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Original Article

FORMULATION, OPTIMIZATION AND EVALUATION OF FLOATING TABLETS CLARITHROMYCIN

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ABSTRACT

Objective: The present aim of this study was to formulate, optimize and evaluation of floating tablets of Clarithromycin.

Methods: Floating tablets of Clarithromycin were formulated using polymer HPMC K15M with sodium bicarbonate as gas generating agent by wet granulation method. A 3^2 factorial design were applied to systematically optimize the drug release profile. The amount of citric acid (X_1) and concentration of polymer HPMC K15M (X_2) was selected as independent variables. The drug release at 6 hours (Q6) and drug release at 12 hour (Q12), and diffusion exponent (n) was selected as dependent variables.

Results: The results of factorial design indicated that low level of HPMC K15M favors the preparation of floating controlled release of Clarithromycin tablets. The tablets were evaluated for thickness, hardness, weight variation, floating lag time, total floating time, swelling index, drug content uniformity and *in vitro* drug release in 0.1N HCL (pH 1.2). The *in vitro* dissolution profiles of all the prepared Clarithromycin floating drug delivery system formulations was found to extend the drug release over a period of 10 to 12 hours and the drug release rate decreased with increase in polymer concentration.

Conclusion: It can be concluded that the decreased in citric acid concentration in the formulation showed decreased in drug release, this is due to citric acid reaction with sodium bicarbonate resulting generation of carbon dioxide gas at a faster rate, increased rate of drug release. Increasing the concentration of HPMC K15M resulted in reduction of drug release.

Keywords: Floating tablets, Gastric retention, Clarithromycin, Factorial design.

INTRODUCTION

Oral route is the most convenient and extensively used route for drug administration. This route has high patient acceptability, primarily due to ease of administration. Over the year, oral dosage forms have become increasingly sophisticated with the major role being played by controlled release drug delivery system (CRDDS) [1, 2]. Drug that are easily absorbed from the gastro-intestinal tract (GIT) and having a short half life are eliminated quickly from the blood circulation. To avoid this problem, the oral controlled release formulations have been developed, as these will release the drug slowly into the GIT and maintain a constant drug concentration in the serum for a longer period of time. One of the feasible approaches to control the gastric residence time (GRT).

Gastro retentive dosage forms significantly extend the period of time over which drug may be released and thus prolong dosing intervals and increase patient compliance. Such retention systems are important for drug that are degraded in the intestine or for drug like antacids or certain antibiotics, enzymes that act locally in the stomach if the drug are poorly soluble in the intestine due to alkaline pH and then its retention in the gastric region may increase the solubility before they are emptied, resulting in increased bioavailability [3, 4]. Dosage forms with prolonged gastric residence time (GRT), i.e. Gastro-remaining or gastro retentive dosage forms (GRDF) will bring about new and important therapeutic options. For instance, they will significantly extend the period of time over which drugs may be released. The gastro retentive drug delivery systems can be retained in the stomach and assist in improving the oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability [5-9].

Drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT). Local or sustained drug delivery to the stomach and proximal part of the small intestine to treat certain conditions. Particularly useful for the treatment of peptic ulcers caused by *H. Pylori* infections. The various pharmacokinetic advantages like maintenance of constant therapeutic level over a prolonged period of time and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in the case of antibiotics [10-12].

For the present study Clarithromycin is selected as drug candidate to formulate floating tablets. Clarithromycin is **(**Chemical Name: 6-O-methylerythromycin) a semi-synthetic broad spectrum macrolide antimicrobial agent. Clarithromycin is soluble in chloroform, acetone, and dilute acids. Slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water. Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration. Clarithromycin is used in combination for the treatment of Helicobacter pylori infection and duodenal ulcer disease and for treatment of upper and lower respiratory tract infections. Floating systems having low density systems that have sufficient buoyancy to float over the gastric contents and remain in the stomach for a prolonged period. While the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastric retentive time and reduces the fluctuation in plasma drug concentration [13-15].

The major objective of the present work is to formulate, optimize and evaluate the floating tablets of Clarithromycin. Clarithromycin floating tablets are prepared by a conventional wet granulation method, by using sodium bicarbonate & citric acid as the gas generating agent and suitable polymer grade of HPMC.

MATERIALS AND METHODS

Materials

Clarithromycin was received as a gift sample from Maxwell Life Science, Mumbai (India). Hydroxy propyl methylcellulose K-15M (HPMC-K100M) was supplied by Colorcon Asia Pvt Ltd (Goa, India) and Sodium bicarbonate, citric acid, magnesium stearate, talc were

purchased from Poona Chemicals Laboratories (Pune, India). PVP K30M was purchased from S. D Fine Chemicals Mumbai. All other ingredients were of analytical grade.

Preparation of Clarithromycin floating tablets

Floating matrix tablets containing Clarithromycin were prepared by wet granulation technique using varying concentrations of different grades of polymers with sodium bicarbonate. Polymers and Clarithromycin were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol was used as granulating agent. Granules were prepared by passing the wet coherent mass through a # 16 sieve. The granules were dried in hot air oven at a temperature of 60 °C for 1 hour.

Dried granules were sieved through # 20 sieves and lubricated with magnesium stearate and talc just 4-5 min before compression. Lubricated granules were compressed using Karnavati Minipress tablet punching machine using 13 mm punches to obtain tablets of desired specifications [16, 17].

Table 1: Composition of Clarithromycin floating tablets

Ingredients(mg.)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Clarithromycin	500	500	500	500	500	500	500	500	500
HPMC K15M	75	100	125	75	100	125	75	100	125
Sod. Bicarbonate	70	70	70	70	70	70	70	70	70
Citric Acid	10	10	10	20	20	20	30	30	30
PVP K30M	40	40	40	40	40	40	40	40	40
Mg stearate	10	10	10	10	10	10	10	10	10
Talc	5	5	5	5	5	5	5	5	5
Total weight (mg)	710	735	760	720	745	770	730	755	780

Full factorial design

A 3^2 randomized full factorial design was constructed to study. In this design 2 factors were evaluated, each at 3 levels and experimental, trials were performed at all 9 possible combinations.

The amount of citric acid (X_1) and HPMC K15M (X_2) was selected as independent variables. The dependent variables chosen were percentage drug release at 6 hours (Q_6), percentage drug release at 12 hours (Q_{12}), and diffusion exponent (n).

Table 2: 3^2 Factorial design of the formulation

Coded values	Batch code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
X_1	-1	-1	-1	0	0	0	+1	+1	+1
X_2	-1	0	+1	-1	0	+1	-1	0	+1

Table 3: Translation of coded values to actual values

Coded values	Actual values	
	X_1	X_2
-1	10	75
0	20	100
+1	30	125

Where X_1-Amount of citric acid, X_2-Amount of HPMC K15 M., Q_6-percentage drug release at 6 hours, Q_{12}-percentage drug release at 12hours, n-diffusion coefficient.

Pre-compression evaluation

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend was taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and an angle of repose was calculated using the following equation.

$$\tan \theta = H/R \quad \text{(Eq.1)}$$

$$\text{Therefore, } \theta = \tan^{-1}(H/R) \quad \text{(Eq.2)}$$

Where, h= height of the powder cone and r= radius of the powder cone.

Bulk density

Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

$$\text{LBD} = \frac{\text{Weight of powder blend}}{\text{Untapped volume of the packing}} \quad \text{(Eq.3)}$$

$$\text{TBD} = \frac{\text{Weight of powder blend}}{\text{Tapped Volume of the packing}} \quad \text{(Eq.4)}$$

Compressibility index

The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's index} = \frac{\text{TBD- LBD}}{\text{TBD}} \times 100 \quad \text{(Eq.5)}$$

Hausner's ratio (HR)

This was calculated as the ratio of tapped density to bulk density of the sample

$$\text{HR} = \frac{\text{Tapped Density}}{\text{Bulk Density}} \quad \text{(Eq.6)}$$

Post-compression evaluation of clarithromycin floating tablets

Weight variation test

To study the weight variation twenty tablets of the formulation were weighed using an electronic balance and the test was performed according to the official method. Twenty tablets were selected randomly from each batch and weighed individually to check for weight variation.

$$\text{Percentage Deviation PD} = \frac{W_{avg} - W_{initial}}{W_{avg}} \quad \text{(Eq.7)}$$

Where,

W_{Avg} = average weight and

$W_{Initial}$ = initial weight

Drug content

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and the drug was extracted in 0.1N HCl. The drug content was determined measuring the absorbance at 288 nm after suitable dilution using a Simadzu UV-Visible double beam spectrophotometer 1800.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and hardness of the tablets was determined.

Thickness

The thickness of the tablets was determined by using Vernier calipers. Five tablets were used, and average value was calculated.

Friability test

The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed and transferred into Friabilator. The Friabilator was operated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again. The % friability was then calculated by

$$\text{Percentage Friability} = \frac{W - W_0 \times 100}{W} \quad \text{(Eq.}$$

Where, W_0 = initially weight

W= weight after friability

Percentages Friability of tablets less than 1% are considered acceptable.

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time method described by Dave B. S. The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of the dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant was measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

***In vitro* drug release study**

The release rate of from floating tablets was determined using The United States Pharmacopoeia (USP) dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37±0.5 °C and 50 rpm. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12h, and the samples were replaced with fresh dissolution medium. The samples diluted with 2 ml Folin-Ciocalteu's phenol reagent and 2 ml of 20% sodium carbonate solution and 0.1N HCl up to 10 ml. Absorbance of these solutions was measured at 760 nm using a Simadzu UV-Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Swelling index of Clarithromycin floating tablets

The swelling index of tablets was determined by using 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation 8.

$$WU\% = \frac{\text{Weight of swollen tablet - Initial weight of tablet}}{\text{Initial weight of the tablet}} \times 100 \quad \text{(Eq.9)}$$

RESULTS AND DISCUSSION

In the present study, FDDS (Floating Drug Delivery System) of Clarithromycin were prepared by using polymer HPMC K15M, using sodium bicarbonate as gas generating agent and PVP K30 as binder. FDDS tablets were prepared by wet granulation technique. Formulation was optimized by using different ratios of polymers, citric acid. The prepared FDDS tablets were evaluated for its hardness, friability, uniformity of weight, uniformity of drug content, drug-polymer interaction studies, *in vitro* floating studies and *in vitro* dissolution studies.

Full Factorial design

A statistical model incorporating interactive and polynomial term was used to evaluate the responses.

$$\mathbf{Y = b_0 + b_1X_1 + b_2X_2 + b_{11}X_1^2 + b_{22}X_2^2 + b_{12}X_1X_2}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_i (b_1, b_2, b_{12}, b_{11} and b_{22} is the estimated coefficient for the factor X_1). The main effect (X_1 and X_2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X_1X_2) showed how the response changes, when 2 factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity.

Table 4: Formulation and dissolution characteristics of batches in 3^{2}factorial designs

Batch code	Coded values		% release at 6 hr (Q_6)	% release at 12hr (Q_{12})	n value
	X_1	X_2			
F1	-1	-1	46.038	97.766	0.9996
F2	-1	0	50.324	93.945	0.7706
F3	-1	+1	55.797	83.321	0.5807
F4	0	-1	52.337	89.753	0.8217
F5	0	0	50.215	80.738	0.8127
F6	0	+1	43.993	76.859	0.9324
F7	+1	-1	57.879	85.006	0.5614
F8	+1	0	53.220	78.187	0.6708
F9	+1	+1	51.105	72.675	0.7290

Table 5: Multiple Regressions output for dependent variables

Parameters	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}	R^2
Q_6	49.7606	2.3276	-0.8932	4.1990	-1.3685	-3.9199	0.75963
Q_{12}	82.4081	-6.5888	-6.6117	2.6386	0.0629	0.3686	0.97623
n value	0.8118	-0.0881	-0.0234	-0.160	0.0657	0.1387	0.87489

The responses of formulation prepared by 3^2factorial designs are indicated in table 6 The data clearly indicate that the Q_6, Q_{12} and diffusion exponent (n) are strongly dependent on the selected independent variables. The fitted equation relating the response Q_6, Q_{12} and diffusion exponent (n) to the transformed factors are shown in equation 10, 11 and 12 respectively.

$Q_6 = 49.76+2.32X_1–0.89X_2+4.19X_1^2-1.36X_2^2-3.91X_1X_2$ (Eq.10)

($R^2 = 0.7596$)

$Q_{12} = 82.40-6.58X_1-6.61X_2+2.63 X_1^2+0.06X_2^2+0.36 X_1X_2$ (Eq.11)

($R^2= 0.97623$)

$n = 0.81-0.08 X_1-0.02 X_2-0.16 X_1^2+0.06 X_2^2+0.13 X_1X_2$ (Eq.12)

($R^2= 0.87489$)

The polynomial equation can be used to draw conclusion after considering the magnitude of coefficient and the mathematical sign it carries, (i.e., positive or negative). Positive or negative signs before a coefficient in quadratic models indicate a synergistic effect or an antagonistic effect for the factor. The high values of correlation coefficient (table 6) for Q_6 ($R^2 = 0.7596$), Q_{12} ($R^2= 0.9762$), n ($R^2= 0.8748$) indicate a good fit.

Equation no 10 for Q_6 showed b_1 & b_{11} positive but b_2, b_{12} & b_{22} negative this reveals that up to certain level increases in X_1 and $X_1^2$from-1 to+1 increases Q_6 after that point again decreases in Q_6 seen. Percentagerelease at 6 hr (Q_6) was found to be 46.038 to 57.879 for batches containing X_2 at-1 level, 43.993 to 55.797 to for batches containing X_2+1 level, 50.215 to 53.22 for batches containing X_2 at 0 level.

Equation no 11 for Q_{12} showed b_{12}, b_{11} & b_{22} positive but b_1 & b_2 negative this revails that up to certain level increases in X_1, X_2, $X_1^2$and $X_2^2$from-1 to+1 increases Q_{12}. Percentagerelease at 12 hr (Q_{12}) was found to be 85.006 to 97.766 for batches containing X_2 at-1 level, 72.675 to 83.321 for batches containing X_2+1 level, 78.187 to 93.945 for batches containing X_2 at 0 level.

Equation no 12 for n showed b_{12} & b_{22} positive, but b_1, b_2 & b_{11} negative this reviles that up to certain level increases in X_{12} and $X_2^2$from-1 to+1 increases n. Value of diffusion exponent (n) was found to be 0.5614 to 0.9996 for batches containing X_2 at-1 level, 0.5807 to 0.9324 to for batches containing X_2+1 level, 0.6708 to 0.8127 for batches containing X_2 at 0 level.

The main effects (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction terms (X_1, X_2, X_1X_2, X_1^2, X_2^2) shows the response changes when two or more factors are simultaneously changed.

The equation for Q_6 (Eq 10) suggested that the factor X_1 has the more significant effect on drug release at Q_6, therefore high level of factor is not selected for increasing drug release. From equation 11 it can conclude that single factor X_1 not more effect on Q_{12}, but factor in combination X_1 and X_2 shows positive effect.

It means that the when the value of X_2 increases Q_{12} decreases. From equation 12 negative sign of X_1 it concludes that diffusion exponent not depend on the value of X_1 but the magnitude of coefficient indicates that the factor X_2 has the more favorable effect on the dependent variables.

Fig. 1, 2 and 3 show the plot of the amount of citric acid (X_1) and an amount of HPMC K15M (X_2) versus Q_6, Q_{12}, and diffusion exponent (n) respectively. The plot was drawn using PCP-Dissso v 3software, India. The data demonstrate that both X_1 and X_2 affect the drug release (Q_6, Q_{12} and diffusion exponent (n)).

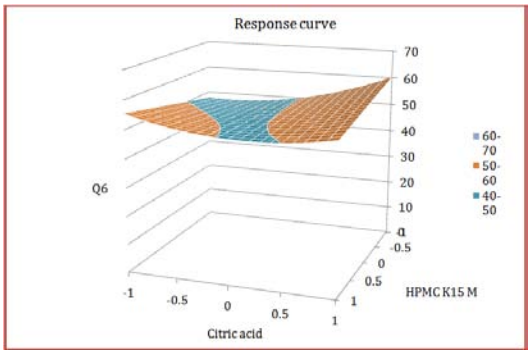

Fig. 1: Response surface plot for Q_6

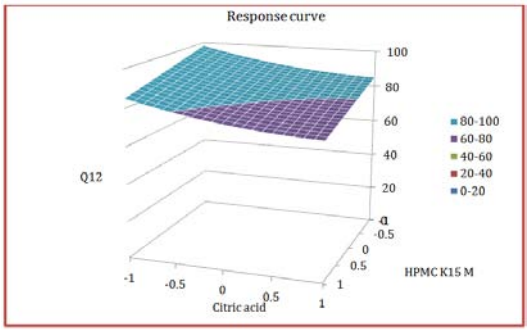

Fig. 2: Response surface plot for Q_{12}

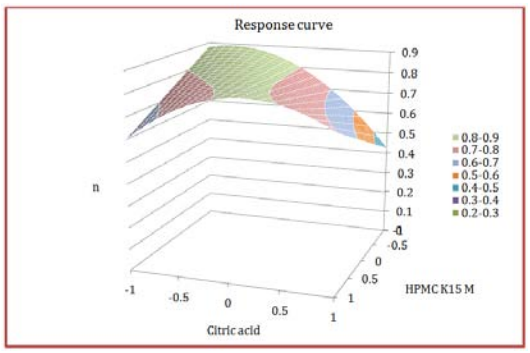

Fig. 3: Response surface plot for diffusion exponent (n)

It may also be concluded that the low level of X_1 (amount of citric acid) and the higher level of X_2 (amount of HPMC K15M) positive effect on diffusion exponent (n) favor the preparation of floating sustained release Clarithromycin tablets. The high value of X_1X_2 coefficient also suggests that the interaction between X_1 and X_2 has a significant effect on Q_{12}. It can be concluded that the drug release pattern may be changed by appropriate selection of the X_1 and X_2 levels. An increase in the concentration of citric acid (X_1) and amount of HPMC K15M (X_2), increase and decrease rate of release of Clarithromycin floating tablet respectively.

Fig. 1 shows the influence of content of HPMC K15M and citric acid on Q_6. It was found that percentage drug release increase with decreases in content of HPMC K15M and citric acid. Although the

content of HPMC K15M and citric acid significant influence on the Q_6 it ranged from 43.99–57.87. From the graph, it is observed that percentage drug release at 6 hr (Q_6) is increases.

Fig. 2 shows multiple regressions analysis for percentage drug release at 12 hr (Q_{12}) showed the significant contribution of both the factors on the response. Increasing the concentration of polymer (X_2) and citric acid (X_1) retardation of the drug release at Q_{12} is observed.

Fig. 3 shows the influence of content of HPMC K15M and citric acid on diffusion exponent. It was found that diffusion exponent rises with increase with content of HPMC K15M and citric acid. When the concentration of polymer is increased, the release of the drug tends to become slower. Although the content of HPMC K15M and citric acid significant influence on the diffusion exponent it ranged from 0.5614-0.9996, indicating anomalous drug release. Regarding the overall effect of both factors, it appeared that the diffusion exponent was affected more by the content of HPMC K15M, when concentration of polymer increases diffusion exponent decreases.

Evaluation of granules

Angle of repose (θ)

The angle of repose for the formulated blend was carried. Values of angle of repose ≤30° generally indicate the free flowing material and angle of repose ≥40° suggest a poor flowing material. The angle of repose of all the formulations fell within the range of 24 °.22' to 27 °.75'. **Compressibility index**

Carr's index below 15 % usually shows good flow characteristics, but above 25% indicates poor flowability. Compressibility index was carried out, it found between 9.52% and 15.90% indicating the powder blend has the required flow property for compression.

Hausner's ratio

Hausner's ratio is the simple method to evaluate stability of powder column and to estimate flow properties. Low range was observed for Hausner's ratio that indicates good flow ability. Many different types of angular properties have been employed to assess flowability. The Hausner's ratio was found between 1.10 and 1.18.

Bulk density & tapped density

Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of granules was found to be between 0.31 to 0.37 g/cm3 (Table.7). This indicates good packing capacity of granules. Bulk density and tapped density measurements found that density of a powder depends on particle packing and that density changes as the powder consolidates. The degree of consolidation is unique to the powder and ratio of these densities is related to interparticulate friction.

Table 6: Micrometric properties of powder blend

Batch Code	Angle of repose (θ)	Bulkdensity (gm/cm³)	Tapped density (gm/cm³)	Hausner's ratio (HR)	Carr's index (IC)
FT-1	24.22	0.37	0.44	1.18	15.90
FT-2	24.44	0.36	0.40	1.11	10.00
FT-3	26.67	0.34	0.38	1.10	9.52
FT-4	24.30	0.37	0.42	1.11	10.638
FT-5	25.19	0.35	0.39	1.10	9.580
FT-6	26.56	0.33	0.385	1.15	13.065
FT-7	25.11	0.36	0.42	1.15	13.095
FT-8	25.9	0.34	0.39	1.15	13.66
FT-9	27.75	0.31	0.35	1.13	11.98

Evaluation of tablets

Hardness and friability

Thus, the tablets found to be of good tensile strength to withstand the handling stress without break. Tablets hardness is a determining factor, with regard to the buoyancy of the tablets. Tablet hardness reflects differences in tablet density and porosity, which are supposed to result in difference release patterns of the drug by affecting the rate of penetration of the dissolution fluid at the surface of the tablet.

The hardness of the prepared GFDDS of Claritromycin was found to be in the range of 5.1 to 5.4 kg/cm² and is given in table 7. It ensures that the tablets can withstand mechanical impacts during packing, transportation and other processing operations. The present study of tablets is in within the limit and the slight variation in friability because of the variation in the compression force applied and its total weight. The friability of tablets is also depends on the moisture contents in it. The friability of all the tablets was to be less than 1% i.e. in the range of 0.79 to 0.99% given in table 7.

Uniformity of weight

All the prepared GFDDS tablets were evaluated for weight variation and the results are given in table 7. The percent deviation from the average weight was found to be within the prescribed official limits.

Uniformity of drug content

The drug content uniformity was examined as per I. P specification. All the batches of tablets were found to comply with uniformity of content test and results are mentioned in table 7. Drug content was in the range of 94.66±0.57% to 97.66±0.57% in the prepared formulation.

Table 7: Evaluation of physical parameters of Clarithromycin floating tablets

Batch Code	Weight variation Averagewt in (mg)±SD	Hardness (kg/cm²) ±SD	Thickness (mm) ±SD	Friability (%)	Drug Content Uniformity (%)±SD
F-1	708±1.15	5.2±0.25	5.10±0.10	0.87	97.66±0.57
F-2	735±2.08	5.2±0.3	5.10±0.20	0.81	96.66±1.52
F-3	759±1.52	5.3±0.25	5.16±0.05	0.92	96.66±2.08
F-4	718±1.52	5.4±0.25	5.23±0.11	0.83	97.66±0.57
F-5	743±0.57	5.3±0.30	5.30±0.10	0.99	97.00±1.00
F-6	770±2.0	5.2±0.17	5.06±0.15	0.90	94.66±0.57
F-7	732±3.05	5.5±0.20	5.13±0.15	0.82	98.66±0.57
F-8	754±0.57	5.1±0.17	5.13±0.11	0.79	96.66±0.57
F-9	778±0.57	5.3±0.20	4.93±0.15	0.89	94.66±2.08

In vitro buoyancy

The gas generated is trapped and protected within the gel, formed by hydration of polymer, thus decreasing the density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. The results presented in table 8. reveled that HPMC K15M produced tablets with good gel strength, entrapping CO_2 gas and imparting stable and persistent buoyancy. Floating lag time was in range of 20 sec to 45 sec. All the factorial design batches showed good *in vitro* buoyancy, also the tablet remained buoyant for 12 hours, but the tablet actually floated throughout the entire study. The above photograph of *in vitro* buoyancy study the optimized batch F1 tablet at initial 0 min seen at the bottom of beaker, at the 20 sec the tablet was seen at center of the beaker that is the floating lag time and at 1 min the tablet was seen at surface of the beaker.

Table 8: Floating properties of clarithromycin floating tablets

Formulation	Floating lag time (seconds)	Matrix integrity	Floating duration (hours)
F1	20	✓	>12
F2	22	✓	>12
F3	28	✓	>12
F4	25	✓	>12
F5	25	✓	>12
F6	30	✓	>12
F7	45	✓	>12
F8	35	✓	>12
F9	28	✓	>12

Swelling study

The swelling indexes of batches F1 to F9 are shown in fig. 4. Polymer matrices representing swellable matrix drug delivery systems are porous in nature. When these matrices come in contact with water or aqueous gastrointestinal fluid, the polymer absorbs the water and undergoes swelling or hydration. The rapid formation of a viscous gel layer upon hydration suggests that swelling is associated with polymer chain relaxation with volume expansion. The liquid diffuses through the polymer matrix at a constant velocity, and the rate of diffusion of the liquid and that of macromolecular relaxation of the polymer are almost of the same magnitude or, possibly, the rate of diffusion of the liquid is relatively higher than that of relaxation of the polymer segment.

This mechanism gives the idea regarding the water uptake study of various grades of polymer. This phenomenon is attributes to that the swelling is more due to water uptake and then gradually decreased due to erosion. Swelling measurement was performed separately in order to collect on the basis of weight increase over time. The swelling is due to presence of hydrophilic polymer, which gets wetted and allows water uptake leads to increase in its weight.

The swelling index was calculated with respect to time. As time increase, the swelling index was increased, because weight gain by tablet was increased proportionally with rate of hydration. Later on, it decreased gradually due to dissolution of outermost gelled layer of tablet into dissolution medium. The direct relationship was observed between swelling index and HPMC K15M increase, swelling index was increased.

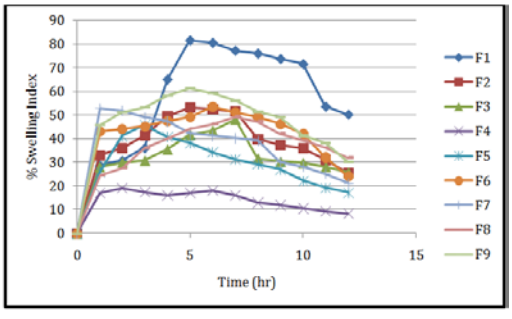

Fig. 4: Relationship between swelling index and time

In vitro dissolution study

Besides the satisfactory buoyancy, the matrix tablets are required to release Clarithromycin gradually over prolonged period. Hence, they were tested for release kinetics by conducting in-vitro dissolution test.

From the dissolution study it was concluded that release from the matrix is largely dependent on the polymer swelling, and drug diffusion. It was observed that all the tablets ascended to the upper one third of the dissolution vessels within a short time, and remained floated until the complete of release studies. The drug release study was carried out up to 12 hrs. The percentage drug release from batch F1 to F9 vary from 97.76 to 72.67% because of increase in concentration of polymer (HPMC K15M). High drug release is observed in F1 batch because of low concentration of polymer (HPMC K15M).

Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix, which may result in the retardation or decreases the drug release. Being water soluble polymers, they dissolve and form pores filled liquid in which drug can there after diffuse in dissolution medium. All the formulations were designed as dosage form for 12 hrs. Dissolution profiles of all batches were shown in fig. 5. From the dissolution study it was concluded that release from the matrix is largely dependent on the polymer swelling, drug diffusion.

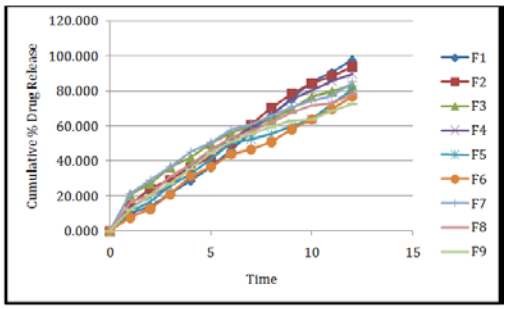

Fig. 5: *In vitro* release profile of clarithromycin all formulation

CONCLUSION

The present work was formulation, optimization and evaluation of floating tablet of Clarithromycin. Clarithromycin floating tablet is promising approach to achieve *in vitro* buoyancy by using hydrophilic polymer HPMC K15M and gas generating agent sodium bicarbonate and citric acid. A systemically study using a 3^2 full factorial design revealed that the amount of citric acid (X_1) and amount of hydroxy propyl methylcellulose (HPMC K15M) (X_2) had a significantly effect on Q_6, Q_{12} & diffusion exponent (n).

Decreased in citric acid concentration in formulation showed decreased in drug release, this is due to citric acid reaction with sodium bicarbonate resulting generation of carbon dioxide gas at a faster rate, increased rate of drug release. Increasing the concentration of HPMC K15M resulted in reduction of drug release. The formulation was optimized on the basis of floating ability, matrix integrity and *in vitro* drug release.

Thus, formulation F1 was selected as an optimized formulation because it gave the best results in terms of the required *in vitro* buoyancy study (Floating lag time 20 sec, Total floating time 12 hours), good matrix integrity and drug release in sustained release manner.

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CONFLICT OF INTERESTS

Declared None

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