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Research Article

FORMULATION AND EVALUATION OF GASTRORETENTIVE CLARITHROMYCIN FLOATING TABLETS

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ABSTRACT

The objective of the present study is to "optimize, formulate and evaluate the gastro retentive Clarithromycin Floating tablets". Clarithromycin is a broad spectrum antibiotic. It has high absorption in the upper part of GIT. It has low oral bioavailability. The GRDDS is able to prolong the retentive time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. The Preparation contains 15 formulations by using different polymers like HPMC K4M, HPMC K15M, HEC and HPC polymers are used. The prepared batches of Gastroretentive clarithromycin tablets can be evaluated forpre compression parameters like bulk density, tapped density, carr's index, hausner`s ratio, and angle of repose and physical evaluation of tablets like weight variation, thickness, hardness test, Floating lag time, dissolution studies. Formulation FHM8has given better controlled drug release and floating properties in comparison to the other formulations. It can be concluded that increase in the sodium bicarbonate concentration decreases the floating lag time and increases the floating time.

Keywords: GRDDS, Hydroxy Propyl Methyl Cellulose, Hydroxy Ethyl Cellulose.

INTRODUCTION

The GRDDS is able to prolong the retentive time of a dosage form in the stomach, thereby improving the oral bioavailability of the drug. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Main advantage of GRDDS is to maintain the constant level of drug over a prolonged period. So GRDDS is suitable drug delivery system to maintain the continuous drug level in the blood[1].

Drug absorption in the gastrointestinal tract is a highly variable procedure and prolonging gastric retention of the dosage form extends the time for drug absorption. FDDS promises to be a potential approach for gastric retention[2].

FACTORS AFFECTING GASTRIC RETENTION[3]

- **Density** – GRT is a function of dosage form buoyancy that is dependent on the density.
- **Size** – Gastric retention time of a dosage form is influenced by its size. Small-size tablets are emptied from the stomach during the digestive phase, while larger-size units are expelled during the house keeping waves. Dosage form units with a diameter of more than 7.5mm are reported to have an increased GRT.
- **Shape of dosage form** – The six shapes tested (ring, tetrahedron, cloverleaf, disk, string and pellet) displayed different gastric retention times, due to their size as well as the geometry of the systems. The tetrahedron resided in the stomach for longer periods than other devices of a similar size; likewise extended gastric retention was observed with the rigid rings. Tetrahedron and ring-shaped devices with a

flexural modulus of 48 and 22.5 kilo pounds per square inch (KSI) are reported to have better GRT 90% to 100% retention at 24 hours compared with other shapes.

- **Single or multiple unit formulation** – Multiple unit formulations show a more predictable release profile and insignificant impairing of performance due to failure of units, allow co-administration of units with different release profiles or containing incompatible substances and permit a larger margin of safety against dosage form failure compared with single unit dosage forms[4].
- **Fed or unfed state** – Under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and if the timing of administration of the formulation coincides with that of the MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer.
- **Nature of meal** – Feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.
- **Caloric content** – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats.
- **Frequency of feed** – The GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.
- **Gender** – Mean ambulatory GRT in males (3.4±0.6 hours) is less compared with their age and race-matched female counterparts (4.6±1.2 hours), regardless of the weight, height and body surface[5].
- **Age** – Elderly people, especially those over 70, have a significantly longer GRT.
- **Posture** – GRT can vary between supine and upright ambulatory states of the patient.
- **Concomitant drug administration** – Anticholinergics like atropine and propantheline, opiates like codeine and prokinetic agents like metoclopramide and cisapride increases the GR [3].

GASTRIC FLOATING DRUG DELIVERY SYSTEMS (GFDDS)[3]

Floating Drug Delivery Systems

Floating drug delivery systems have a bulk density lower than the gastric content. They remain buoyant in the stomach for a prolonged period of time, with the potential for continuous release of drug. Eventually, the residual system is emptied from the stomach. Gastric emptying is much more rapid in the fasting state and floating systems reply heavily on the presence of food to retard emptying and provide sufficient liquid for effective buoyancy[3].

Mechanism of Floating

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating in gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied form the stomach. This results an increased GRT and a better control of the fluctuations in the plasma drug concentration. However, besides a minimal gastric content needed to allow the proper achievement of the buoyancy retention principle, a minimal level of floating force (F) is also required to keep the dosage form reliably buoyant on the surface of the meal. To measure the floating force kinetics, a novel apparatus for determination of resultant weight (RW) has been reported in the literature. The RW apparatus operates by measuring continuously the force equivalent to F (as a function of time) that is required to maintain the submerged object. The object floats better if RW is on the higher positive side. This apparatus helps in optimizing FDDS with respect to stability and durability of floating forces produced in order to prevent the drawbacks of unforeseeable intragastric buoyancy capability variations. The Co_2 is released, causing the formulation to float in the stomach[5].

$$RW = F_{buoyancy} - F_{gravity}$$
$$= (D_f - D_s)\, g\, V,$$

Where RW =total vertical force

D_f =fluid density

D_s =object density

V =volume

G = acceleration due to gravity.

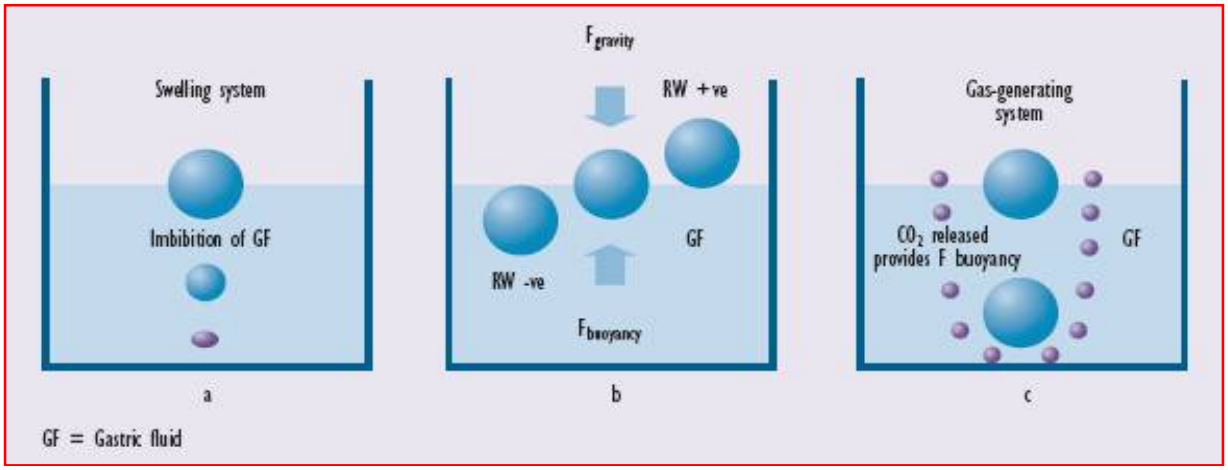

Fig.1: Mechanism of floating systems

MATERIALS AND METHODS

Clarithromycin was obtained as a gift sample fromAurobindopharma Ltd., Hyd.Hydroxypropyl methyl cellulose (HPMC) was obtained from Oxford Laboratory, Mumbai. Hydroxypropyl cellulose, Sodium carboxy methyl cellulose was obtained as a gift sample from S.D. Fine Chem. Ltd, Mumbai. All other chemicals used were of analytical grade.

Preparation of tablets

Matrix tablets each containing 250 mg of clarithromycin were prepared in different proportions of drug and polymer as per the formulae given in Table.1. The required quantities of medicament and matrix materials were mixed thoroughly in a glass mortar by following geometric dilution technique. Isopropyl alcohol (1.5%) solution was added and mixed thoroughly to form dough mass. The mass was passed through Sieve. No.12 to obtain wet granules. The wet granules were dried at 60^0C. The dried granules were passed through Sieve. No. 16 mixed with sodium bicarbonate and lubricated with magnesium stearate (1%) and talc (1%). They were then passed through mesh No. 100 just 4-5 min before compression and blended in a closed polyethylene bag. The tablet granules were compressed into tablets on a rotary multi- station punching machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) to a hardness of 4-6 kg/sq.cm using 12 mm punches[6].

Pre compression parameters[7,8]

Angle of Repose

The angle of repose of each powder blend was determined by glass funnel method. Powders were weighed accurately and passed freely through the funnel so as to form a heap. The height of funnel was so adjusted that the tip of funnel just touched the apex of the heap. The diameter of the powder cone so formed was measured and the angle of repose was calculated by using the following equation,

$$\tan \theta = \frac{h}{r}$$

Where,
h = height of cone
r = radius of powder cone

Bulk Density

Bulk density of the granules was determined by pouring gently 5 gm of sample through a glass funnel into a 10 ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density was calculated by the following formula,

$$\text{Bulk Density} = \frac{\text{Weight of samples in grams}}{\text{Volume occupied by the sample}}$$

Tapped Density

About 5 gm of granule was poured gently through a glass funnel into a 10 ml graduated cylinder. The cylinder was tapped from height of 2 inches until a constant volume was obtained. Volume occupied by the sample after 50 tappings were recorded and tapped density was calculated by the following formula,

$$\text{Tapped Density} = \frac{\text{Weight of samples in grams}}{\text{Volume of sample}}$$

Carr's Index

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, which is determined by the following equation,

$$\text{Compressibility Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

Hausner'sratiois related to interparticle friction and as such used to predict powder flow properties.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

ANALYTICAL METHOD FOR ESTIMATION OF CLARITHROMYCIN

UV- SPECTROSCOPY

The concentration of drug is estimated using uv-spectrophotometer at maximum wavelength. An UV Spectrophotometric method based on measurement of absorbance at 210 nm in a simulated gastric fluid pH 1.2 was used for the estimation of clarithromycin[6].

Preparation of standard solution:

An accurately weighed amount of 100mg of clarithromycin was transferred into a 100ml volumetric flask containing methanol to dissolve and then the volume was made up to mark with methanol.

Simulated Gastric Fluid pH 1.2:

Simulated gastric fluid of pH 1.2was made by dissolving 8.5 ml of Hcl in 1000ml ofdistilled water.

Procedure

The standard solution of clarithromycin was diluted with simulated gastric fluid of pH 1.2 to obtain a series of dilutions containing 5,10,15,20 and 25 µg of clarithromycin in 1 ml. The absorbance of these solutions was measured in UV spectrophotometer at 210 nm by taking simulated gastric fluid of pH 1.2 as blank[1, 2].

EVALUATIONS

Estimation of Clarithromycin in tablets

Five tablets were accurately weighed and powdered. Tablet powder equivalent to 250mg of medicament was taken into 25ml volumetric flask and 20 ml of methanol was added[38]. The mixture was shaken thoroughly for about 30 min. while warming in hot water bath to dissolve the clarithromycin. The solution was then made up to volume with methanol. The methanolic solution was subsequently diluted suitably with simulated gastric fluid of pH 1.2 and assayed for clarithromycin at 210 nm. Four samples of tablet powder were analyzed in each case[6].

Weight Variation

Ten tablets were selected and weighed in an electronic balance and average weight was calculated. The uniformity of weight was determined according to I.P. specification. As per I.P not more than two of the individual tablet weights may deviate from average weight by more than twice the percentage.

Hardness

For each formulation, the hardness of the matrix tablets prepared was tested using a Monsanto Hardness Tester.

Friability

For each formulation, the friability of 10 tablets was determined using Roche Friabilator, respectively. In friability test tablets were subjected to the combined effect of abrasion and shock by using a plastic chamber that resolves at 25 rpm droppings. The tablets fall from a distance of 6 inches with each revolution. Previously weighed 10 tablets were placed in friabilator, which is then set for 100 revolutions. Then the tablets were dusted and weighted.

$$\text{Friability} = \frac{\text{Weight loss}}{\text{Initial weight of the tablet}} \times 100$$

Floating lag time

The in vitro buoyancy was determined by floating lag time as per the method described by Rosa *et al*[38]. The tablets were placed in a 100-mL glass beaker containing simulated gastric fluid (SGF), pH 1.2, as per USP. The time required for the tablet to rise to the surface and float was determined as floating lag time[7].

Drug release study

Clarithromycin release from matrix tablets prepared was studied using 8 station dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37± 0.5^{0}C. 0.1N hydrochloric acid (900 ml) was used as dissolution fluid. A sample (5ml) of solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with 0.1N hydrochloric acid. Absorbances of these solutions were measured at 210nm using an ElicoUV-1700 UV/VIS double beam spectrophotometer. Cumulative percentage drug release was calculated[6].

Table 1: Formula for Clarithromycin Floating tablets containing HPMC K4M

Ingredients (mg)	FHM1	FHM2	FHM3	FHM4	FHM5
Clarithromycin	250	250	250	250	250
HPMC K4M	90	120	150	180	210
$NaHCo_3$	70	70	70	70	70
NaCMC	30	30	30	30	30
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6
MCC	148	118	88	58	28
Total weight	600	600	600	600	600

Table 2: Formula for Clarithromycin Floating tablets containing HPMC K15M

Ingredients (mg)	FHM6	FHM7	FHM8	FHM9	FHM10
Clarithromycin	250	250	250	250	250
HPMC K15M	60	90	120	150	180
$NaHCo_3$	70	70	70	70	70
NaCMC	30	30	30	30	30
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6
MCC	178	148	118	88	58
Total weight	600	600	600	600	600

Table 3: Formula for Clarithromycin Floating tablets containing HEC

Ingredients (mg)	FHE1	FHE2	FHE3	FHE4	FHE5
Clarithromycin	250	250	250	250	250
HEC	90	120	150	180	210
$NaHCo_3$	70	70	70	70	70
NaCMC	30	30	30	30	30
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6
MCC	148	118	88	58	28
Total weight	600	600	600	600	600

Table 4: Formula for Clarithromycin Floating tablets containing HPC

Ingredients (mg)	FHP1	FHP2	FHP3	FHP4	FHP5
Clarithromycin	250	250	250	250	250
HPMC K15M	90	120	150	180	210
$NaHCo_3$	70	70	70	70	70
NaCMC	30	30	30	30	30
Magnesium stearate	6	6	6	6	6
Talc	6	6	6	6	6
MCC	148	118	88	58	28
Total weight	600	600	600	600	600

RESULTS AND DISCUSSION

Table 5: Standard curve of clarithromycin in pH 1.2 at 210nm

Concentration µg/ml	Absorbance nm
0	0
5	0.0614
10	0.127
15	0.1803
20	0.2404
25	0.3095

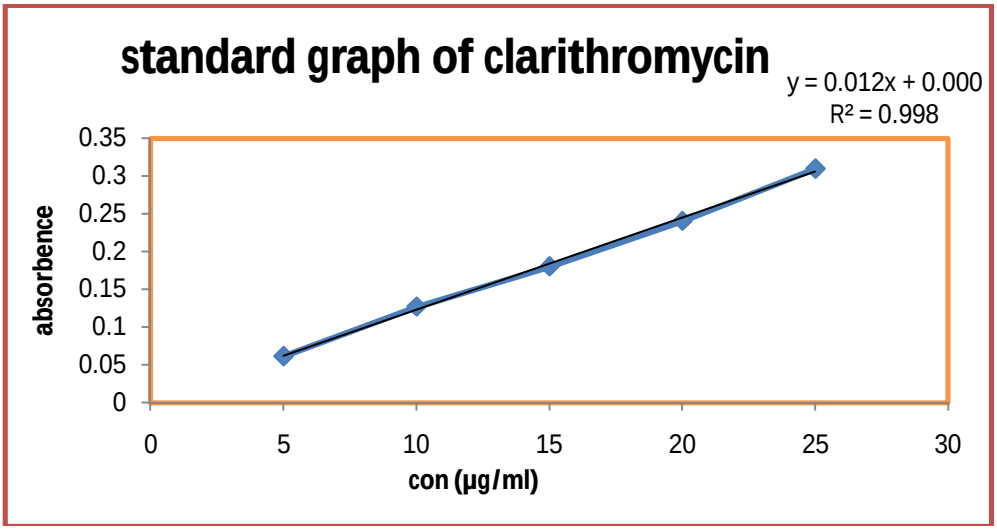

Fig. 2: Standard graph of Clarithromycin

PRECOMPERSSION PARAMETERS

Table 6:Preformulation studies of clarithromycin floating tablets containing HPMC K4M

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (degrees)	Carr's index	Hausner's ratio
FHMI	0.4294±0.002	0.498± 0.003	29.74 ± 0.05	13.89±0.2	1.16 ± 0.04
FHM2	0.508 ±0.003	0.653± 0.004	28.43 ± 0.04	22.21± 0.3	1.2± 0.02
FHM3	0.501± 0.005	0.601± 0.006	31.11 ± 0.06	16.6± 0.3	1.2 ± 0.05
FHM4	0.469± 0.002	0.536± 0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03
FHM5	0.487±0.003	0.602± 0.006	28.43 ± 0.04	16.6± 0.3	1.24± 0.05

Table 7: Preformulation studies of clarithromycin floating tablets containing HPMC K15M

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (degrees)	Carr's index	Hausner's ratio
FHM6	0.469± 0.002	0.536± 0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03
FHM7	0.487±0.003	0.602± 0.006	28.43 ± 0.04	16.6± 0.3	1.24± 0.05
FHM8	0.507±0.008	0.512± 0.003	30.23 ± 0.04	13.25 ± 0.24	1.16 ± 0.07
FHM9	0.469± 0.002	0.536± 0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03
FHM10	0.469± 0.002	0.536± 0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03

Table 8: Preformulation studies of clarithromycin floating tablets containing HEC

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (degrees)	Carr's index	Hausner's ratio
FHE1	0.487±0.003	0.602± 0.006	28.43 ± 0.04	16.6± 0.3	1.24± 0.05
FHE2	0.507±0.008	0.512± 0.003	30.23 ± 0.04	13.25 ± 0.24	1.16 ± 0.07
FHE3	0.469±0.002	0.536± 0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03
FHE4	0.507±0.008	0.512± 0.003	30.23 ± 0.04	13.25 ± 0.24	1.16 ± 0.07
FHE5	0.469±0.02	0.536±0.005	33.66 ±0.03	12.5±0.2	1.14 ± 0.03

Table 9: Preformulation studies of clarithromycin floating tablets containing HPC

Formulation	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (degrees)	Carr's index	Hausner's ratio
FHP1	0.487±0.003	0.602±0.006	28.43 ± 0.04	16.6± 0.3	1.24± 0.05
FHP2	0.507 ±0.008	0.512±0.003	30.23 ± 0.04	13.25 ± 0.24	1.16 ± 0.07
FHP3	0.507 ±0.008	0.511±0.003	30.23 ± 0.04	13.25 ± 0.24	1.16 ± 0.07
FHP4	0.469± 0.002	0.536±0.005	33.66 ± 0.03	12.5 ± 0.2	1.14 ± 0.03
FHP5	0.487±0.001	0.5023±0.21	31.66±0.02	13.5± 0.2	1.15± 0.03

Post-compression parameters

Table 10: Post compression of Clarithromycin Matrix Tablets containing HPMC K4M

Formulation Cod	Hardness (Kg/cm^2)	Weight Variation (%)	Friability (%)	Drug content (M	Floating Lag Time (sec)	Floating Time (Hrs)
FHM1	4-6	0.896±0.05	0.34±0.04	241.5±0.45	65	12
FHM2	4-6	1.08±0.15	0.53±0.12	243.2±0.57	62	12
FHM3	4-6	0.96±0.08	0.62±0.14	242.6 ±0.90	60	12
FHM4	4-6	0.997±0.12	0.48±0.04	245±0.63	52	12
FHM5	4-6	1.027±0.06	0.43±0.08	246 ±0.55	63	12

Table 11: Post compression of Clarithromycin Matrix Tablets containing HPMC K15M

Formulation Cod	Hardness (Kg/cm^2)	Weight Variation (%)	Friability (%)	Drug Content (Mg)	Floating Lag Time (sec)	Floating Time (Hrs)
FHM6	4-6	0.984±0.06	0.55±0.04	247 ±.034	58	12
FHM7	4-6	1.03±0.07	0.56±0.12	248 ±0.54	57	12
FHM8	4-6	0.895±0.06	0.45±0.14	247±0.90	38	12
FHM9	4-6	0.996±0.08	0.42±0.04	246 ±0.63	58	12
FHM10	4-6	1.052±0.10	0.53±0.10	248 ±0.55	56	12

Table 12: Post compression of Clarithromycin Matrix Tablets containing HEC

Formulation Coc	Hardness (Kg/cm²)	Weight Variation (%)	Friability (%)	Drug Content (Mg)	Floating Lag Time (sec)	Floating Time (Hrs)
FHE1	4-6	0.89±0.08	0.52±0.06	245.6±0.46	67	12
FHE2	4-6	0.99±0.15	0.29±0.07	246.6 ±0.50	69	12
FHE3	4-6	1.02±0.04	0.44±0.08	247.2±0.22	64	12
FHE4	4-6	0.96±0.04	0.38±0.12	245.6±0.91	69	12
FHE5	4-6	0.98±0.06	0.28±0.06	243.2±0.73	65	12

Table 13: Post compression of Clarithromycin Matrix Tablets containing HPC

Formulation Coc	Hardness (Kg/cm²)	Weight Variation (%)	Friability (%)	Drug Content(Mg)	Floating Lag Time (sec)	Floating Time (Hrs)
FHP1	4-6	0.97±015	0.45±0.02	246.3±0.46	71	10
FHP2	4-6	1.24±0.02	0.52±0.14	245.3±0.12	71	10
FHP3	4-6	0.998±0.18	0.26±0.08	247.5±0.34	69	10
FHP4	4-6	0.875±0.06	0.43±0.17	248.5±0.90	70	10
FHP5	4-6	1.09±0.12	0.53±0.02	247.5±0.66	69	10

Table 14: *In Vitro*drug release from floating tablets containing HPMC K4M

Time (hrs)	FHM1	FHM2	FHM3	FHM4	FHM5
0.5	31.54±1.08	29.96±0.99	23.85±0.86	22.46±0.97	13.81±0.97
1	37.54±0.94	34.65±0.94	27.55±1.19	28.65±1.05	15.72±1.10
2	43.61±0.87	41.70±0.15	32.16±0.68	32.73±0.99	21.52±0.92
3	54.53±1.31	49.27±1.11	37.43±0.91	38.92±0.97	25.84±1.07
4	61.82±0.98	59.44±1.06	42.67±0.99	44.56±1.01	30.62±0.90
5	68.39±0.99	67.33±0.97	47.67±1.05	49.98±0.91	35.67±0.94
6	76.54±0.78	70.58±1.11	51.23±0.69	56.51±1.06	40.49±1.05
7	81.39±1.03	76.45±0.94	55.40±1.14	61.29±0.85	44.66±1.05
8	90.56±0.98	82.55±0.86	59.51±0.95	66.38±0.90	48.60±0.91
9	96.53±1.56	89.40±1.13	61.49±1.14	70.64±.96	51.76±0.82
10	-	92.73±.95	65.47±0.99	75.92±1.13	56.31±1.00
11	-	94.99±.056	75.57±1.00	84.65±0.70	62.49±0.96
12	-	-	80.18±1.07	89.94±0.47	68.1±0.63

***Mean Percent of Clarithromycin Released ($\bar{x}$ ± s.d) (n = 3**

Table 15: *In vitro* drug release from floating tablets containing HPMC K15M

Time (hrs)	FHM6	FHM7	FHM8	FHM9	FHM10
0.5	32.60±0.08	28.96±0.99	22.12±0.90	20.65±0.84	15.39±0.84
1	38.45±0.99	35.83±0.91	34.56±0.93	24.55±1.05	19.85±1.05
2	47.60±0.90	46.32±0.95	39.11±0.89	28.16±0.99	24.68±0.95
3	55.26±1.06	52.87±1.05	45.67±0.92	32.58±1.01	27.58±0.97
4	64.40±0.98	62.22±0.92	54.63±0.99	37.53±0.94	33.07±1.01
5	71.54±1.09	69.68±1.04	59.89±1.04	45.39±0.91	38.42±1.06
6	77.47±0.78	76.39±0.95	65.73±1.05	52.44±0.92	46.84±0.96
7	82.39±1.00	80.88±0.98	69.99±0.98	58.55±1.06	54.66±0.85
8	89.56±0.81	85.56±0.86	74.83±0.99	61.54±0.98	58.77±0.91
9	96.89±0.99	89.51±0.84	80.99±1.04	67.43±0.96	61.83±1.04
10	-	95.39±1.07	85.68±0.92	73.70±0.83	66.40±0.75
11	-	-	94.35±1.00	78.51±0.90	71.62±0.98
12	-	-	98.67±0.83	85.36±1.07	78.10±1.09

*** Mean Percent of Clarithromycin Released ($\bar{x}$ ± s.d) (n = 3)**

Table 16: *In vitro* Drug release from floating tablets containing HEC

Time (hrs)	FHE1	FHE2	FHE3	FHE4	FHE5
0.5	33.35±1.03	26.72±1.08	21.52±0.86	26.48±0.94	20.25±0.93
1	37.82±0.99	32.54±1.01	26.36±1.05	31.65±0.89	25.63±1.05
2	48.89±1.03	40.36±0.69	32.84±0.91	38.16±0.99	31.48±0.95
3	57.85±1.06	48.59±1.06	38.56±1.02	47.65±1.09	37.65±1.02
4	66.48±0.95	57.48±0.85	43.82±0.99	56.53±1.07	42.28±0.94
5	73.31±1.03	65.70±1.04	52.56±0.94	64.33±1.10	50.71±0.98
6	79.46±0.89	73.71±0.95	56.88±1.05	70.54±0.92	54.88±0.96
7	88.20±0.89	80.80±1.04	67.64±0.98	75.76±0.86	59.63±0.85
8	94.83±1.06	87.58±0.88	78.56±0.76	81.30±1.02	65.92±0.88
9	-	90.91±1.01	86.991±0.93	87.44±1.06	71.06±1.03
10	-	95.39±1.07	94.67±0.92	93.80±0.84	76.38±0.97
11	-	-	-	94.51±0.89	81.94±1.05
12	-	-	-	-	85.98±0.86

*** Mean Percent of Clarithromycin Released ($\bar{x}$ ± s.d) (n = 3)**

Table 17: *In vitro*Drug release from floating tablets containing HPC

Time (hrs)	FHP1	FHP2	FHP3	FHP4	FHP5
0.5	23.85±1.09	27.45±0.99	28.77±0.86	19.87±0.94	22.56±0.96
1	29.72±0.89	33.69±1.05	36.86±1.02	26.56±0.89	29.56±1.05
2	35.99±1.03	41.11±0.98	43.68±0.99	33.61±0.99	35.61±0.75
3	47.65±1.06	49.88±0.85	48.78±1.05	39.15±1.09	40.49±0.99
4	56.98±0.95	58.76±1.04	54.15±0.97	42.72±1.07	44.35±1.07
5	63.53±1.06	66.32±0.89	63.67±0.85	47.56±1.10	49.51±0.98
6	79.96±0.89	75.68±0.95	68.88±0.86	52.92±0.92	54.28±1.05
7	88.82±1.05	83.86±1.02	78.85±0.76	58.16±0.86	59.63±0.87
8	95.87±0.98	89.18±0.76	86.74±0.89	65.39±1.02	64.31±0.98
9	-	95.96±1.05	91.38±1.08	68.53±1.06	69.84±0.89
10	-	-	94.64±0.86	70.22±0.84	72.66±0.98
11	-	-	-	73.64±0.89	75.46±1.01
12	-	-	-	76.39±0.86	78.93±0.96

*** Mean Percent of Clarithromycin Released ($\bar{x}$ ± s.d) (n = 3)**

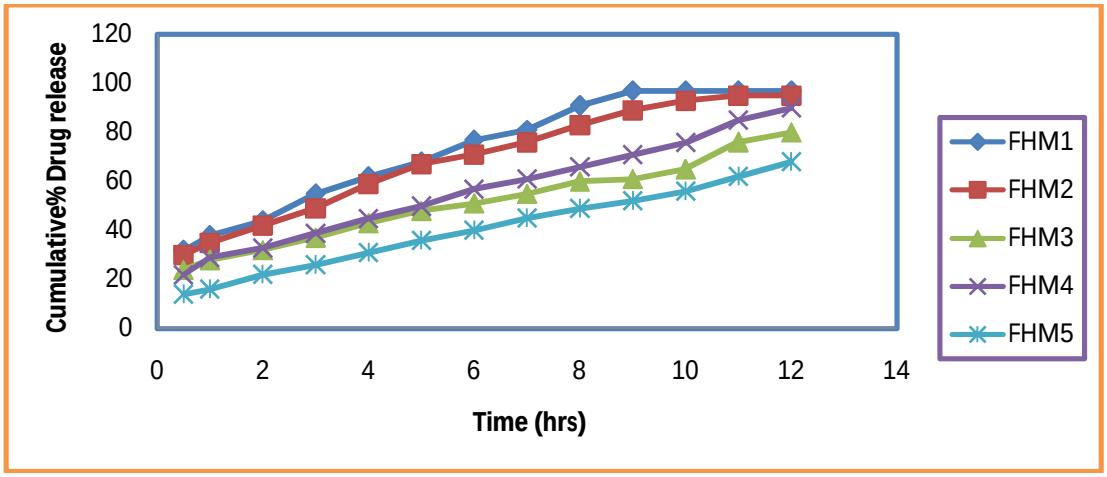

Fig. 3: Cumulative% Drug Release Vs Time Curve of tablets containing HPMC K4M

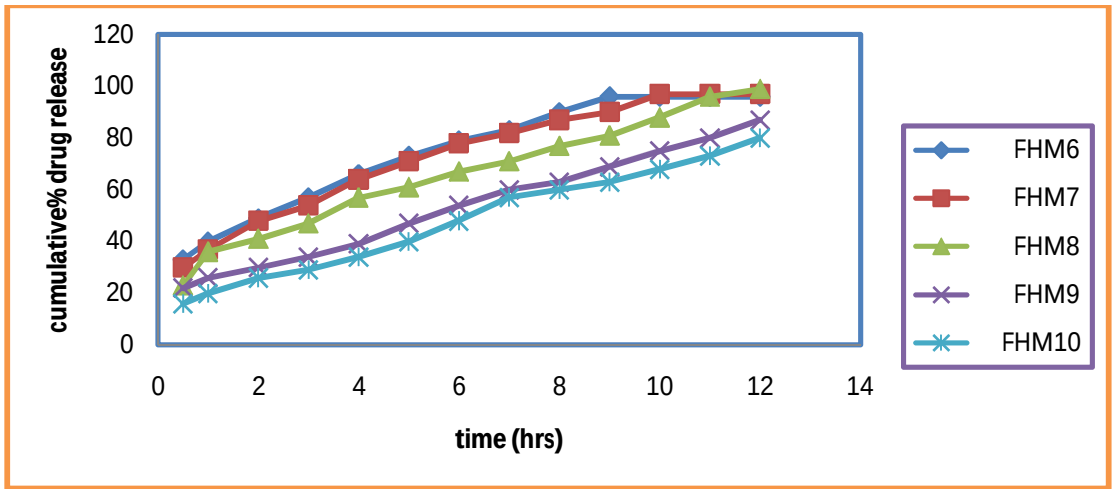

Fig. 4: Cumulative% Drug Release Vs Time Curve of tablets containing HPMC K15M

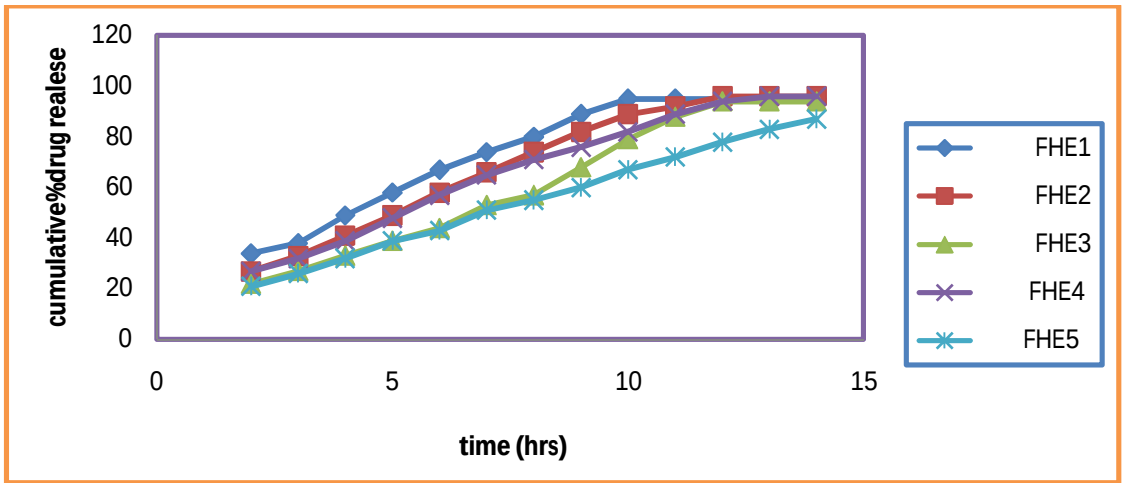

Fig. 5: Cumulative% Drug Release Vs Time Curve of tablets containing HEC

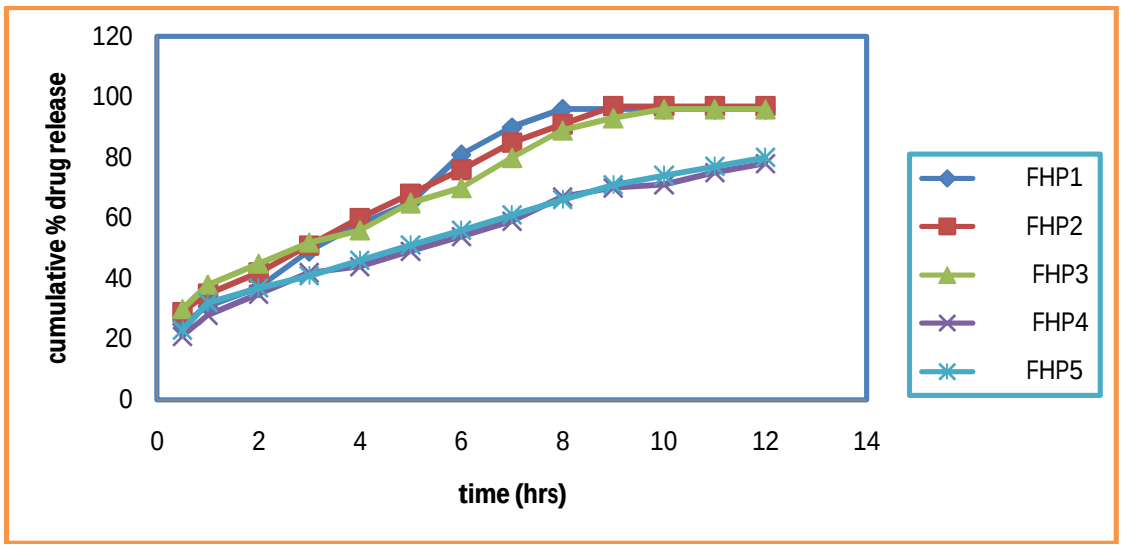

Fig. 6: Cumulative% Drug Release Vs Time Curve of tablets containing HPC

Table 18:Comparative Studies of Clarithromycin Floating Matrix Tablets

Formulation code	Polymer Concentration %(w/w)	Cumulative% Drug Release
FHM4	30	89.95
FHM8	20	98.63
FHE5	35	85.94
FHP5	35	78.93

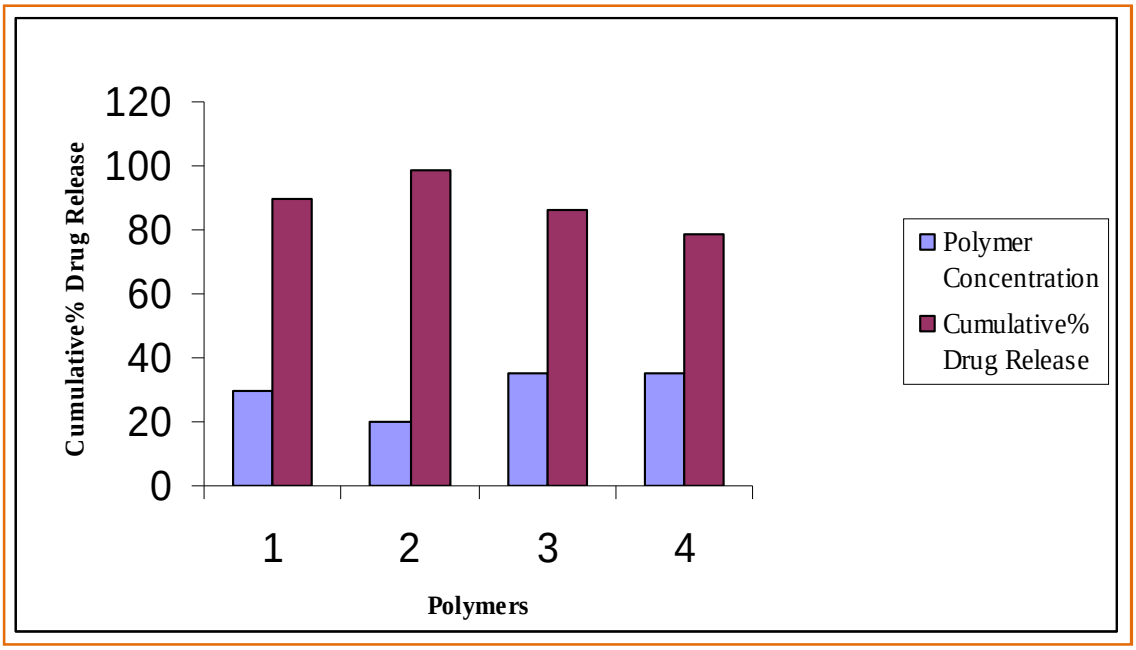

Fig. 7: Bar diagram showing the release of Clarithromycin at the end of twelve hour from various Gastroretentive floating tablets.

Drug release profile of all the optimized floating tablets

Table 19: Drug release profile of all the optimized floating tablets

Time (hrs)	FHM4	FHM8	FHE5	FHP5
0.5	22.46±0.97	22.12±0.90	20.25±0.93	22.56±0.96
1	28.65±1.05	34.56±0.93	25.63±1.05	29.56±1.05
2	32.73±0.99	39.11±0.89	31.48±0.95	35.61±0.75
3	38.92±0.97	45.67±0.92	37.65±1.02	40.49±0.99
4	44.56±1.01	54.63±0.99	42.28±0.94	44.35±1.07
5	49.98±0.91	59.89±1.04	50.71±0.98	49.51±0.98
6	56.51±1.06	65.73±1.05	54.88±0.96	54.28±1.05
7	61.29±0.85	69.99±0.98	59.63±0.85	59.63±0.87
8	66.38±0.90	74.83±0.99	65.92±0.88	64.31±0.98
9	70.64±.96	80.99±1.04	71.06±1.03	69.84±0.89
10	75.92±1.13	85.68±0.92	76.38±0.97	72.66±0.98
11	84.65±0.70	94.35±1.00	81.94±1.05	75.46±1.01
12	89.94±0.47	98.67±0.83	85.98±0.86	78.93±0.96

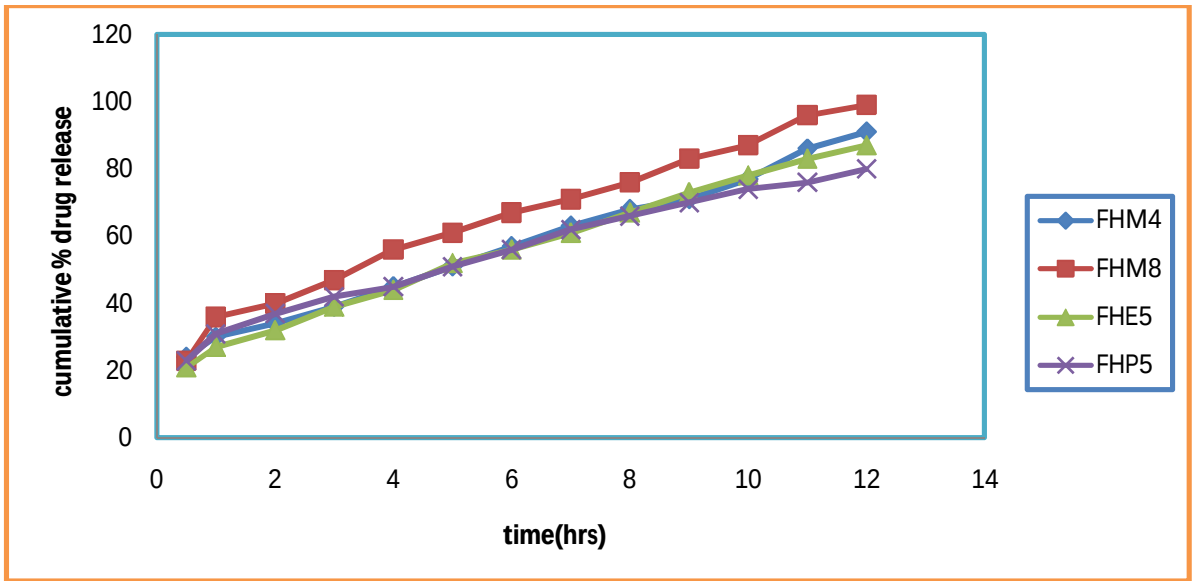

Fig. 8: Drug release profile of all the optimized floating tablets

DISCUSSION

In the present investigation the drug clarithromycin was selected for the design of GFDDS. This drug has its high absorption window in stomach and upper small intestine. But the sudden gastric emptying often affects their therapeutic efficacy. There are no reports on the use of floating concept in the formulation of gastric retention systems of clarithromycin. Hence in the present investigation, it is aimed to develop GFDDS of clarithromycin (effervescent floating tablets) with three different swellable polymers hydroxy propyl methyl cellulose (HPMC), hydroxyl propyl cellulose (HPC), hydroxyl ethyl cellulose (HEC).The current practice in preparing pharmaceutical products particularly aoral solid dosage forms is to have adequate and steady release of drug, since leads to controlled absorption with prolonged action with minimal side effects and maximal safety. Also the products are designed to deliver the drug at the required site or as close as possible.

Pre-compression evaluations

I. Bulk density, Tapped density, Carr's index, Hausner ratio and Angle of repose

Precompression parameters of clarithromycin are shown in **Table 11-14.** The bulk density of the formulation ranged between 0.42 ± 0.002 g/mL and 0.508 ± 0.003 g/mL. Tapped density varied between 0.498 ± 0.001 g/mL and 0.653 ± 0.026 g/mL. Carr's index value ranged between 12.5 ± 0.122% to 16.68 ± 0.274%. Hausner ratio was found between 1.12 ± 0.001 and 1.24 ± 0.003 and Angle of repose has been used as indirect method of quantifying power flow ability, and fallen between 28.43 ± 0.004 to 33.66 ± 0.439.

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include bulk density, tapped density, Carr's index, Hausner ratio and Angle of repose. Before formulation of floating tablets, the drug and ingredients were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP. All the formulations were fallen in good flow character based on angle of repose, compressibility index and Hausner ratio reports.

PREPARATION

The tablets were prepared by wet granulation method.

Post-compression evaluations

I. Weight variation, Thickness and diameter, Hardness, Friability and Drug content

Post-compression parameters of clarithromycin floating tablets are showed in Table16-19.. Weight variation of floating tablets ranged from 0.875 ± 0.06 to 1.24 ± 0.002. The hardness lies between 4.24 ± 0.164 and 5.91

± 0.109. The friability of all gastro retentive floating tablets of clarithromycin was found between 0.263 ± 0.002 and 508 ± 0.002. Drug content ranged between 96.92 ± 0.627 and 98.79 ± 0.242.
The average weights were found to be within (± 7.5) the prescribed official limits. The thickness of the floating tablet indicated that die fill was uniform. The thickness depends upon the size of the punch (12 mm) and the weight of the tablet (600 mg). Friability is needed for tablets to withstand force of compression applied during the manufacture of tablets and all the formulated floating tablets of clarithromycin were shown the percentage friability within the official limits (i.e. not more than 1 %). Formulations showed favorable drug content which were within the limits of specifications
Clarithromycin release from matrix tablets prepared was studied using dissolution rate test apparatus (Lab India, Disso 2000) employing a paddle stirrer at 50 rpm and at 37± 0.5^{0}C. 0.1N hydrochloric acid (900 ml) was used as dissolution fluid. A sample (5ml) of solution was withdrawn from the dissolution apparatus hourly for 12 hrs, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µ membrane filter and diluted to suitable concentration with 0.1N hydrochloric acid. Absorbances of these solutions were measured at 210nm using an ElicoUV-1700 UV/VIS double beam spectrophotometer. Cumulative percentage drug release was calculated.
The drug release was found to be better with 98% release in 12 hrs (Table no: 20). Thus the formulation prepared with HPMC k15 were found to be superior to the rest, among themFHM8was found to be as best formulation. Reasons for fluctuations of release depend on the selection of polymer . The FTIR picture indicates that the polymer and drug were compatible and there was no interaction.Thus the controlled release effervescent floating tablets of clarithromycin were prepared and evaluated.

CONCLUSIONS

Sodium bicarbonate in the acidic environment reacts with the acid and produces carbon dioxide. The evolved gas will get entrapped in the matrix leading to floating of the tablet. The floating lag time decreased as the concentration of the sodium bicarbonate increased.
Gastroretentive clarithromycin tablets can be formulated to increase the gastric residence time and thereby increase the oral bioavailability.Formulation FHM8has given better controlled drug release and floating properties in comparison to the other formulations.Formulated tablet showed satisfactory results for their evaluations like hardness, weight variation, floating lag time, floating time and *in vitro* drug release.Finally, it can be concluded that clarithromycin is a good alternative for to improve its oral bioavailability for the preparation of gastroretentive dosage forms because of its gastric stability, gastric absorption, less bioavailability and shorter biological half-life. It can be concluded that increase in the sodium bicarbonate concentration decreases the floating lag time and increases the floating time.

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