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POMEGRANATE PEEL POWDER FLOATING TABLETS OF CLARITHROMYCIN WITH ENHANCED BIOAVAILABILITY

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ABSTRACT

Clarithromycin is abroad-spectrum macrolide antibiotic utilized in the treatment of peptic ulcers,respiratory, skin, Helicobacter pylori and otolaryngal infections. It possess short elimination half-life of 3-4 hours and thereforean ideal drug candidate for the developmentof Floating matrix tablets. Floating tablets of Clarithromycin with natural polymer i.e. Pomegranate peel powder was prepared through 3^2 factorial design. The optimized formulationF5had afloating lag time of 55 seconds and total floating time of upto12 hours. The DSC thermograms of the pure drug was observed at 232°C and that of the F5 formulation was at 233°C.The obtained FTIR values are in aacordance with the literature. The F5 formulation was stable without any interaction between Drug, polymer and other additives.The I*n-vitro* drug release was 98.67 %.The discharge exponent (n) from the Korsmeyer-Peppas model was found to be between 0.57 and 0.58 indicating non-Fickian or anomalous drug release behavior.The *In-vivo* X-ray photographsof rabbits shows that the floating tablets remained in the gastric region even after 8 h of administration.

INTRODUCTION

Drug absorption might be scarce and irregular in gastrointestinal tract because of the gastric retention time of the dosage form. The duration of stay a dosage formwithin the stomach depends upon physiological pH, size of the dosage form, food intake, and biological factors which include age, body mass index, gender, posture, and diseased states such ashepatic failure, diabetes, Chron's disease, etc.[1] Innumerable approaches for enhancing the gastric retention time of a dosage form within the gut have been developed such as bioadhesive system[2], swelling and expanding systems, [3]Floating systems,[4] and other delayed gastric emptying devices. [5]Among all the other gastric retention systems Floatingmethod has several advantages like less irascibility, random Gastric emptying, enhanced bioavailability, site-specific drug delivery, fewer side effects, etc.[6,7]. Clarithromycin (CLM)is abroad-spectrum macrolide antibiotic, utilized in the treatment of respiratory, skin, otolaryngal infections,it is havinghighest rate of eradication of H. pylori used in the treatment of peptic ulcersand Helicobacter pylori infections. It possess short elimination half-life of 3-4 hours and having substantial stability in acidic medium, thereforeCLM is an ideal drug candidate for the developmentof Floating matrix tablets[8] Synthetic polymers are used extensively in pharmaceuticals and possesses numerous disadvantages such as high cost, toxicity, environmental pollution during synthesis, non-renewable sources, side effects, and poor patient compliance. Skin and eye irritationis observed while handling the related substances of methyl methacrylate and poly-

(methyl methacrylate) polymers. Acute low oral toxicity is observed in animals while using oral carbomer-934P, also Carbomer dust is irritating to the eyes, mucous membranes and respiratory tract. [9]Hence to overcome all these drawbacks of synthetic polymers Floatinggastrioretentivedosage forms was prepared with natural polymer Pomegranate (PMG) peel powder.A 3^2 factorial design was utilized for optimizing Floating tablets of CLM [10].

MATERIAL AND METHODS

Material

Clarithromycin was purchase from Century Pharmaceuticals LTD, Gujarat. Pomegranate peel powder was purchase from Heilen Biopharm. Xanthan gum, Gellan gum, Sodium bicarbonate, PVP K30, Lactose and magnesium stearate are purchased from local market.

Methods

Preparation of Floatingtablets by direct compression technique.

Tablets were produced as per 3^2 factorial design by direct compression technique as shown in Table 1 and 2.The independent variable selected wasconcentration of PMG peel powder designated as $X_1$and sodium hydrogen carbonate as X_2 and dependent variable selected was percentage drug released.CLM, Sodium bicarbonate(gas generating agent), PMG peel powder(release-controlling polymer), Polyvinyl Pyrrolidone K30 (dry binder), Lactose (diluent) and magnesium stearate (lubricant) were sifted through mesh 40#. CLM was blended with all other additives excluding magnesium stearate. The resulting mixture was lubricated with magnesium stearate in a polybag. Thenthe finalblend was compressed on Karnavati mini tab eight-station tableting machine using a round-shaped 12 mm punch.

Evaluation of the pre-compression parameters of powder mixtures: Pre-compression parameters such as bulk density, tapped density, angle of repose, Carr's index, and Hausner's ratio are measured as per the following method.[11]

Angle of repose: The angle of repose is the maximum angle between the surface heap of granules and flat planes. A fixed quantity of the mixture, was precisely taken and deliberately poured through the channel whose tip was made at a height of 2.5 cm over the graph paper which is kept on an even surface. The mixture was poured until the summit of the cone-shaped heap just contacts the tip of the channel. The angle of repose is determined by the following formula. $\theta = \tan^{-1}(h/r)$

Where, θ = angle of repose, r = radius of the pile, h = height of the pile.

Bulk density: Bulk density is characterized as the proportion mass of an untapped blend partitioned by the mass volume including the entomb particulate void space. Bulk density (BD) was calculated by emptying the mix into a graduated chamber. The mass volume (V) and the heaviness of the powder (M) were resolved. The bulk density was calculated using the formula.

$BD = M/V$

Tapped density: The tapped densityobtained after precisely tapping a graduated measuring cylinder containing the powder test by raising the chamber or vessel and permitting it to drop, under its mass. The measuring cylinder containing a known mass of mix was tapped for a fixed time (around 100). The minimum volume (Vt) involved in the cylinder and the weight (M) of the mix were estimated. The tapped density (TD) was calculated using the formula,

$$TD = M/(V_t)$$

Compressibility index: The compressibility index is an indirect measure of bulk density, size, and shape, surface area, moisture content, and cohesiveness of materials. The correlation between compressibility index and powder flow properties is given in the formula,

CI (%) = Tapped density (TD) – Bulk density (BD) / Tapped density (TD) × 100

Hausner's ratio: It is an indirect index of ease of powder flow and is measured by the ratio of the tapped density to bulk density.

Hausner's ratio = Tapped density/ Bulk density

Evaluation of the post-compression parameters of Floating tablets: Compressed Floating tablets were characterized byfriability, diameter, thickness, and weight variation the methods are given below: [12, 13]

Tablet thickness

The thickness in millimeters was measured individually for 20 pre-weighed tablets by using Vernier Calipers. The average thickness and standard deviation were reported.

Tablet hardness: Tablet hardness was measured using Monsanto hardness tester. The average crushing strength of the 10 tablets with known weight and thickness of each was reported.

Friability test: Ten tablets were precisely gauged and set in the friability test (Roche friabilator), turned at 25 rpm for 4 min. The tablets were taken, dedusted, and rechecked. Friability results of less than 1% are considered satisfactory. The friability was determined as the percentage weight reduction given by the formula.

Percent Friability = (W1 – W2) /W1 × 100

Where, W1 = initial weight of the tablets, W2 = final weight of the tablets

Weight Variation Test: To examine weight variation 20 tablets from every formulation were taken and recorded. The percentage weight variation was determined by the formula.

Percentweight variation = $(W_A–W_I) / W_A$ x 100

Drug content

Twenty tablets were gauged and taken into a mortar and crushed into a fine powder. A precisely weighed quantity of the powder equivalent to 100 mg of CLM was taken in 100 ml volumetric flaskand methanol was added upto the mark. It was shaken by mechanical methods for 1hr. At that point it was filtered through Whatman filter paper. From this solution 1 ml was taken anddiluted to 10 ml with 0.1N HCl, and absorbance was taken at 422 nm in UV-Spectrophotometer. The percent drug content should be with in90% to 110%.[14]

Buoyancy / floating test

The tablets is introduced into a 100 ml beaker containing 0.1N HCl and the time gap between the introduction and time for the tablet to emerge onto the surface of the medium is called floating lag time. The total duration of time by which the dosage form remainsFloating is called Total floating time.[15]

Swelling studies

Water-uptake was carried out for all Floating tablets following the approach adopted through Chinthala CSK et al [16]. Tablets weighed and introduced into a beaker containing 25 ml 0.1 N HCl at 37 ± 0.5°C and stirred at 25 RPM. At the species time intervals each tablet used to be gently wiped with a filter paper to put off surface water, and reweighed. The degree of swelling used to be calculated following the following equation.

$S=W_S - W_d/W_d$ x100

Where: S = the degree of swelling/swelling index or water-up-take (%); Ws= Weight of the swollen tablet and W_d = W weight of the dry tablet.

In vitro dissolution studies

The tablet were introduced in dissolution test equipment USP type II, containing 900 ml of 0.1N HCl and runat 50 RPM. Aliquot of 5 ml were withdrawn after every 1 hour up to 12 hours and changed with 5 ml of fresh dissolution medium. Each sample was analyzed at 422 nm by double beam UV spectrophotometer.[14]

Fourier transforms infrared (FTIR) spectroscopy

FTIR spectra of CLM andPMG peel powder carried out using FTIR Spectrophotometer. Samples were prepared using Potassium Bromide disks and measured from 4000 to 400 cm^{-1}.[17]

Thermal analysis

Differential scanning calorimetry thermograms of CLM, PMG peel powder,and final blend of the optimized Floating tablet were generated by Differential scanning calorimeter (Q200, TA Instruments, MIT, Aurangabad, Maharashtra, India). samples of 3 to 6 mg were kept in an aluminum pan and scanned over the temperature range of 30-300°C and the rate of the heating was 10°C per minute.[18]

Determination of gastric retention by x-ray imaging studies

Evaluation of gastric retention of CLMFloating tablet was performed on the rabbit by the use of radio-opaque marker barium sulfate. X-Ray imaging studies are the non-invasive method, provides identification or monitoring of total

GI residence time without affecting normal gastrointestinal motility.The CLM was replaced by using equivalent quantity of barium sulfate and rest of the ingredients were kept constant. Healthy rabbits of approximately 2.0 kg were fasted overnight and next day F5tablet was administered through plastic tubing followed by flushing of 25–30 ml of water. During the entire study, the rabbits had free access to water only. At different time intervals of 0, 1, 2, 4, 6, and 8 h, rabbits abdominal region was X-ray photographed in the supine position and observed for the nature and position of the Floating tablet.

Accelerated stability studies

The Optimized formulation F5 was subjected to stability studies at 40ºC ± 2 ºC/75% ± 5% RH and room temperature and analyzed after 3 monthsfor its physical characteristics, drug content, and dissolution after one month.

RESULTS AND DISCUSSION

Calibration Curve of CLM

The calibration curve of CLM was plotted by taking the absorbance of solutions (5-25 µg/ml) at 422 nm in 0.1 N HCl solution. The curve was drawn taking concentration on X-axis and corresponding absorbance on Y-axis. The curve was found to be linear at an R^2 value of 0.998 and thus obeyed Beer Lambert's law.

Pre-compression parameters

The angle of repose of the powder mixture for all formulations (F1–F9) ranged from 25.36±0.45 to 27.88±0.49 indicating excellent flow properties. Bulk and tappedof the powder mixture for all formulations varied from 0.40 ± 0.004 to 0.42 ± 0.002 gm/ml and from 0.463 ± 0.028 to 0.488 ± 0.030 gm/ml, respectively.[19] Hausner's ratios and Carr's index ranged from 1.12 ± 0.06 to 1.21 ± 0.07 and 11.11 ± 5.09 % to 16.60 ± 5.77 %, respectively. The results of flow properties are acceptable for granules.[20] The values of compressibility indices further confirmed the good compressibility of the prepared granules.[21]The Pre-compression parameters of the powder blends are shown in Table 3.

Post-compression parameters: The diameter of the obtained tablets were 12 mm while the mean thickness ranged from 4.1±0.36 to 4.4±0.48 mm. Mean hardness was in the range of 4.3±0.47 and 4.9±0.59 kg/cm2 indicating that the tablets are of sufficient strength to stand up to physical abrasion.[22] The percentage friability for all formulations was less than 1% which is an indication of exceptional mechanical resistance of the tablets.[23] The tablets confirmed no proof of capping, cracking, cleavage, or breaking after being removed from the friabilator. The percentage of mean drug content ranged from 95.63 to 99.06 % which met the standard pharmacopeial requirements i.e. 90–110%.[24] Since the powder blendwas free flowing, the obtained tablets were of uniform weight due to uniform die fill. The mean weight of tablets was found to be 594±0.58 to 599±0.59 mg. The USP specification is generally ±5 percent for tablets weighing 330 mg or more.[25] This means that no distinction was found in the weight of individual tablets from the labeled weight indicating uniformity of weight. The Post-compression parameters of the Floating tablets are shown in Table 4.

In vitro buoyancy

In the present study the floating system employed sodium bicarbonate as a gas-forming agent.[26]Sodium bicarbonate induced effervescence that leads to pore formation and consequently rapid hydration of the tablets thus enhancing their floating ability for up to 12 hours.The total floatingtimeof batches i.e. F1 to F3 areupto 8 hours and F4 to F9 beyond 12 hours andthe floating lag time was between 55 seconds and 100 seconds of all the batches.The F5 formulation exhibited 55 seconds. Effervescent formulations containing PMG peel powder showed good floating lag time and total floating time. This is due to the rapid hydration and subsequent formation of a viscous gelatinous layer when PMG peel powder was exposed to an aqueous medium.[27]This viscous gelatinous layer prevented the escape of evolved carbon dioxide from the formed matrices leading to decreased density, consequently a short lag time was needed for floating.[28]

Swelling studies: Swelling studies were performed on all batches from F1 to F9 for 12 hours. Result concluded that as time passes the swelling increases. The amount of polymer has a major impact on the swelling process, matrix integrity, floating capability and therefore a linear relationship exists between the swelling process and amount of polymer.The results of*in-vitro* swelling studies shows that after 12 hours the swelling index was between 94.20±2.3 and 99.20±5.5 % of formulations.

In vitro drug dissolution

The *In-vitro* drug dissolution of formulations F1 to F9 is subjected to dissolution studies. Formulation F5containing PMG peel powder of 100 mg and sodium bicarbonate 100 mg has shown sustained release for 12 hours. It was observed that as the concentration of $NaHCO_3$ increases the effervescence or liberation of CO_2 increases thereby reduces the Floating lag time and increases Floating buoyancy due to increased porosity by the gas-forming agent. The in-vitro drug release for the different formulation of PMG peel powder was found to be between 95.61±0.14 and 98.67±0.44.From the results obtained it may be concluded that optimum concentration for drug release is 100 mg of PMG peel powder. If it increased from 100 mg to 140 mg the drug release decreases and below 100 mg the total floating time increases.So F5 batch tablets containing 100mg PMG peel powder hada drug release of 98.67±0.44 which is selected as an optimized formulation

In vivo buoyancy study

In vivo buoyancy was determined by X-ray imaging studies on healthy rabbits. The animal dose was calculated using dose translation based on Body Surface Area. Figure5 depicts the position and nature of the tablets at different time intervals after oral administration.From the X-ray photographs it was concluded that the Floating tablets formulated with CLM and PMG peel powderremained in the gastric region even after 8 h of administration indicating good retention of the tablets in the stomach region.

FT-IR spectroscopy and DSC studies: Drug-excipients compatibility study of F5 formulation was conducted using FT-IR spectroscopy and DSC study. FTIR spectra were obtained for PMG polymer and total blend of F5 formulation prepared by direct compression technique the results are shown in Table 8. The F5 formulation exhibited characteristic peak for the OH group at 3297.17 cm^{-1}, CH_3group at 2918.26, Ether group (-O-)at1060.82 cm^{-1}. C=O from the keto group in the lactone ring appears at 1625.50 cm^{-1}. Charts for the blend of F5 formulation with PMG peel powder used in tablet formulations exhibited characteristic absorption peaks in the same range of pure drug peaks. Hence, it could be confirmed that there is no interaction between drug and excipients in this formulation the FTIR spectra are shown in Figure 3.

The DSC thermograms of pure drug, physical mixture of drug, PMG peel powder, and F5 formulation blend are shown in Figure4. The F5 formulationendothermic peakswere in agreementwith the documented DSC peaks in the literature under the same heating rate of 10°C/min. The obtained thermograms indicated that there is no positive evidence for theinteraction between Drug and ingredients of the optimized formulation.

Drug release kinetics

From the results given in Table 5,release kinetics for different formulations were calculated using Microsoft Office Excel 2007 version. The release data were analyzed by fitting the drug release profiles of all the formulations into zero, first, Higuchi, and Korsmeyer-Peppas model. Regression coefficients (R^2) were calculated for all the formulations. It is found that the passage of the drug through the matrix is dependent on the square root of time. When the release profile was plotted versus square root of time a linear relationship was observed with the regression coefficient close to one. Batches show 'n' higher than 0.5 and lower than 1, which concludes that the formulation exhibit anomalous transport mechanism. To analyze the release of a drug release mechanism in vitro drug release data is fitted in the various release equation and kinetic model i.e. Zero order, First order, Higuchi and Korsmeyer-Peppas for all formulated batches.

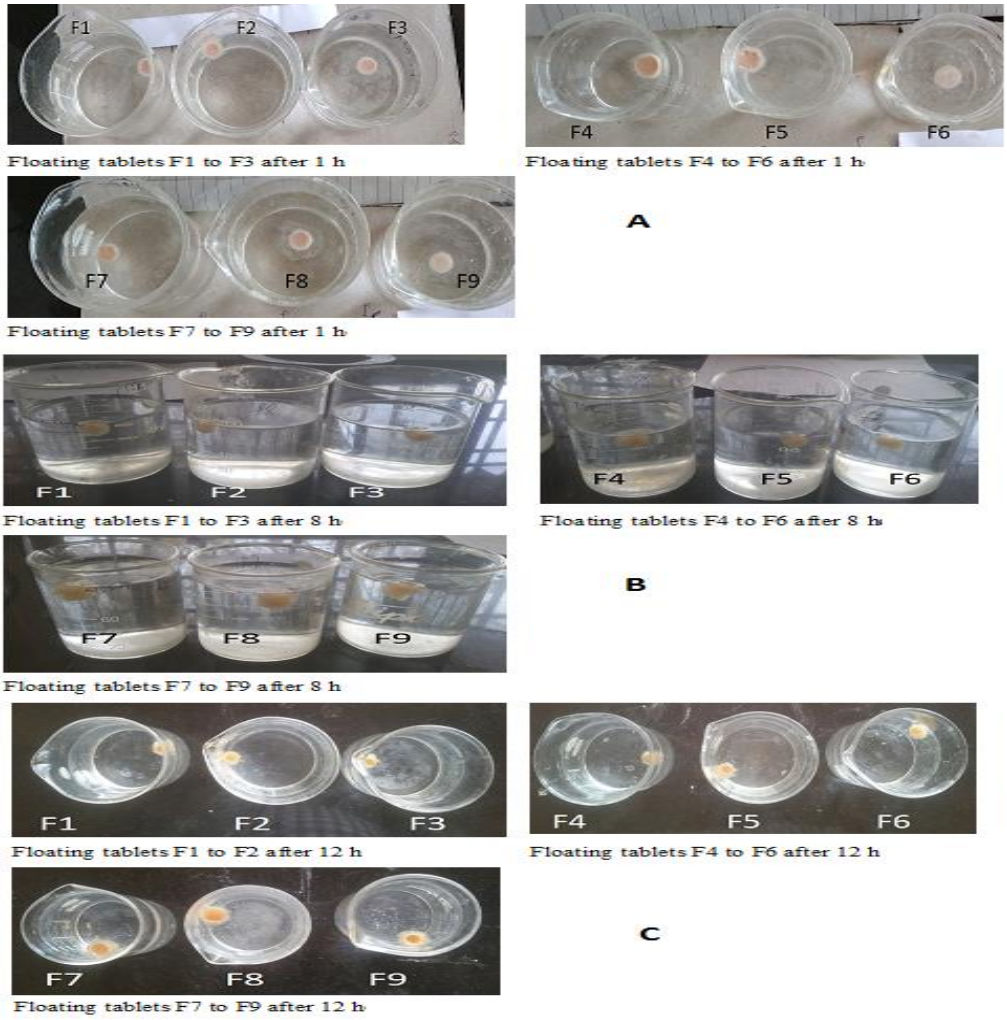

Fig. 1. Floating lag time and total Floating time of all floating formulations tabletsF1 to F9. (A) After 1 h, (B) After 8 h, (C)After 12 h.

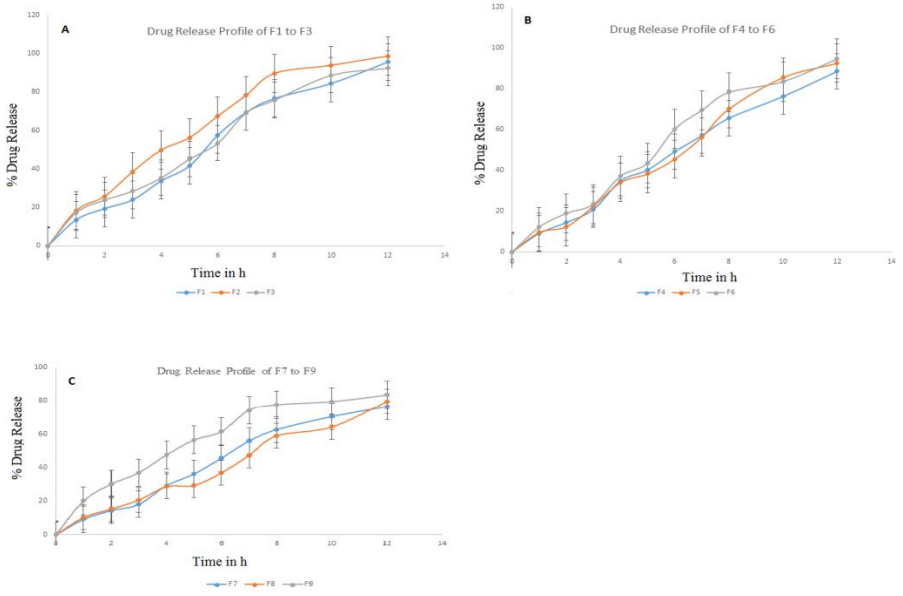

Fig. 2. The *In-vitro* drug release profile of all batches (A) F1 to F3, (B) F4 to F6, (C)F7 to F9.

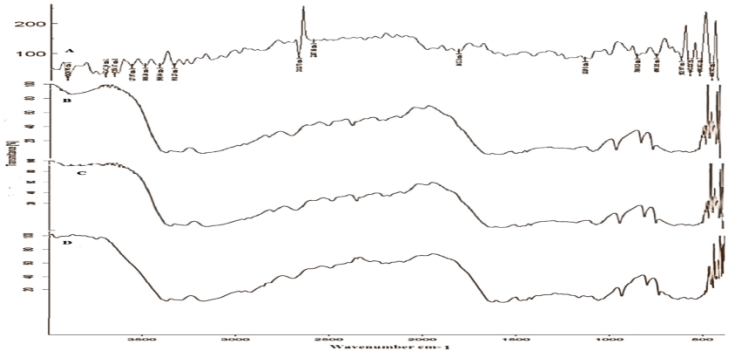

Fig. 3- FTIR Spectra of A) PMG peel powder, B) CLM pure drug C) Physical mixture of CLM and PMG peel powder D) F5 Formulation.

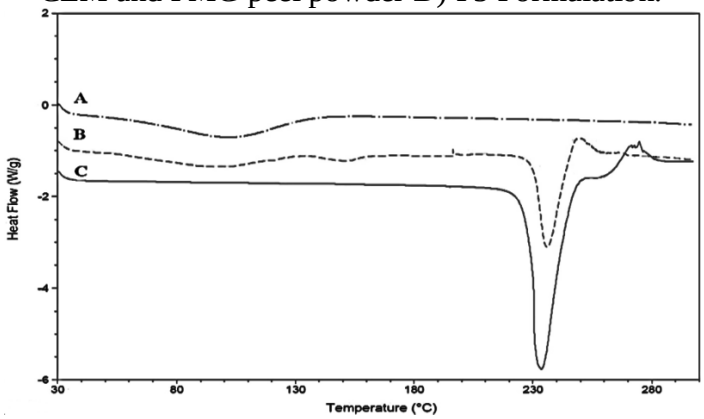

Fig. 4. DSC thermographs of A) PMG peel powder B) F5 formulation blend C) CLM.

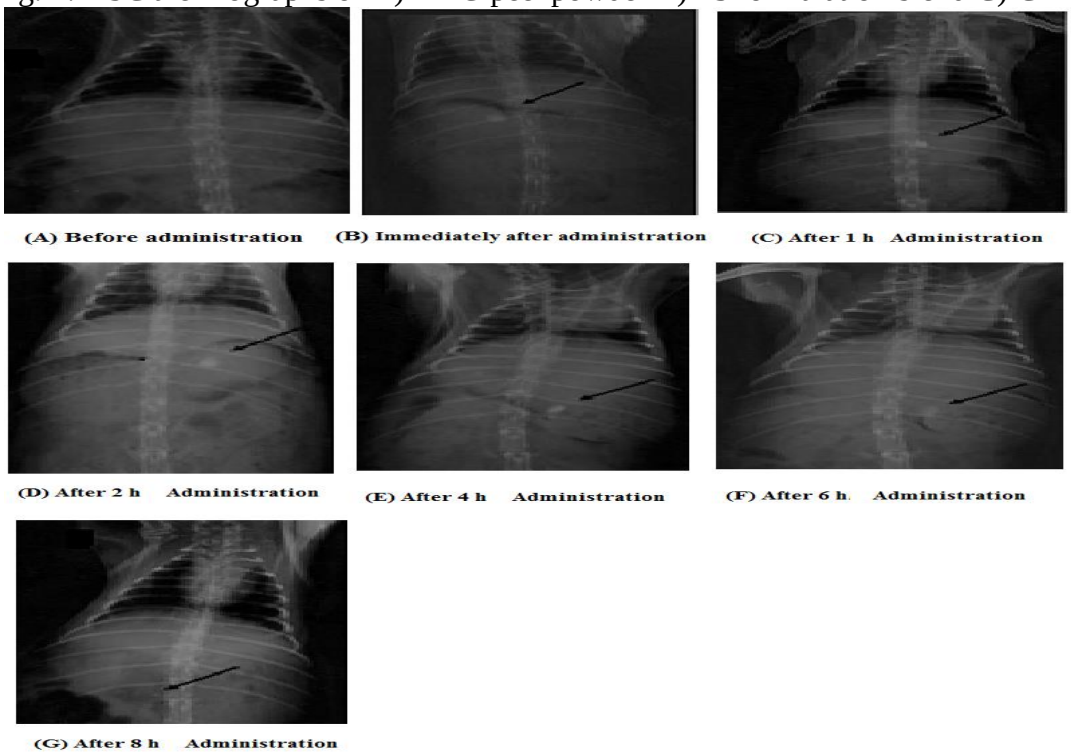

Figure5. X-ray photographs of GIT of rabbit at different time intervals after administration of Floating tablets. (A) Before administration, (B) Immediately after administration, (C) After 1 h, (D) After 2 h (E)After 4 h, (F) After 6 h, and (G) After 8 h post administration.

Table 1. Factorial design batches with different variables and their levels.

Formulation codes	Variable level code	
	X_1	X_2
F1	-1	-1
F2	-1	0
F3	-1	+1
F4	0	-1
F5	0	0
F6	0	+1
F7	+1	-1
F8	+1	0
F9	+1	+1

X_1- Amount of PMG peel powder (-1=50, 1=100, +1=140), X_2- Amount of sodium bicarbonate (-1=25, 1=50, +1=100)

Table 2. Formulation of CLMFloating tablets

Ingredients	Formulation codes								
(mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8	F9
CLM	250	250	250	250	250	250	250	250	250
PMG Peel powder	60	60	60	100	100	100	140	140	140
Sodium bicarbonate	25	50	100	25	50	100	25	50	100
PVP K30	10	10	10	10	10	10	10	10	10
Lactose	174	134	94	114	74	34	144	114	84
Magnesium stearate	06	06	06	06	06	06	06	06	06
Total	600	600	600	600	600	600	600	600	600

Table 3. Pre-compression parameters of the powder blends

Formula code	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's Index (%)
F1	25.36±0.45	0.40 ± 0.004	0.469 ± 0.038	1.15 ± 0.08	13.30 ± 6.66
F2	27.88±0.49	0.41 ± 0.001	0.479 ± 0.037	1.15 ± 0.08	13.33 ± 6.66
F3	25.65±0.43	0.40 ± 0.003	0.488 ± 0.030	1.20 ± 0.08	16.60 ± 5.77
F4	26.45±0.44	0.42 ± 0.002	0.470 ± 0.029	1.14 ± 0.06	12.20 ± 5.09
F5	25.66±0.45	0.41 ± 0.005	0.508 ± 0.028	1.21 ± 0.07	17.77 ± 5.09
F6	25.44±0.45	0.43 ± 0.007	0.476 ± 0.025	1.15 ± 0.07	13.33 ± 5.77
F7	25.65±0.44	0.40 ± 0.002	0.463 ± 0.037	1.14 ± 0.09	12.21 ± 6.93
F8	25.44±0.40	0.42 ± 0.002	0.463 ± 0.028	1.12 ± 0.06	11.11 ± 5.09
F9	27.44±0.39	0.40 ± 0.403	0.467 ± 0.034	1.15 ± 0.08	13.33 ± 6.66

Table 4. Post-compression parameters for Floating tablets.

Batches code	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Average Weight (mg)
F1	4.1±0.36	4.3±0.47	0.44±0.51	96.33±0.54	598.36±0.56
F2	4.2±0.39	4.3±0.56	0.42±0.52	99.12±0.54	599.35±0.59
F3	4.1±0.32	4.4±0.54	0.42±0.59	98.12±0.53	598.82±0.54
F4	4.3±0.35	4.5±0.54	0.45±0.56	95.75±0.49	594.32±0.58
F5	4.3±0.34	4.3±0.53	0.43±0.59	95.63±0.52	597.36±0.57
F6	4.4±0.45	4.4±0.59	0.46±0.58	98.23±0.59	598.65±0.49
F7	4.4±0.48	4.3±0.45	0.48±0.54	99.53±0.56	598.12±0.41
F8	4.3±0.49	4.3±0.55	0.47±0.51	96.06±0.59	597.13±0.49
F9	4.2±0.47	4.9±0.59	0.45±0.53	97.31±0.51	596.30±0.47

Table 5.Model dependent kinetic analysis.

Formulation code	Regression coefficient (R^2)				
	Zero order	First order	Higuchi	Korsmeyer Peppas	Release exponent 'n'
F1	0.6483	0.9135	0.9586	0.9701	0.5866
F2	0.9980	0.9520	0.9980	0.9810	0.5758
F3	0.6945	0.9788	0.9756	0.9961	0.5720
F4	0.7962	0.9490	0.9915	0.9860	0.5580
F5	0.9055	0.9830	0.9955	0.9747	0.5565
F6	0.8640	0.9770	0.9840	0.9865	0.5454
F7	0.2262	0.7940	0.8960	0.9820	0.5260
F8	0.7120	0.9362	0.9680	0.9675	0.5225
F9	0.7140	0.9410	0.9620	0.9230	0.5150

Table 6. Evaluation of optimized formulation during stability.

Parameters	**Initial**	**After 3 month**
Floating lag time (Sceonds)	55 ± 0.3	61 ± 0.5
Total floating time (Hours)	12	12
Hardness (kg/cm^2)	4.4±0.54	4.6±0.23
Drug content (%)	98.12±0.53	98.01±0.61
Drug release (%)	98.62±0.44	97.45±0.75
Thickness (mm)	4.1±0.32	4.1±0.33
Friability (%)	0.42±0.59	0.43±0.48
Weight of tablet (mg)	599 ± 0.54	599.5 ± 0.21
Swelling index (%)	99.41±1.4	101.1±1.7

For matrix treatment the R^2 value for F2, F3, and F4 shows close to one which exhibit matrix release kinetics. Whereas F5 exhibit Korsmeyer-Peppas kinetics of drug release.[29]

Accelerated stability studies: Optimized formulation F5 was subjected to stability studies and results are given in Table 6.Based on the results it can be concluded that, optimized tablets were stable during accelerated stability studies, without significant change in the Floating lag time, Floating time, drug content, and in vitro drug release characteristics.

CONCLUSION

Clarithromycin and PMG peel powder Floating tablets offered best-controlled release along with floating lag time of 55 sec and total floating time of 12 hours. TheTheDSCand FTIR study of the optimized formulaF5 showed the absence of interaction betweenDrug and the usedpolymer/additives which confirmed the compatibility among its ingredients. The*In-vivo* X-ray photographsof rabbits shows that the floating tablets remained in the gastric region even after 8 h of administration.

REFERENCES

1. Streubel A, Siepmann J, Bodmeier R. Drug delivery to the upper small intestine window using gastroretentive technologies. Curr. Opin. Pharmacol. 2007; 6: 501-508.
2. Santus G et.al. An in vitro in vivo investigation of oral bioadhesive controlled release furosemide formulations. Eur. J. Pharm. Biopharm. 1997;44: 39-52.
3. Deshpande AA, Shah NH, Rhodes CT, Malick W. Development of a novel controlled release system for gastric retention. Pharm. Res. 1997;14: 815-819.
4. Whitehead L et.al. Floating dosage forms: An in vivo study demonstrating prolonged gastric retention. J. Control. Rel. 1998;55: 3-12.

5. Chawla G, Bansal A. A means to address regional variability in intestinal drug absorption. J. Pharm. Tech. 2003;27: 50-68.
6. Moes AJ. Gastro retentive dosage forms. Crit. Rev. Ther. Drug Carr. Syst. 1993;10: 143-195.
7. Tavakoli N et.al. Development and evaluation of a monolithic Floating drug delivery system for acyclovir. Chem. Pharm. Bull. 2012;60: 172-177.
8. Labenz J. Current role of acid suppressant in Helicobacter pylori. Eradication therapy. Best. Pract. Res. Clin. Gastr. 2001;15: 413-431.
9. Darekar D. An overview on natural gum and its pharmaceutical application. International journal of universal pharmacy and biosciences. 2013; 2:535–547.
10. Prasanthi S and Vidyavathi M. Optimization of valsartan Floating tablets by 3^2 factorial design. Asian J. Pharm.2017; 11: S625-S634.
11. VishnumurthyV, Dheeraj N,Srikar S. Formulation and optimization of famotidine Floating tablets using 2^3 factorial design. Journal of Pharmacy Research 2012;5(12): 5280-5284.
12. Hadi MA, Babu VL, Pal N. Formulation and evaluation of sustained release matrix tablets of glimepiride based on combination of hydrophilic and hydrophobic polymers. J. Appl. Pharm. Sci. 2012; 2:101–107.
13. Jagdale SC et.al. Formulation and evaluation of gastroretentive drug delivery system of propranolol hydrochloride. AAPS PharmSciTech. 2009; 10:1071–1079.
14. Rao NGR, Hadi MA, Panchal H, Reddy BM, Formulation and evaluation of biphasic drug delivery system of Montelukast sodium for chronotherapy. World J. Pharm. Res. 2012;1: 757–775.
15. United States Pharmacopeia 24 and National Formulary 19, 2000 by United States Pharmacopeial Convention, INC, pp. 1941-43.
16. Tadros MI. Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: development, optimization, and in vitro–in vivo evaluation in healthy humanvolunteers. Eur. J. Pharm. Biopharm. 2010;74:332–339.
17. Chinthala CSK et.al. Formulation and evaluation of Gastroretentive floating tablets of gabapentin using effervescent technology. Int. J. Pharm. Biomed. Res. 2012;3: 202–208.
18. Doodipala N, Palem C, Reddy S, Rao Y. Pharmaceutical development and clinical pharmacokinetic evaluation of gastroretentive floating matrix tablets of levofloxacin. Int. J. Pharm. Sci. Nanotech. 2011; 4:1463–1469.
19. Kitaoka H, Wada C, Moroi R, Hakusui H. Effect of dehydration on the formation of levofloxacin pseudo polymorphs. Chem. Pharm. Bull. 1995;43: 649–653.
20. Couto RO et.al. Spray drying of Eugenia dysenterica extract: effects of in-process parameters on product quality. RevistaBrasileira de Farmacognosia 2013;23: 115–123.
21. Trivedi P, Verma A, Garud N, Preparation and characterization of aceclofenac microspheres. Asian J. Pharm. 2008;2: 110–115.
22. Wilson B, Sitarambhai PH, Sajeev M, Vinothapooshan G. Design and evaluation of sustained release matrix tablets of levofloxacin for effective treatment of microbial infections. Int. J. Drug Deliv. 2011;3: 305–314.

23. Manivannan R, Chakole V. Formulation and development of extended-release floating tablet of atenolol. Int. J. Recent Adv. Pharm. Res. 2011;3: 25–30.
24. Savic IM et.al. Application of mathematical modeling for the development andoptimization formulation with bioactive coppercomplex. Drug Dev. Ind. Pharm. 2013;39:1–7.
25. Garg A, Gupta M. Taste masking and formulation development & evaluation of mouth dissolving tablets of levocetirizinedihydrochloride. J. Drug Deliv. Ther. 2013;3: 123–130.
26. Bano R,Gauhar S, Naqvi SBS, Mahmood S. Pharmaceutical evaluation of different brands of levofloxacin tablets (250 mg) available in the local market of Karachi (Pakistan). Int. J. Curr. Pharm. Res. 2011;3: 15–22.
27. Pare A, Yadav S, Patil U. Formulation and evaluation of effervescent floating tablet of amlodipine besylate. Res. J. Pharm. Tech. 2008;1: 526–530.
28. Basak S, Jayakumar Reddy B. Formulation and release behavior of sustained-release ambroxol hydrochloride HPMC matrix tablet. Indian J. Pharm. Sci. 2006;68: 594–598.
29. Prajapati ST, Patel LD, Patel DM. Gastric floating matrix tablets: design and optimization using a combination of polymers. Acta Pharm. 2008;58: 221–229.
30. Dwarakanadha Reddy Peram, Swarnalatha, Design, development and *In vitro* characterization of Clopidogrel bisulfate floating drug delivery system, Journal of Comprehensive Pharmacy 2 (2), 48-56, 2015
31. Rocca JG, Omidian H, Shah K. Progress in gastroretentive drug delivery system, Business Briefing: Pharmatech: 2003;152-156.