232	0.9664
FR3	2.0316	0.8253	0.0411	0.9357	0.9821	0.9820	0.4053	0.9652
FR4	1.0925	0.7467	0.0266	0.9111	0.9512	0.9655	0.3166	0.9857
FR5	4.9995	0.8781	0.1000	0.9797	0.9852	0.9978	0.2816	1.0000
FR6	1.0909	0.7306	0.0365	0.9128	0.9416	0.9728	0.2849	0.9927
FR7	1.3406	0.6695	0.0297	0.9669	0.9096	0.9293	0.2260	0.9747
FR8	1.9581	0.6838	0.0559	0.9891	0.9193	0.9438	0.2232	0.9538
FR9	1.3829	0.7172	0.0320	0.9377	0.9391	0.9559	0.2797	0.9859
FR10	4.9995	0.7864	0.2000	0.9620	0.9489	0.9648	0.0720	1.0000
FR11	4.9495	0.7686	0.0998	0.9330	0.9303	0.8526	0.0362	1.0000
FR12	1.0862	0.7515	0.0264	0.9173	0.9531	0.9693	0.3054	1.0000
FR13	1.3076	0.6192	0.0312	0.9633	0.8788	0.9052	0.1912	0.9819
FR14	1.9287	0.6709	0.0454	0.9923	0.9117	0.9194	0.2072	0.9606
FR15	1.3584	0.6637	0.0388	0.9658	0.9074	0.9541	0.2235	0.9896
FR16	1.8996	0.6541	0.0556	0.9463	0.9003	0.9419	0.1797	0.9935
FR17	3.1168	0.7134	0.0913	0.9951	0.9199	0.9405	0.1449	0.9371

Table 10: Correlation coefficient values and release kinetics of clarithromycin controlled release tablets with natural gums (neem, damarand copal)

Formulation	Zero order		First order		Higuchi	Hixson-Crowell		Peppas
	K_0	R	K_1	r	r	R	n	r
NG01	18.493	0.8719	0.388	0.8828	0.9795	0.9594	0.5706	0.9546
NG02	15.283	0.9006	0.289	0.9115	0.9848	0.9729	0.5623	0.9499
NG03	10.387	0.9519	0.224	0.7716	0.9906	0.9617	0.8588	0.9887
NG04	8.272	0.9974	0.209	0.6021	0.9681	0.8664	0.8121	0.9927
NG05	6.924	0.9931	0.141	0.6686	0.9735	0.8942	0.7164	0.9876
DM01	31.681	0.8935	0.596	0.9331	0.9392	0.9855	0.6719	0.9161
DM02	24.657	0.9187	0.521	0.9324	0.9753	0.9988	0.6772	0.9736
DM03	19.104	0.9673	0.458	0.7399	0.9927	0.9317	0.6586	0.9926
DM04	15.478	0.9876	0.343	0.6200	0.9671	0.8408	0.7330	0.9838
DM05	12.218	0.9939	0.218	0.7374	0.9676	0.8977	0.7828	0.9945
CP01	32.647	0.8845	0.921	0.8930	0.9334	0.9940	0.6676	0.9210
CP02	24.012	0.9114	0.471	0.9429	0.9789	0.9986	0.6252	0.9758
CP03	18.279	0.9643	0.483	0.6731	0.9878	0.8908	0.5747	0.9937
CP04	14.944	0.9789	0.381	0.5875	0.9662	0.8285	0.6009	0.9832
CP05	11.965	0.9860	0.267	0.6868	0.9620	0.8845	0.6542	0.9800

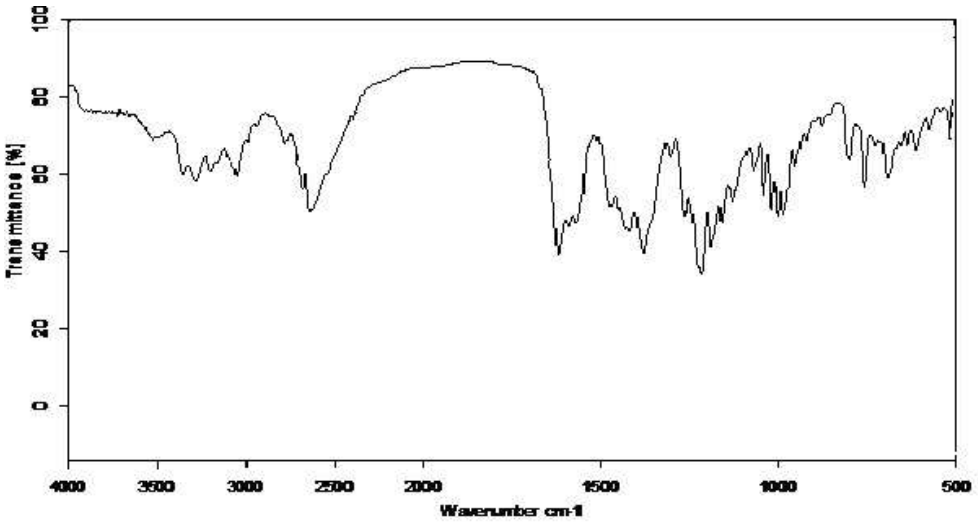
Table 11: Correlation coefficient values and release kinetics of effervescent GFT of clarithromycin natural gums

Formulation	Zero order		First order		Higuchi	Hixson-Crowell		Peppas
	K_0	r	K_1	r	r	R	n	r
NG06	9.909	0.9670	0.172	0.8184	0.9889	0.9585	0.7390	0.9950
NG07	8.144	0.9969	0.167	0.6538	0.9655	0.8742	0.7802	0.9860
NG08	6.824	0.9944	6.442	0.7270	0.9714	0.9036	0.7368	0.9886
DM06	9.453	0.9694	0.169	0.7685	0.9949	0.9304	0.6912	0.9967
DM07	7.935	0.9662	0.176	0.6453	0.9905	0.8886	0.7192	0.9957
DM08	6.665	0.9867	0.136	0.6072	0.9788	0.8537	0.7264	0.9959
CP06	9.541	0.9599	0.187	0.7619	0.9915	0.9377	0.6499	0.9957
CP07	7.965	0.9585	0.168	0.7312	0.9925	0.9363	0.6625	0.9887
CP08	6.908	0.9775	0.103	0.8636	0.9902	0.9680	0.7258	0.9968

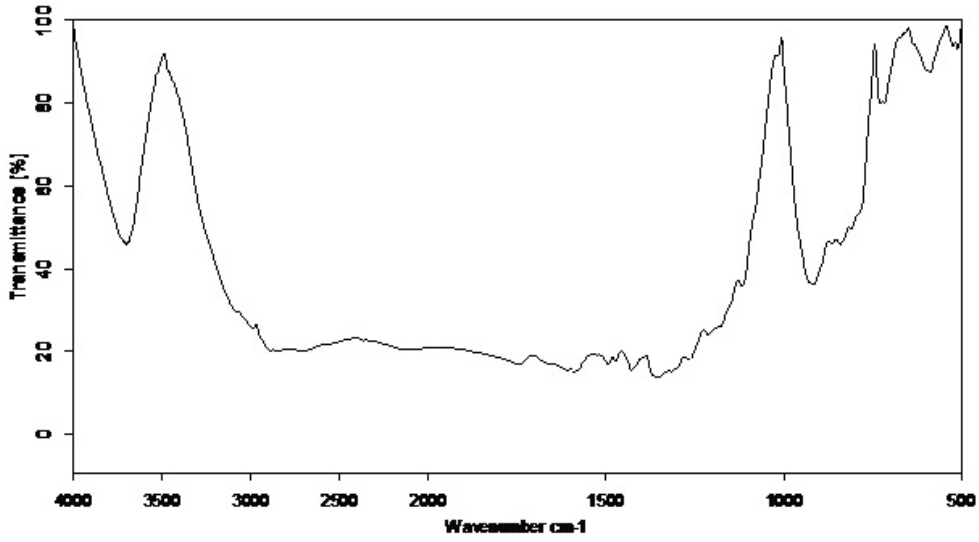
Where GFT-gastroretentive floating tablets

Table 12: Correlation coefficient values and release kinetics of BGRFT and marketed products

Formulation	Zero order		First order		Higuchi	Hixson-Crowell		Peppas
	K_0	r	K_1	r	r	r	n	r
Ranitidine HCl from BGRFT	179.64	0.6139	8.696	0.8960	0.8146	0.8022	0.0335	0.8702
Clarithromycin from BGRFT	8.324	0.9984	0.189	0.6207	0.9593	0.8635	0.8519	0.9872
Histac® 150	80.26	0.6533	1.951	0.9834	0.9661	0.9328	0.2159	0.9864
Biomycin 250	15.42	0.9624	0.340	0.6542	0.9897	0.8792	0.6991	0.9817



a



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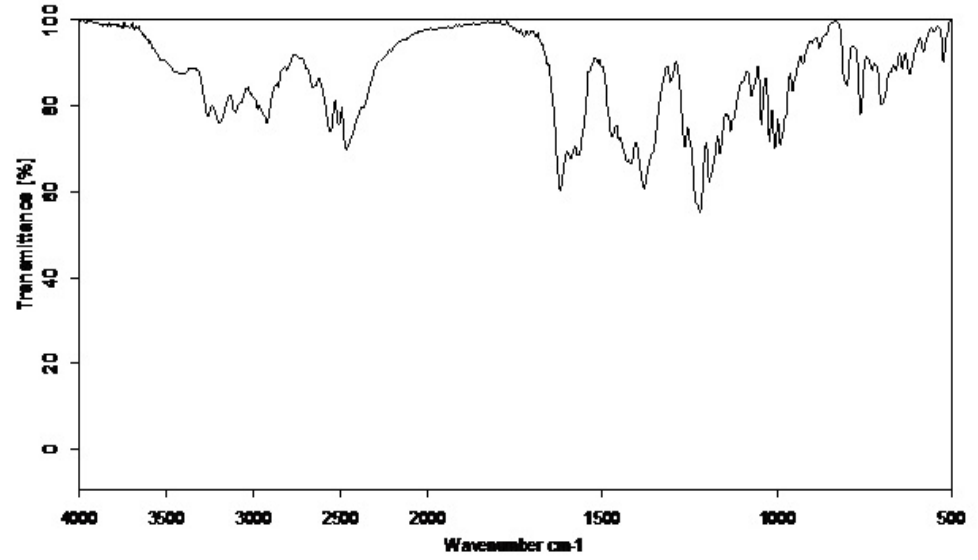

c

Fig. 7: FTIR spectra of (a) Ranitidine HCl (b) Sodium starch glycolate (c) Ranitidine HCl optimised formulation (FR10)

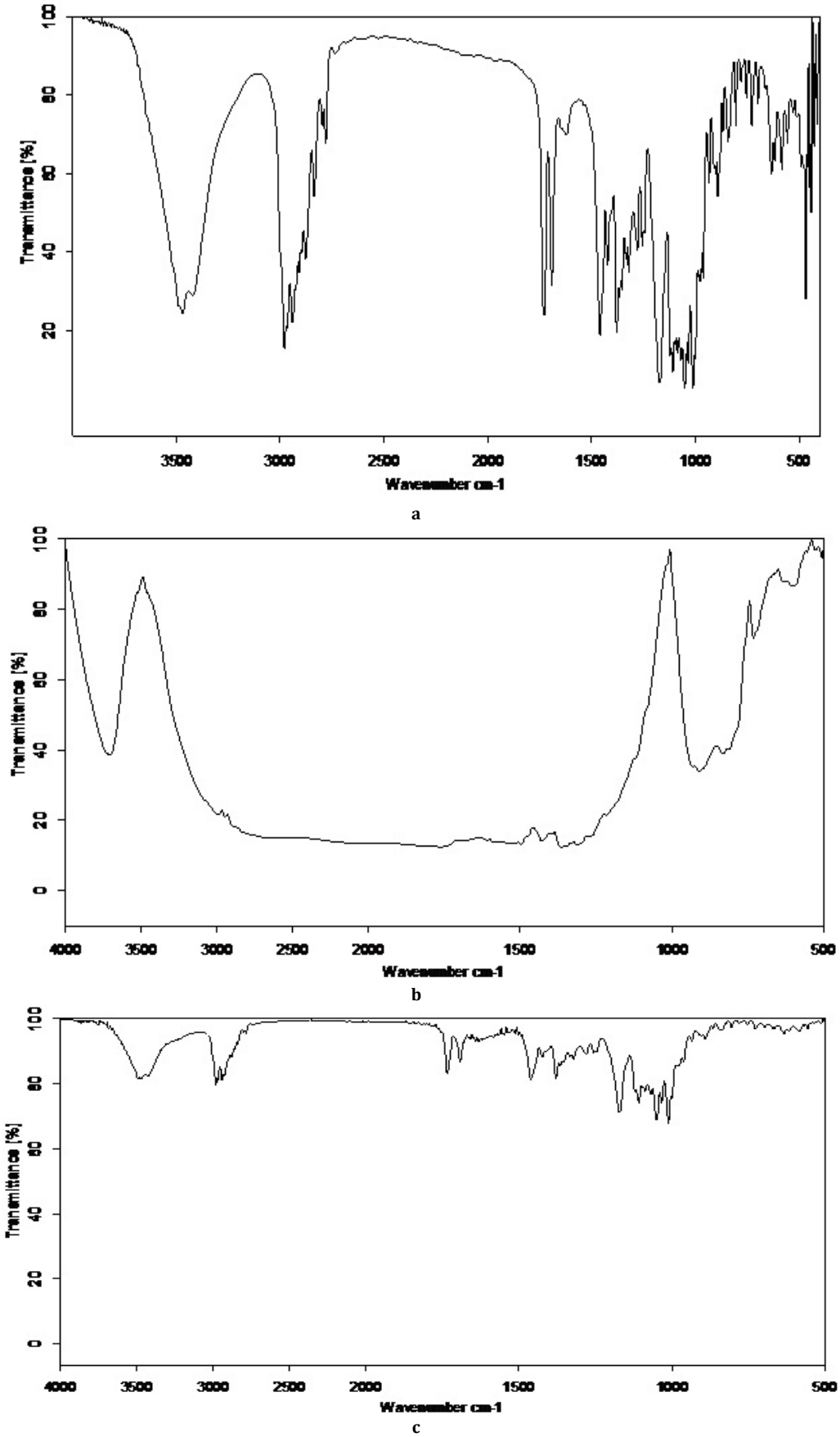

Fig. 8: FTIR spectra of (a) clarithromycin (b) Neem gum (c) clarithromycin optimised formulation (NG07)

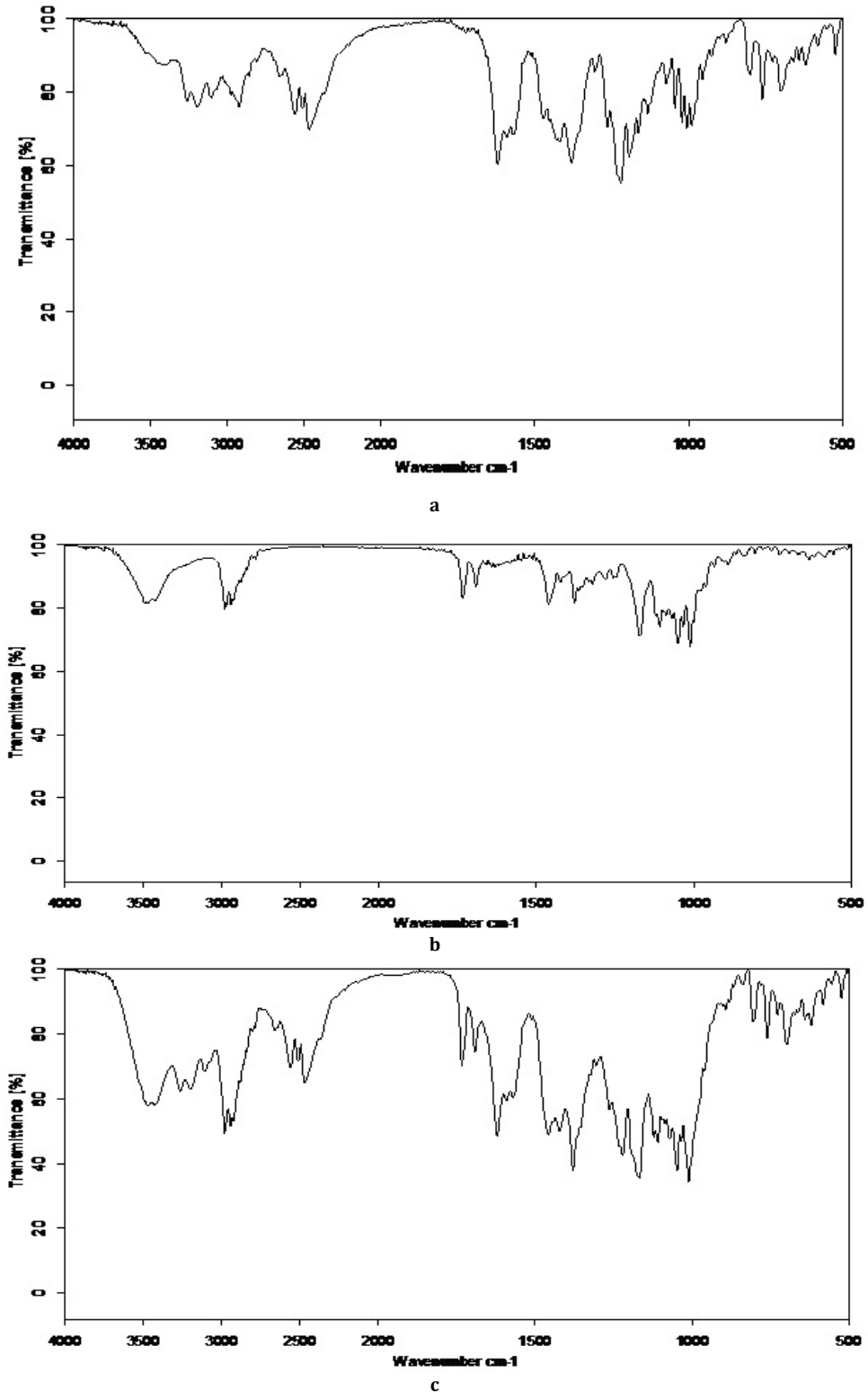

Fig. 9: FTIR spectra of (a) ranitidine HCl optimised formulation (FR10) (b) clarithromycin optimised formulation (NG07) (c) bilayer gastric retentive floating tablets (BGRFT)

The FTIR spectra of neem gum showed the characteristic N-H secondary amines stretch at 3702 cm-1, alcoholic O-H stretch at 2988 cm-1, C-O carboxylic acid anhydride stretch at 1763 cm-1, C=C aromatic stretch at 1494 cm-1, C-H alkanes stretch at 1428 cm-1and 1365 cm-1 and C-H alkenes stretch at 911 cm-1.

The optimised neem gum based formulation NG07 showed all characteristic peaks of clarithromycin with minor shifts in its FTIR spectrum. The spectrum showed O–H stretch at 3468 cm–1, aliphatic stretch C-H at 2978 cm–1, C-O carboxylic acid anhydride stretch at 1763 cm-1, C=O ketone stretch at 1725 cm–1 and 1692 cm–1, C=C aromatic stretch at 1495 cm-1, C-H aromatic stretch at 1460 cm–1, C-H alkanes stretch at 1365 cm-1, C-O tertiary alcohol stretch at 1172 cm–1, C-N stretch aliphatic amines at 1012 cm–1, C-

H alkenes stretch at 911 cm-1 and C-H cis-disubstituted alkenes stretch at 633 cm–1.

The prepared bilayer gastric retentive floating tablets BGRFT showed all the characteristic peaks of clarithromycin and ranitidine HCl with minor shifts in its FTIR spectrum. The spectrum showed–O–H stretch at 3465 cm–1, aliphatic stretch C-H at 2977 cm–1, N-H bond in protonated tertiary amine group at 2466 cm-1, C=O ketone stretch at 1725 cm–1 and 1691 cm–1, a strong primary amine at 1620 cm-1 which corresponds to the C=N stretch in an aci-nitro group of nitronic acid, C-H alkanes stretch at 1365 cm-1, nitro group attached to a saturated carbon atom with a stretch alkanes at 1420 cm-1 and amines at 1264 cm-1, C-O tertiary alcohol stretch at 1172 cm–1 and C-Cl stretch at 761 cm-1.

The FTIR spectra data indicated the absence of any chemical interaction between clarithromycin, ranitidine HCl and studied polymers sodium starch glycolate and neem gum.

In vivo buoyancy studies

The main aim of this study was to examine the buoyancy and gastric retention of the floating tablet system under both fasted and fed state conditions of healthy volunteers participated in the study. A radiological method was employed to monitor the gastric region of volunteers in different feeding conditions after administration of the developed GRFT. The GRFT of BGRFT remained buoyant on gastric content under both fasted and fed states in volunteers participated in the present study but variations in gastric retention time and buoyancy were observed in fasting and fed state conditions, given in table 13.

Table 13: *In vivo* residence time of the optimized BGRFT ofranitdine HCl and clarithromycin containing barium sulphate (BGRFTsoB)

Time (h)	Position of the tablet in GIT	
	Fed state	**Fasted state**
0.5	Stomach	Stomach
2	Stomach	Stomach
4	Stomach	Small intestine
6	Stomach	Disappeared from gastric region
8	Disappeared from gastric region	-

Where BGRFT-bilayer gastri retentive floating tablets, and BGRFTsoB)-optimized bilayer gastric retentive floating tablet of ranitidine HCl and clarithromycin containing barium sulphate.

The buoyancy of developed BGRFT under fasted conditions was observed on the gastric fluid at 2nd hr as shown in fig. 10 (aandb) and in the small intestine after 4 h as shown in fig. 10 (c) and was disappeared at 6th h as shown in fig. 10 (d). As a result of this activity, dosage form administered to fasted subjects could be emptied as rapidly as within an hour or two, depending on the presence of the strong motor induced contractile activity [19].

In the fed state after the high calorie high fat breakfast, the BGRFT was observed to be buoyant on the gastric contents up to 6 h after administration as shown in fig. 11 (a) at 0.5 h, fig. 11 (b) at 2 h, fig. 11 (c) at 4 h, fig. 11 (d) at 6 h and disappeared at 8 h shown in fig. 11 (e). Hence, in the fed condition, the floating system showed a 5 to 6 h of prolonged GRT over the fasted state. The evaluation of the BGRFT of ranitidine HCl and clarithromycin intragastric behaviour in humans, showed the actual floatability of the tablet on the gastric content. This study has demonstrated that in the fasted state under the influence of strong motor activity, there was no enhancement of GRT of gastro retentive floating tablet, whereas there was a prolonged GRT of approximately 6 h in a fed state.

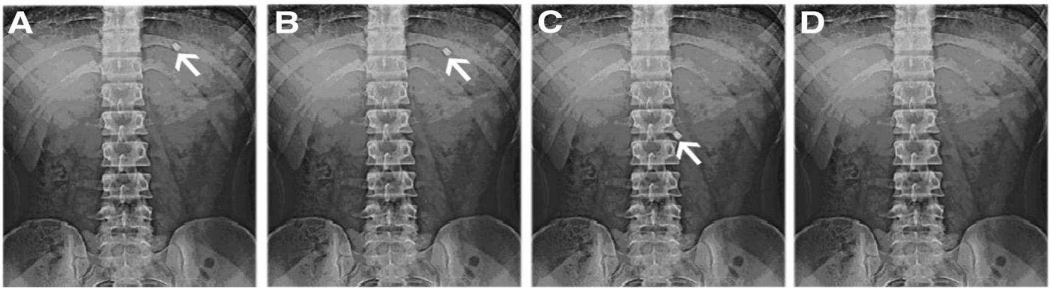

Fig. 10: X-ray photographs of gastric floating tablets of bilayer gastric retentive floating tablets containing ranitidine HCl and clarithromycin under fasted state after (a) 0.5 h (b) 2 h (c) 4 h and (d) 6 h

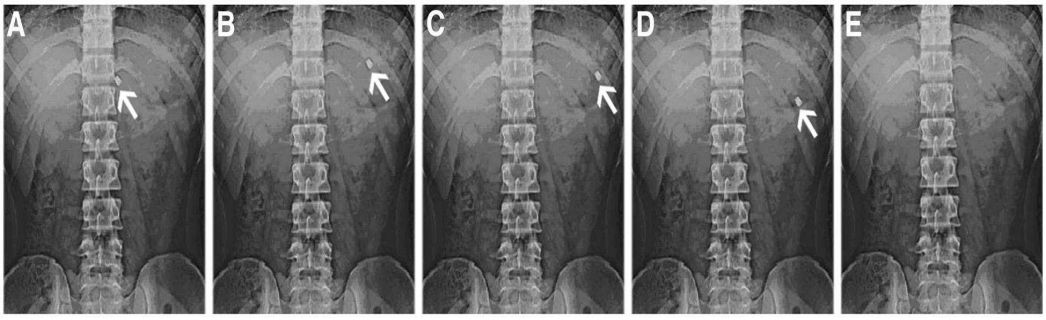

Fig. 11: X-ray photographs of gastric floating tablets of bilayer gastric retentive floating tablets containing ranitidine HCl and clarithromycin under fed state after (a) 0.5 h (b) 2 h (c) 4 h (d) 6 h and (e) 8 h

CONCLUSION

Natural polymers have been used in the design of oral controlled drug delivery systems. In recent years, polymers derived from plant origin have evoked interest among pharmaceutical suitability because they are readily available, less-toxic, capable of chemical modifications, biodegradable and also biocompatible.

In the present investigation three natural gums neem, damar and copal were selected for their applicability in the design of bilayer tablets having gastric floating layer of clarithromycin along with immediate release layer of ranitidine HCl. The reason behind the preparation of BGRFT of clarithromycin and ranitidine HCl is to overcome failure of *H. Pylori* eradication rates with conventional dosage forms of clarithromycin with concomitant administration of PPIs.

Among the different diluents and super disintegrants used in the preparation of ranitidine HCl immediate release tablets, formulation FR10 prepared with low concentration of sodium starch glycolate (3%) and low quantity of the lactose gave maximum %drug release within 30 min was optimised for the preparation of the immediate release tablets. As we want to minimise the total bulk of the tablet for the immediate release layer hence this is considered as the optimised formulation which is used for further preparation of bilayer tablet because the drug release completed within 30 min and bulk is low.

As less concentration of polymer is required in formulation NG07 to retard the drug release for 12 h, NG07 was considered as promising formulation prepared with natural gum (neem gum) when compared with the GFT prepared with other natural gums. Hence, neem gum can be suggested as a controlled release polymer for the development of dosage formulations in the design of GRFDDS.

By conducting all the preliminary studies, the BGRFT with the optimised individual layers were selected as optimized formulation as the floating parameters and drug release studies were same even after preparation of BGRFT.

From the comparison studies, it can be concluded that the prepared BGRFT seem to be the better alternative when compared with marketed conventional tablets Histac® 150 and Biomycin 250.

The prepared formulations were found to be stable and exhibited no drug-excipient interactions. Further, it can be concluded that all the optimised formulations FR10, NG07 and BGRFT of clarithromycin and ranitidine HCl with sodium starch glycolate and neem gum are stable in formulation.

BGRFT enhanced the drug release and finally the bioavailability of clarithromycin when compared with commercial tablet (Biomycin 250). The aim of the research project, viz., the preparation of a sustained action system that gives enhanced bioavailability for clarithromycin, through the design of BGRFT with immediate release layer of ranitidine HCl, was thus achieved through the design of the BGRFT.

The present study could establish the suitability of neem gum as a matrix and gel forming material in the design of BGRFT of clarithromycin and ranitidine HCl and the results were compared with the individual marketed products of ranitidine HCl (Histac® 150) and clarithromycin (Biomycin 250).

AUTHORS CONTRIBUTION

All persons who meet authorship criteria are listed as authors and all authors certify that they have participated sufficiently in the work. Dr. Saripilli Rajeswari, performed experiments, interpreted data, wrote manuscript and acted as corresponding author. Dr. Sravya Kudamala has helped in development of work, data interpretation and manuscript preparation. And Prof. K. V. Ramana Murthy had supervised the study and helped to evaluate and edit the manuscript.

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CONFLICT OF INTERESTS

We declare that we have no conflict of interest

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