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# Formulation and In Vitro Evaluation of Garstroretentive Floating Tablets of Clarithromycin

**Swathi P[1], Heera B[1], Srinivas Rao Y[2], Bhavani B[2*]**
*1.AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam*
*2 .Vignan Institute of Pharmaceutical Technology, Visakhapatnam*

## ABSTRACT

Clarithromycin drug in the form tablet was formulated with different polymers. The object of the present work is preparing floating tablets in controlled fashion. The gas generating agent, sodium bicarbonate was added in different concentrations with varying amount of retardation polymers. Different grades of HPMC polymers HPMC K4M, K15M & K100M were used as retarding polymers. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F9 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits. From the dissolution data it was evident that formulation F7 was found to be best with maximum percent drug release of 96.90% upto 24 hours.

**Keywords:** Clarithromycin, HPMCK4M, HPMCK15M, HPMCK100M, Floating tablets.

*Corresponding Author Email: bhavani2008@gmail.com
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## INTRODUCTION

Oral drug administration still remains the preferred route of choice for delivery of drugs into systemic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half-lives are eliminated quickly from the systemic circulation. Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs.[1] Drugs that are easily absorbed from GIT have a short half life are eliminated quickly from the blood circulation and require frequent dosing. Prolonging the gastric retention of drugs is sometimes desirable for achieving therapeutic benefits of drug that are absorbed from the proximal part of GIT or those are less soluble in or are degraded by [2-4] alkaline pH or they encounter at lower part of the GIT

GRDDS improve controlled delivery of drugs that have an absorption window, by continuously releasing the drug for prolonged period of time before it reaches its absorption site.[5] Some of the drugs are characterized by a narrow absorption window in upper part of GIT (stomach and small intestine)[6] this is because the proximal part of the intestine exhibits extended absorption properties. Despite this, the extent of absorption at these sites is limited because the passage through this region is rapid. After a short period of time, the drug delivery system leaves the upper GIT and releases the drug in the non-absorbing digital segments of the GIT. As a sequence their oral bioavailability can be affected.[7]

Floating drug delivery system or hydro-dynamically controlled systems are low density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach, without affecting the gastric emptying rate for a prolonged period of time.[8] Floating drug delivery system is used particularly for drugs which act locally in the stomach, are absorbed in the stomach, have a narrow window of absorption, have poor solubility in alkaline pH or are unstable in the intestinal or colonic environment.[9]

Hence, the present investigation was carried out in the view of to design prolonged release clarithromycin GRDDS floating tablets of by direct compression technique to improve bioavailability and reduce dosing frequency.

## MATERIALS AND METHOD

Clarithromycin a gift sample from Aurabino Labs, Hyderabad, HPMC K100M, PVP, $NaHCO_3$ were purchased from Yarrow Chemicals, Mumbai. All the chemicals and sovents used were of

analytical grade.

**PREPARATION OF FLOATING TABLETS OF CLARITHROMYCIN:**

**Optimization of Sodium bicarbonate concentration:**

Sodium bicarbonate was employed as effervescent gas generating agent. It helps the formulation to float. Various concentrations of sodium bicarbonate were employed; floating lag time and floating duration were observed. Based on the efficiency of gas generating concentration of sodium bicarbonate was selected and preceded for further formulations.

**Table 1: Preliminary studies for optimizing sodium bicarbonate concentration**

| S.No | Excipients (mg) | EF1 | EF2 | EF3 |
|---|---|---|---|---|
| 1 | Clarithromycin | 15 | 15 | 15 |
| 2 | HPMC K 100M | 100 | 100 | 100 |
| 3 | PVP K30 | 25 | 25 | 25 |
| 4 | $NaHCO_3$ | 25 | 50 | 75 |
| 5 | Mg.Stearate | 2.5 | 2.5 | 2.5 |
| 6 | Talc | 2.5 | 2.5 | 2.5 |
| 7 | MCC pH 102 | Q.S | Q.S | Q.S |

**Preparation of clarithromycin gastro retentive tablets:**

Direct compression method has been employed to prepare floating matrix tablets of clarithromycin with HPMC K15M, HPMC K4M & HPMC K100M. All the ingredients were accurately weighed as per given table 2 and passed through mesh # 60. In order to mix the ingredients thoroughly drug and polymer were blended geometrically in a mortar and pestle for 15 min then PVP K 30, Micro crystalline cellulose, sodium bicarbonate, talc and magnesium stearate were mixed one by one. After thoroughly mixing these ingredients, the powder blend was passed through # 40mesh. Tablets were compressed by direct compression method on a multi punch12 station Rotary tablet compression machine (Cemach, machineries ltd, lab press 8 station, India) using 7mm flat round punches.

**Table 2: Composition of different batches of clarithromycin gastro retentive floating tablets**

| Formulation code | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Clarithromycin(mg) | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| HPMC K4M (mg) | 50 | 100 | 150 | - | - | - | | | |
| HPMC K15M (mg) | - | - | - | 50 | 100 | 150 | - | - | - |
| HPMCK100M(mg) | - | - | - | - | - | - | 50 | 100 | 150 |
| PVPK-30(mg) | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| $NaHCO_3$(mg) | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Magnesium stearate (mg) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| Talc (mg) | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 | 2.5 |
| MCC pH 102 (mg) | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S | Q.S |
| Total weight (mg) | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 | 250 |

**EVALUATION OF FLOATING TABLETS:**

Tablets were evaluated for both pre-compression parameters like bulk density, Carr's index , Hausner's ratio as well as their post compression parameters like various quality control tests such as tablet Thickness and Diameter, Hardness, Friability, uniformity of weight and content uniformity of drug and other specific evaluation tests for FDDS like floating lag time and total floating time & release rate of drug.

**Evaluation of Post Compression Parameters of Floating Tablets**

**Physical appearance**

The general appearance of tablets, its visual identity and overall elegance is essential for consumer acceptance. The control of general appearance of tablet involves measurement of number of attributes such as tablet size, shape, colour, presence or absence of odor, taste, surface texture and consistency of any identification marks.

**Tablet thickness and Diameter**

Thickness and diameter of tablets were important for uniformity of tablet size. The diameter size and punch size of tablets depends on the die and punches selected for making the tablets. Thickness and diameter were measured using vernier calipers. The thickness of the tablet related to the tablet hardness and can be used an initial control parameter. Tablet thickness should be controlled within a ±5%. In addition thickness must be controlled to facilitate packaging.

**Hardness**

This test is used to check the hardness of a tablet which may undergo chipping or breakage during storage, transportation and handling. In this five tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of $kg/cm^2$.

**Friability**

The friability test was carried out to evaluate the hardness and stability instantly to withstand abrasion in packing, handling and transporting.

**Uniformity of weight**

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range, this is done by sampling and weighing 20 tablets at random and average weight is calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage and none deviate by more than twice the percentage. The mean and standard deviation were determined.

**Content Uniformity**

This test is performed to maintain the uniformity of weight of each tablet which should be in the prescribed range according to the Indian Pharmacopoeia .The content uniformity test is mandatory for tablets whose average weight is below 50mg. This test is performed by taking twenty tablets were selected randomly, weighed and powdered. A quantity of powdered tablet equal to 100 mg of Clarithromycin was dissolved in 0.1 N HCL in 100ml volumetric flask.

***In vitro* buoyancy determination**

The floating characteristics of the GFDDS are essential, since they influence the *in vivo* behaviors of the drug delivery system. However there seemed to be no threshold value for the floating system to remain afloat under a physiological condition due to the latter's complication

**Floating Lag Time:**

The time taken by the tablet to emerge onto the surface of the liquid after adding to the dissolution medium simulated gastric fluid without pepsin, at pH 1.2, temperature 37±0.5$^{o}$C, paddle rotation at 50 rpm and 900ml as volume, it is measured using stopwatch

**Total Floating Time:**

The time taken by the tablet to float constantly on the surface of the gastric fluid without pepsin, at pH 1.2, temperature 37±0.5$^{o}$C, paddle rotation at 50 rpm, it is measured using stopwatch.

**Swelling behavior of tablets:**

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behavior of all formulation was studied. One tablet from teach formulation was kept in a petridish containing 0.1N HCl. At the end of 0.5 h and 1 h, the tablet was withdrawn, dried with tissue paper, and weighed.

***In vitro* dissolution studies**

Dissolution test was carried out using USP XXIV (model DISSO, M/s. Lab India) rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 0.1 N hydrochloric acid was used as dissolution medium 900ml and was maintained at 37±0.5$^{o}$C. Samples of 5ml were withdrawn at predetermined time intervals, filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, wherever necessary and were analyzed for the clarithromycin at 278 nm by using a double beam UV spectrophotometer (Shimadzu-2000). Each dissolution study was performed for three times and the mean values were taken.

**Release kinetics:** Data of *in vitro* release was fit into different equations to explain the release kinetics of prepared tablets. The kinetic equations used were zero – order and first order equations.

# RESULTS AND DISCUSSION

**Calibration curve of clarithromycin:**

The standard curve of clarithromycin was obtained and good correlation was obtained with $R^2$ value of 0.998.

**Standard Graph of clarithromycin in 0.1N HCl at 274nm**

The standard graph values of clarithromycin are tabulated as below in Table 3 and figure 1.

**Table 3: Standard Graph values of clarithromycin**

| Concentration (µg/ml) | Absorbance |
|---|---|
| 2 | 0.235±0.05 |
| 4 | 0.356±0.06 |
| 6 | 0.468±0.87 |
| 8 | 0.565±0.03 |
| 10 | 0.685±0.12 |

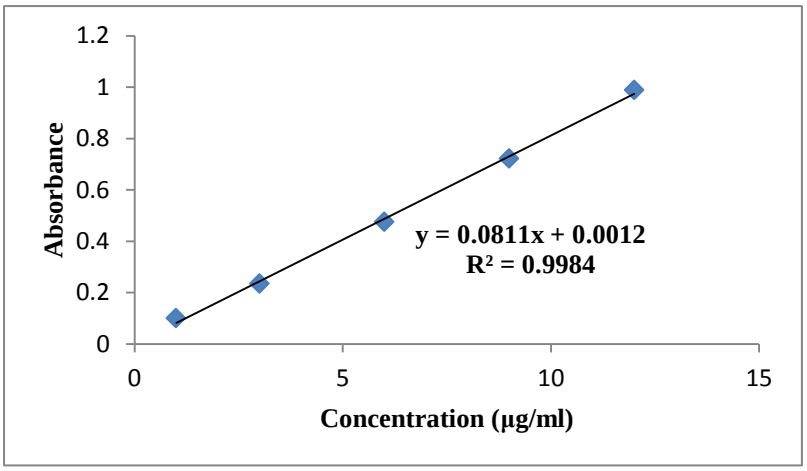


**Figure 1: Standard plot of clarithromycin**

**Pre-compression evaluation parameters of clarithromycin floating formulation blend:**

The powder blends were prepared by mixing of various ingredients mentioned (Table 4) and used for characterization of various flow properties of powder.

**Table 4: Micromeritic properties of powder blend**

| Formulation Code | Bulk density | Tapped density | Compressibility Index | Hausner's ratio |
|---|---|---|---|---|
| F1 | 0.49±0.07 | 0.57±0.01 | 16.21±0.06 | 0.86±0.06 |
| F2 | 0.56±0.06 | 0.62±0.05 | 16.87±0.05 | 0.98±0.05 |
| F3 | 0.52±0.03 | 0.68±0.07 | 17.11±0.01 | 0.64±0.03 |
| F4 | 0.54±0.04 | 0.64±0.08 | 17.67±0.08 | 1.12±0.04 |
| F5 | 0.53±0.06 | 0.67±0.03 | 16.92±0.04 | 1.2±0.08 |
| F6 | 0.56±0.05 | 0.66±0.06 | 17.65±0.09 | 1.06±0.09 |
| F7 | 0.58±0.06 | 0.69±0.04 | 16.43±0.05 | 0.76±0.03 |

| | | | | |
|---|---|---|---|---|
| F8 | 0.48±0.05 | 0.57±0.02 | 17.97±0.02 | 1.15±0.09 |
| F9 | 0.54±0.08 | 0.62±0.03 | 17.54±0.09 | 1.17±0.02 |

**Bulk density:**

The bulk density of all the formulations was found to be in the range of 0.43±0.07 to 0.671±0.06 (gm/cm$^3$) showing that the powder has good flow properties.

**Tapped density:**

The tapped density of all the formulations was found to be in the range of 0.57 to 0.69 showing the powder has good flow properties.

**Compressibility index:**

The compressibility index of all the formulations was found to be ranging between 16 to 18 which indicate that the powder has good flow properties.

**Hausner ratio:**

All the formulations has shown the hausner ratio ranging between 0 to 1.76 indicating the powder has good flow properties.

**Post compression evaluation parameters of clarithromycin floating tablets:**

**Appearance:**

The tablets were observed visually and did not show any effect such as capping, chipping and lamination.

**Physical characteristics:**

The physical characteristics of clarithromycin floating mini tablets (F1 to F9) such as weight variation, thickness, hardness, friability and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books as given Table 5.

**Thickness:**

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness can result in problems with packaging as well as consumer acceptance. There no marked variation in the thickness of tablets within each formulation indicating uniform behaviour of powders throughout the compression process. The thickness of the tablets of all formulations was found to be within the range of 4.11 to 4.33 mm.

**Hardness:**

A difference in tablet hardness reflects difference in tablet density and porosity. The hardness of tablets was found to be in the range of 3.9 Kg/cm$^2$ to 4.5 Kg/cm$^2$

**Percentage friability:**

Percentage friability of all formulations was found to be in the range of 0.38% to 0.60%.This indicates good handling property of the prepared tablets.

**Weight variation:**

The average weight of the tablet is 150mg. The Pharmacopeial limit for percentage deviation is ±5%. The weights of all tablets were ranged from 149.2mg to 150.5mg.

**Drug content:** All the floating tablets formulations shown good uniformity in drug content and they contain 97.2 to 101.33% of clarithromycin which is within the specified limit.

***In-vitro* buoyancy studies**

To provide in vitro buoyancy, an effervescent approach was selected. Sodium bicarbonate was added as a gas-generating agent. As the dissolution medium (0.1N HCl) imbibed into the tablet matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the generation of $CO_2$. The generated gas was entrapped and protected within the polymer and thus decreasing density of the tablet. As the density of the tablet falls below 1, the tablet became buoyant. The system should float in a few minutes after contact with gastric fluid to prevent the dosage form from transiting into the small intestine together with food. All the formulations (F1to F12) showed the floating lag time of <146 sec.

**Table 5: Evaluations of post-compression parameters of tablets**

| F. Code | Weight variation (mg) (±SD) | Thickness (mm) (±SD) | Hardness (Kg/cm$^2$) (±SD) | Friability (%) | Drug content (% ±SD) | Floating lag time (sec) | Floating buoyancy time (hrs) |
|---|---|---|---|---|---|---|---|
| F1 | 245±0.04 | 4.11±0.07 | 4.4±0.01 | 0.48±0.01 | 100.8±0.01 | 89 | 2 |
| F2 | 251±0.01 | 4.13±0.01 | 4.2±0.05 | 0.38±0.06 | 97.8±0.02 | 112 | 3 |
| F3 | 249±0.02 | 4.14±0.02 | 4.5±0.02 | 0.46±0.04 | 99.9±0.09 | 134 | 4 |
| F4 | 256±0.05 | 4.14±0.06 | 4.1±0.09 | 0.40±0.09 | 101.33±0.03 | 104 | 5 |
| F5 | 261±0.08 | 3.96±0.04 | 4.4±0.05 | 0.60±0.03 | 100.07±0.08 | 114 | 7 |
| F6 | 243±0.09 | 4.26±0.09 | 4.5±0.02 | 0.43±0.08 | 95.6±0.09 | 145 | >24 |
| F7 | 256±0.01 | 4.31±0.02 | 4.2±0.03 | 0.5±0.02 | 98.9±0.07 | 87 | >24 |
| F8 | 255±0.08 | 4.18±0.09 | 3.9±0.09 | 0.52±0.05 | 100.2±0.04 | 134 | >24 |
| F9 | 261±0.07 | 4.28±0.08 | 4.2±0.08 | 0.45±0.09 | 99.8±0.08 | 176 | >24 |

***In Vitro* drug release studies**

From the above graph it was evident that the formulations prepared with HPMC K4M showed complete drug release within 4 hrs only. The tablets were floated immediately but they were unable to retain their shape and integrity for not more than 4 hrs. Hence they were not considered.

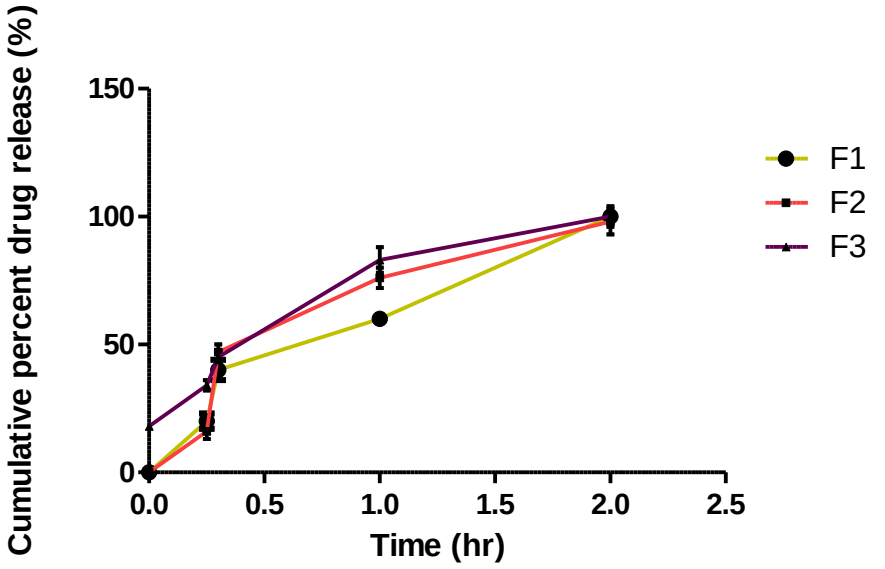


**Figure 2: *In vitro* drug release profile of tablets with HPMC K4M as polymer**

From the above graph it was evident that the formulations prepared with HPMC K15M retarded drug release. Formulations F4 & F5 were unable to retard drug release upto desired time period. F6 formulation was retarded the drug release up to 12 hrs and showed maximum of 89.87% in 12 hrs.

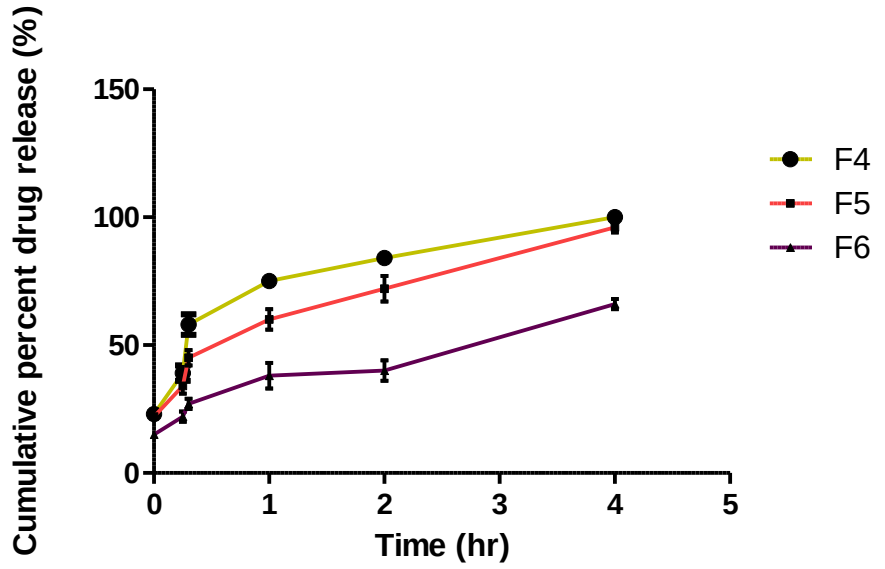


**Figure 3: *In vitro* drug release profile of tablets with HPMC K15M as polymer**

The *In vitro* dissolution studies of floating tablets of Clarithromycin were conducted in simulated gastric fluid 0.1N HCl for 12 hr. The cumulative percentage drug release after 12hrs was found to be 96.90%, 89.87% and 84.58% for formulations F7, F6 & F8 respectively. Formulation F7

obtained the desired drug release profile and floated with Lag time of 87sec, for the reasons it was considered as the best formulation.

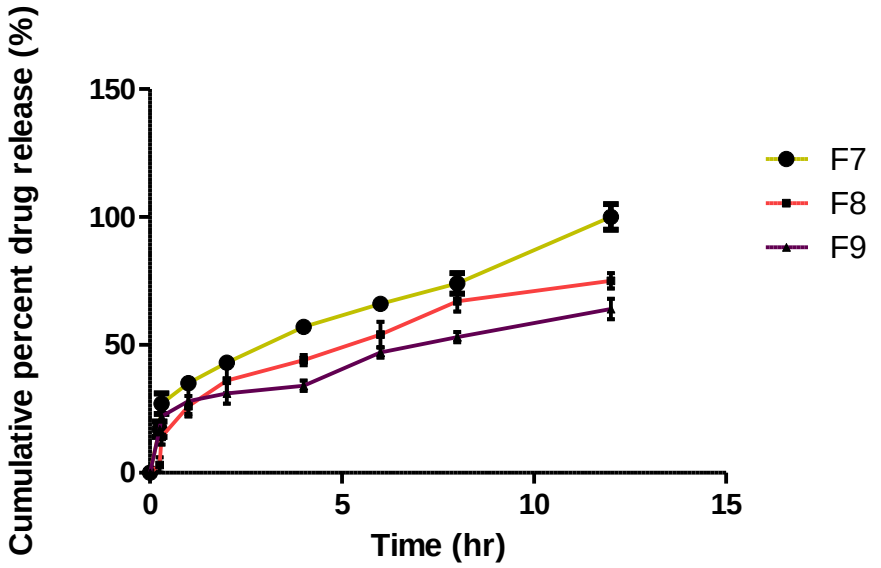


**Figure 4: *In vitro* drug release profile of tablets with HPMC K100M as polymer**

From the above graph it was evident that the formulations prepared with HPMC K100M retarded drug release. Formulations F7, F8 & F9 were retarded the drug release up to 12 hrs. As the concentration of polymer increases the drug release was also retarded. The formulation F7 was shown 96.90% in 12 hrs .Whereas the others shown less drug release.

## CONCLUSION

In the present study, nine formulations (F1-F9) floating tablets of clarithromycin floating tablets were prepared by direct compression method by using HPMC of different grades and concentration. The gas generating agent sodium bicarbonate was added in different concentrations with varying amount of retardation polymers. Different grades of HPMC polymers HPMC K4M, K15M & K100M were used as retarding polymers. The formulation blend was evaluated for various physicochemical properties and all the parameters were found to be within limits. The formulations F1-F9 were formulated and evaluated for various quality control parameters. All the formulations were passed the tests and the results were within limits.

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