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ResearchArticle

Formulation and Evaluation of Clarithromycin Floating Tablet

Oriental College of Pharmacy, Bhopal

1. PriyankaGolhani 2. Dr. Gaurav Gupta 3. Dr.Udit NarianSoni

Abstract

Hydrodynamically Balanced Tablets of an antibacterial drug Clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability.Among the polymers used to improve the gastric residence, cellulose polymers HPMC K4M, HPMC K15M showed better control over drug release in comparison to polysaccharide polymer Chitosan. Formulated tablets gave satisfactory results for various physicochemical evaluations for tablets like Tablet dimensions, Hardness, Friability, Weight variation, Tablet density, Swelling index and Content uniformity. Overall, tablets of batch F3 possessed quick buoyancy lag time and good total floating time.Variation on hardness on tablet of batch F3 was found to effect the floating lag time of the tablet as hardness increased. In-vitro release rate showed that the drug release was better controlled in formulation F3 shows better control drug release in comparision to other formulation.Formulation F3 has better Sustained drug release in comparison to marketed product Clarithro ER.

Keywords: clarithromycin, floating, HPMC, H.pylori, peptic ulcer

Introduction:

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received the more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes. Development of a successful oral controlled release drug delivery dosage form requires an understanding of three aspects:

(1) gastrointestinal (GI) physiology

(2) physiochemical properties of the drug and

(3) dosage form characteristics (1,2).

Novel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches forNovel oral controlled dosage form that is retained in the stomach for prolonged and predictable period is of major interest among academic and industrial research groups. One of the most feasible approaches for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT).

Dosage form with prolonged GRT or gastro-retentive dosage form (GRDF) provides an important therapeutic option (3). Various approaches for preparation of gastroretentive drug delivery system include floating systems, swellable and expandable systems, high density systems, bioadhesive systems, altered shape systems, gel forming solution or suspension system and sachet systems. Among these, the floating dosage form has been used most commonly. The floating systems include gas-generating systems, noneffervescent systems and raft forming systems (4-5).

Helicobacter pylori is a prevalent humanspecific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of

Corresponding Author

1.

E.mail: asthashu2620@gmail.com

cancer in humans (6) and its eradication requires high concentration of drug within the gastric mucosa for long duration. Thus, floating oral delivery system is expected to remain buoyant in a lasting way upon the gastric contents and enhance bioavailability of all drugs which are well absorbed from the GI tract.

Materials and Methods[6-13]

Preformulation Studies (7)

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included solubility, melting point, Flow properties, and compatibility studies.

A. **Solubility: -** Solubility of Clarythromycin was determined in ethanol (95%), Chloroform, acetone, ether, and 0. 1 N HCL. Solubility studies were performed by taking excess amount of Clarythromycin in different beakers containing the solvent. The mixture was shaken for 10 hrs at regular intervals. The solution was filtered by using Whitman's filter paper grade no 41. The filtered solution was analyzed spectrophotometrically.

B. **Melting point: -** Melting point of the clarythromycin was determined by capillary method.

C. **Flow properties(8)**

Angle of Repose: - The frictional forces in a loose powder or granules can be measured by angle of repose. This is the maximum angle possible between the surface of a pile of powder or granules and the horizontal plane(9).

Compressibility Index: (10) The flow ability of powder can be evaluated by comparing the bulk density (Do) and taped density (Df) of powder and the rate at which it packed down.

Compressibility index is calculated by - Compressibility index (%) =

Df Do X 100
Df Where
Do = Bulk density
Df = Tapped density

Evaluation of tablet

Shape of Tablets: Directly compressed tablets were examined under the magnifying lens for the shape of the tablet(11).

Tablet Dimensions: Thickness and diameter were measured using a calibrated dial caliper. Three tablets of each formulation were picked randomly and thickness was measured individually(12).

Thickness: The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported(13).

Hardness: Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm2. Three tablets were randomly picked and hardness of the same tablets from each tablet was determined(14).

Friability test: The friability of tablets was determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (Winitial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal)(15). The % friability was then calculated by -

$$f\frac{dW\ initial\ -\ Wy}{Final\ w\ initial} \times 100$$

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

Weight Variation Test: Ten tablets were selected randomly from each batch and weighed individually to check for weight variation. A little variation is allowed

in the weight of a tablet by U.S. Pharmacopoeia. The following percentage deviation in weight variation is allowed(16).

In all formulations, the tablet weight is more than 324mg, hence 5% maximum difference allowed.

Test for Content Uniformity

Tablet containing 500mg of drug is dissolved in 100ml of 0.1N HCl taken in volumetric flask. The drug is allowed to dissolve in the solvent. The solution was filtered, lml of filtrate was taken in 50ml of volumetric flask and diluted up to mark with O. lNHCl and analysedspectrophotometrically at 203nm. The concentration of Clarithromycin in mg/ml was obtained by using standard calibration curve of the drug. Claimed drug content was 500mg per tablet. Drug content studies were carried out in triplicate for each formulation batch. (17)

Tablet Density: Tablet density is an important parameter for floating tablets. The tablet will only float when its density is less than that of gastric fluid (1.004). The density was determined using following relationship. (18)

v= r2 h
v = volume of tablet (cc)
r = radius of tablet (cm)
h = crown thickness of tablet (g/cc)

m = mass of tablet

ResultandDiscussion

All the formulations were prepared by direct compression method using different polymers. (Designated as F-1 to F-8).

Procedure: Direct Compression

1. Clarythromycin and all other ingredients were individually passed through sieve -No- 60.
2. All the ingredients were mixed thoroughly by triturating up to 15 min.
3. The powder mixture was lubricated with talc, Magnesium stearate.
4. The tablets were prepared by using direct compression method.

Preformulation studies

Hydro dynamically balanced tablets of Clarythromycin were prepared and evaluated for their use as gastroretentive drug delivery systems to increase its local action and bioavailability. In the present work total eight formulations were prepared and complete composition of all batches shown in Table. The tablets were then characterized for various physicochemical parameters.

Preformulation Studies

Physical state: -White to off white crystalline powder odour less Solubility Analysis: - Insoluble (354mg/lit)

Bulk density: - 2.14 g/cm3

Tap density: - 0.452g/ml Compressibility index: - 52.45%

EVALUATION OF HYDRODYNAMICALL Y BALANCED TABLET FORMULATIONS:

1. **Evaluation of granules:**

a) **Angle of Repose**: - The values obtained for angle of repose for all formulations are tabulated in Tables. The values were found to be in the range from 24.30' to 29.88'. This indicates good flow property of the powder blend.

b) **Compressibility Index: -** Compressibility index value ranges between 12.30% to 16.34% indicating that the powder blend have the required flow property for direct compression.

2. Evaluation of tablet:

a) Shape of the tablet: - Microscopic examination of tablets from each formulation batch showed circular shape with no cracks.

b) Tablet dimensions: - The dimensions determined for formulated tablets were tabulated in Table. Tablets mean thickness (n=3) were almost uniform in all the five formulations and were found to be in the range of 5.12mm to 5. l 8mm. The diameter of the tablet ranges between 12.98mm to 12.99mm.

c) Thickness: - The dimensions of the tablet like thickness, length were measured using vernier-calipers. Ten tablets were selected randomly for this test and the average value was reported.

d) Hardness test: - The measured hardness of tablets of each batch ranged between 5. 1 to 5.5 kg/cm^2. This ensures good handling characteristics of all batches.

e) Friability Test: - The values of friability test were tabulated in. The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

f) Weight Variation Test: - The percentage weight variation for all formulations was shown in Table .

g) All the tablets passed weight variation test as the % weight variation was within the pharmacopoeia limits of ±5% of the weight. The weight of all the tablets was found to be uniform with low standard deviation values.

h) Drug Content Uniformity: - The percentage of drug content was found to be between 95.40% to 99.40% of Clarithromycin , which was within acceptable limits. Table 6 showed the results of drug content uniformity in each batch

i) Buoyancy Study: - On immersion in O. lNHCl solution pH (1.2) at 37°C, the tablets floated, and remained buoyant without disintegration. Table shows the results of Buoyancy study & shows Buoyancy character of prepared tablet. From the results it can be concluded that the batch containing only HPMC polymers showed good Buoyancy lag time (BLT) and Total floating time (TFT).

Formulation F3 containing HPMC K l5M showed good BLT of 48 sec, while the formulation containing chitosan alone and in combination with HPMC K l5M showed highest BLT, and TFT of less than 12 hrs. This may be due to the amount of polymer and gas generating agent, which were kept constant in the present study. The gas generated cannot be entrapped inside the gelatinous layer, and it escapes leading to variation in BLT and TFT.

j) Tablet density: - To provide good floating behavior in the stomach, the density of the device should be less than that of the gastric contents (1.005g/cm3). All the batches showed density

below than that of gastric fluid (1.005). The values are shown in Table.When tablet contacts the test medium , tablet expanded (because of swellable polymers) and there was liberation of C02 gas (because of effervescent agent, NaHC03). The density decreased due to this expansion and upward force of C02 gas generation. This plays an important role in ensuring the floating capability of the dosage form.

k) Conclusion

l) In the present study Gastroretentive delivery systems of Clarithromycin were successfully developed in the form of Hydrodynamically Balanced Tablets to improve the local action and ultimately its bioavailability. The tablets were formulated using different grades of polymers (HPMC K4M, HPMC K15M and Chitosan) and effervescing agent (NaHCO3). Buoyancy lag time, , tablet density showed satisfactory results for batch F1, F2, F3, F5, F6 and F8. The formulation F3 was evaluated for effect of hardness on floating lag time, and the results showed that the floating lag time increased as hardness increased due to reduction in porosity.

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Table 1: Solubility of Saxagliptin

Solvent used	Saxagliptin
Distilled Water	Sparingly Soluble
0.1 N Hydrochloric acid	Soluble
Ethanol	Freely Soluble
Methanol	Freely Soluble
Ethyl acetate	Slightly Soluble
0.1 N NaOH	Sparingly Soluble

Table 2: Melting point of Saxagliptin

S. No.	Melting Point of Saxagliptin	Average Melting Point of Saxagliptin
1.	103-106°C	103-106°C
2.	103-107°C	
3.	103-106°C	

Table 3 : pH of the Saxagliptin

S. No.	pH of the solution	Average pH of the solution
1.	6.68	6.683±0.057
2.	6.69	
3.	6.68	

Table4:Loss of drying of drug sample

S.No.	Initial weight	Final weight after15 minutes	%lossofdrying	Avg.%lossofdrying
1.	1gm	0.998gm	0.2%	0.366±0.152
2.	1gm	0.995gm	0.5%	
3.	1gm	0.996gm	0.4%	

Table4: Formulations ofthefloatingMicrocapsulesprepared

Sr. No	FormulationCode	Saxagliptin (mg)	HPMC (mg)	EC (mg)
1.	**F1**	50	50	50
2.	**F2**	50	50	75
3.	**F3**	50	50	100
4.	**F4**	50	100	50
5.	**F5**	50	100	75
6.	**F6**	50	100	100

Table 7: Drug Entrapment for Different formulations*Table 6:* **Percentage Yield for Different Formulation**

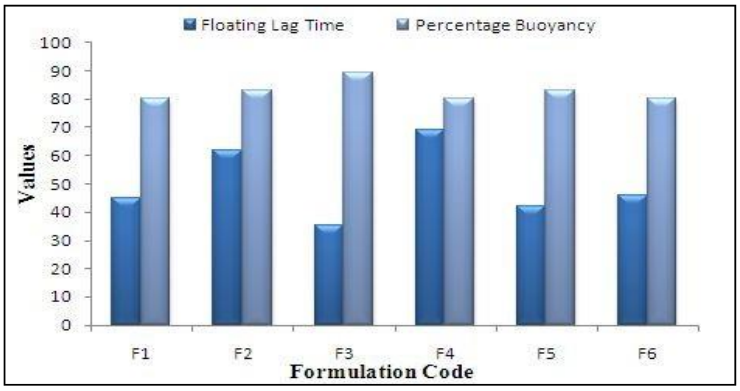
S. No.	Conc. (µg/ml)	Absorbance
1	5	0.139±0.002
2	10	0.275±0.003
3	15	0.395±0.001
4	20	0.524±0.002
5	25	0.645±0.001

Formulation	Percentage Yield
F1	82.32±0.51
F2	79.89±0.32
F3	85.45±0.56
F4	82.10±0.41
F5	78.21±0.62
F6	76.65±0.32

Table 8: Percentage Buoyancy and floating lag time of floating Microcapsule

Formulation	Floating Lag Time	Percentage Buoyancy
F1	45±3	80.23±0.45
F2	62±1	82.85±0.65
F3	35±2	89.45±0.21
F4	69±5	79.95±0.32
F5	42±3	83.14±0.47
F6	46±4	80.14±0.74

Figure 1: Floating Lag Time and Percentage Buoyancy for Different Formulatiion



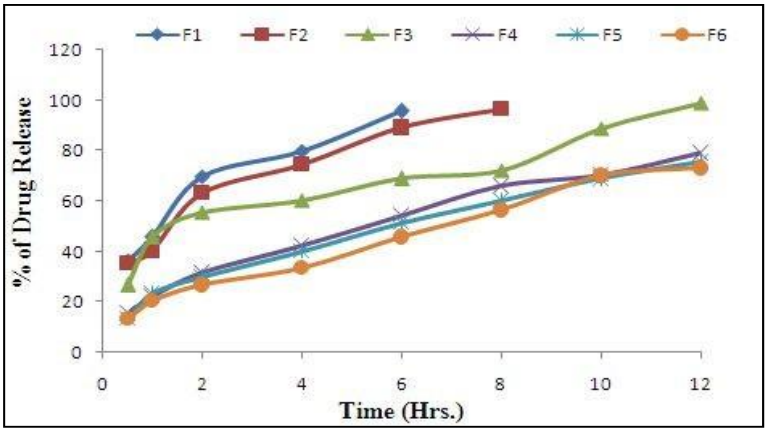


Figure 3: Graph of release study of formulation F1-F6

Table : Release Study data of formulation F1-F6

Time	% of Drug Release					
(hr)	F1	F2	F3	F4	F5	F6
0.5	36.45	35.45	26.65	15.65	13.24	13.25
1	45.65	40.25	45.65	22.12	23.56	20.23
2	69.89	63.12	55.32	31.48	29.89	26.65
4	79.98	74.65	60.36	42.23	40.12	33.65
6	95.65	88.98	68.89	54.45	51.15	45.65
8	-	96.32	72.32	65.85	60.12	56.45
10	-	-	88.95	70.23	68.89	69.98
12	-	-	98.89	78.89	75.45	73.12