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Rajesh Sharma, Ashwani Mishra
Department of Pharmacy, Barkatullah University, Bhopal

Correspondence

Rajesh Sharma
Department of Pharmacy, Barkatullah University, Bhopal

Email: rajxsharma33@gmail.com

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Development and Characterization of Gastro Retentive Tablets of Clarithromycin for Antiulcer effect

Rajesh Sharma, Ashwani Mishra

ABSTRACT

Gastroretentive floating drug delivery system (GFDDS) is used to prolong the gastric residence time after oral administration, at a particular site and controlled or modified the release of drug from the formulation.The purpose of the present study is to develop a gastro retentive floating drug delivery system to achieving controlled release so that is improves bioavailability of the formulation, Structure activity relationship based on Biopharmaceutical Properties of Clarithromycin indicates good biopharmaceutical Properties. Floating dosage form of Clarithromycin was designed for the treatment of gastric ulcer caused by *Helicobacter pylori*. The granules were prepared by wet granulation method and evaluated for flow property, Carrs' index, bulk density, tapped density and Hausner ratio. The dosage form was designed by using polymers of different viscosity as gelling agents, sodium bicarbonate as gas generating agent and other excipients. The granules were further subjected to tablet preparation and the prepared tablets were subjected for evaluated on the basis of different evaluation parameters like hardness, *in vitro* buoyancy, *in vitro* drug release. Incorporation of gas generating agent together with polymer improved drug release Optimized formulation (F7) containing Clarithromycin, HPMC, 90 SH , HPMC K4M , sodium bicarbonate, released approximately 86.6% drug in 10 hrs. and the floating lag time was found to be 25 sec.

Key words: GFDDS, Helicobacter pylori**,** gelling agents, *in vitro* buoyancy, HPMC, wet granulation.

1. INTRODUCTION

In recent years, various attempts have been made to potentiate the drug bioavailability and therapeutic effectiveness of oral dosage forms. Many gastroretentive drug delivery systems (GRDDS) have been used to improve the therapeutic efficacy of drugs that possess narrow absorption window, Some drugs are also unstable at alkaline pH they are also suitable candidate for gastroretentive drug delivery systems , Some drugs are soluble in acidic conditions, and are active locally in the stomach can be used to prepared gastroretentive drug delivery systems.[1] These gastroretentive drug delivery systems are modified release dosage form that retained in the stomach for desired time period .The Method this system follow by controlling the gastric residence time (GRT).[2-3]There are various approaches for preparation of gastro retentive drug delivery system include swellable, floating systems, and expandable systems, high and low density systems, bioadhesive systems, altered shape systems, gel forming systems. Among these approaches the floating dosage form has been used most commonly due to it feasibility and entrapment efficiency of wide spectrum of drugs . The floating systems include gas-generating systems, non-effervescent systems and raft forming systems.[4-5] *Helicobacter pylori* is a human specific pathogen, causes chronic gastritis, peptic ulcer and adenocarcinoma. It ranges from 40% in developed countries up to 80% in underdeveloped countries

As per estimates, 10 - 20% of H. pylori-infected patients develop different degrees of peptic ulcer diseases, and average 1–2% are at risk of developing stomach cancer and requires high concentration of drug for its eradication within the gastric mucosa for long duration. [6-7] Thus, floating oral delivery system expected to remain buoyant in gastric contents and enhance bioavailability of drugs which are well absorbed from the GI tract. Biopharmaceutical Properties such as absorption, distribution, metabolism, excretion, and toxicity, play key roles in drug discovery and development. A best drug candidate should have sufficient efficacy against the therapeutic target, but also capable to show desirable properties of absorption, distribution, metabolism and excretion at a therapeutic dose. A number of *in silico* models are developed and available for the prediction of chemical absorption, distribution, metabolism and excretion properties. Clarithromycin is a semi synthetic macrolide antibiotic that is proved to be extremely effective mono therapy in treating *H. pylori* infection. [8-10]

It is rapidly absorbed from GIT , undergoes first-pass metabolism and have shorter half-life To avoid this limitation of shorter half life , It was aimed to prepare oral modified release floating of Clarithromycin long period of time. [11] As biological half life of drug is 3-4 hrs and this causes frequent dosing of drug 12 Therefore, to get high drug level must be the goal of the therapy.The half-life of clarithromycin (3-6 h), makes it a useful drug for controlled release dosage form. [12-13]

2. MATERIALS AND METHODS

Clarithromycin was obtained as gift sample from IPCA laboratries Ratlam India as a gift sample. HPMC K4M (hydroxypropyl methylcellulose viscosity of 2% aqueous solution 4000 cP) and HPMC K15M (hydroxypropyl methylcellulose viscosity of 2% aqueous solution 15000 cP) were obtained from Yasham bioscience, Mumbai. Sodium bicarbonate and All other chemicals used were of analytical grade.

Structure activity relationship of Biopharmaceutical Properties - This study was done using software available online to check the drug polarity, log P and affinity of drug with different receptor of human body.as shown in Table 1 and Figure 1.

2.1 Granules Preparation

Granules were prepared by using three techniques (direct compression, dry granulation and wet granulation) and evaluated on the basis of flow properties. Granules prepared by direct compression and dry granulation were rejected because of non-uniform flow, and finally wet granulation method was selected and used for further preparation of granules. Polymers and clarithromycin were mixed homogeneously using glass mortar and pestle. Isopropyl alcohol and water (80:20) 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 60^0C. Dried granules were sieved through #20 sieves and mixed with sodium bicarbonate used as gas generating agent and lubricated with magnesium stearate and talc 4-5 min before subjecting the blend for compression using hand operated tablet punching machine.

2.2 Evaluation of Pre compression parameters

The flow properties of granules (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio.

Flow property Determination - It was determine using Angle of Repose method. For determination of angle of repose (θ), the granules were poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The granules were poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The $\tan\Theta^{-1}$ of the (height of the pile/radius of its base) gave the angle of repose.

2.2.1 Density Determination

Granules weighed quantity of granules were poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark.. The cylinder was then tapped from a height of 2.0 cm until the time when there was no more decrease in the volume was observed). Bulk density (ρb) and tapped density (ρt) were calculated using formula-

$$Pb = \frac{Weight\ of\ the\ granules}{Bulk\ volume\ of\ the\ granules}$$

$$Pt = \frac{Weight\ of\ the\ granules}{Tapped\ \ volume\ of\ the\ granules}$$

Hausner ratio (H_R) and Carr index (I_C) were calculated according to the two equations).

$$\mathrm{HR} = \frac{pt}{pb}$$

$$CI = \frac{pt - pb}{pt}$$

2.2.2 Tablet Preparation

Granules prepared were sifted and compressed by hand operated tablet compression machine Different batches were further taken by varying the concentration ratio of polymer, diluent, gas generating agent and lubricant and effect on response variables were studied as shown in Table 2.

2.3 Evaluation of Post Compression Parameters

2.3.1 Weight variation

Twenty tablets of different batches were are taken and weighed variation of individual batch was determined .The Pharmacopoeia provides the weight variation test by weighing 20 tablets individually, calculating the variation of average weight, and comparing the individual tablet weights to the average. The tablets meet the USP test if no more than 2 tablets are outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

2.3.2 Hardness and Friability

Hardness of tablet was measured by Pfizer hardness tester. Friability was determined using Roche friability tester-A pre weighed quantity of tablet sample is placed in the friabilator which is then operated for 100 revolutions. Compressed tablets that lose less than 0.5 to 1.0 % of their weight are generally considered acceptable .

$$\text{Friability} = \frac{Initial\ weight\ of\ tablet - final\ weight\ of\ tablet}{Initial\ weight\ of\ Tablet} X100$$

2.3.3 Buoyancy/Floating test

The time between introduction of dosage form and its buoyancy on the simulated gastric fluid and the time during which the dosage form remained buoyant were measured. The tablets were placed in a 250mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was taken as the floating lag time..

2.3.4 In vitro Dissolution studies

The in vitro release study for all the formulations carried out by USP Dissolution Test Apparatus Type-II The temperature of the dissolution medium (0.1 M HCl, 900 mL) was maintained at $37^{O}C \pm 1^{O}C$ with a stirring rate of 50 rpm. This study was done for 10 hrs. The tablet was placed inside the dissolution vessel. At time of 1, 2, 3, 4, till 10^{th} hr, 5 mL of aliquots were withdrawn ,diluted with 0.1 M HCl up to 10 mL and assayed spectrophotometrically at λ=283 nm in a double beam UV and visible spectrophotometer (zesco Double Beam) against reagent blank. The drug concentration was calculated using standard calibration curve. The volume of dissolution fluid in USP in vitro dissolution apparatus was adjusted every time to 900 mL.

3. RESULTS AND DISCUSSION

3.1 Evaluation of Pre compression properties of Granules

Biopharmaceutical Properties of Drug Clarithromycin revealed its good partition coefficient, surface polarity, volume and This drug showed binding with number of receptors in to the body as shown in table 1.

The granules prepared for compression of floating tablets were evaluated for their flow properties. Angle of repose (θ) was in the range of 24.62±0.37 with granules prepared by wet granulation techniques. Carr index (Ic) was found to be 0.15± 0.26 and Hausner ratio (Hr) ranged from 1.182± 0.15 for granules of different formulations. These values indicate that the granules prepared by wet granulation showed excellent flow property.

Table 3 showed Flow property of granules prepared by different techniques.* Where WG represents wet granulation.

3.1.1 Weight variation

The variation in weight of the prepared tablet was within the range of ±5% complying with pharmacopoeial specifications (Indian Pharmacopoeia. 1996). Tablets prepared by wet granulation were under the limits.

(a) Weight variation of tablets (in mg) prepared F1 to F7.

3.1.2 In vitro buoyancy study

The tablet floating lag time (FLT) was found to be less than 30 sec and total floating time was 10 hrs. The floating lag time may be explained as a result of the time required for dissolution medium to penetrate the tablet matrix and develop the swollen layer for entrapment of CO_2 generated in situ. The tablet mass decreased progressively due to liberation of CO_2 and release of drug from the matrix. On the other hand, as solvent front penetrated the glassy polymer layer, the swelling of HPMC K4M and 90SH caused an increase in volume of the tablet. The combined effect is a net reduction in density of the tablets, which prolongs the duration of floatation beyond 10hrs.

Both the swelling polymers (HPMC K4M and HPMC 90 SH) shoed concentration based response to prolong the lag time (positive coefficients of K4 and 90 SH in FLT model equation),

while sodium bicarbonate appeared to reduce the lag time as expected. This is in perfect agreement with release rate and mechanism observed, since the polymers did not swell initially, but helped in keeping the tablet afloat during the late hours of dissolution.

In vitro buoyancy study of tablet formulated by wet granulation.

3.1.3 Hardness

The hardness of all formulas was in the range of 4 -6 Kg/cm^2 .

3.1.4. In vitro drug release

The primary objective of the study was to design a floating tablet of Clarithromycin with a release profile sufficient to maintain adequately high local/systemic concentration.

A rigorous study of their dissolution profile yielded some insight into the effect of polymeric fillers and gas generating agent on release profile of the formulations. From the release profiles, it could be easily visualized that the variation of polymers from 0 - 23% of the formula weight varied drug release approx. 5 - 15%. From figure, the effects of HPMC K4M and 90 SH could be observed at constant sodium bicarbonate level. The presence of HPMC 90 SH increased the release rate and extent slightly compared to HPMC K4M. This may be further inferred from the model equations for release parameters, where the coefficients of HPMC 90 SH term are almost equal or greater than those of HPMC K4M .

This may be due to the time taken for both the polymers in tablet matrix to get hydrated before changing from glassy to rubbery state. Thus, during the first hour of dissolution, there was no significant polymer chain relaxation due to which a rate controlling gel barrier could not be formed. Most of the sodium bicarbonate present on the outer layer of the tablet was involved in reaction with acidic medium. Thus, during this period channels for later absorption of solvent were being formed along with liberation of CO_2 that imparted initial buoyancy to the tablets. This also explains the absence of any lag phase in the release profile. The in vitro release profile of the best batch of Floating tablet shown in Figure 2.

3.1.5 Release Kinetics

The data obtained from in-vitro drug release study was subjected to determine the kinetic of drug release from the Floating tablets using O order, First order, Higuchi and Korsmeyer kinetics .The best formulation revealed that it follows non-fickian transport of the drug from tablets.

4. CONCLUSION

Thus, from the above study it can be concluded that floating tablet of an antibacterial drug Clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability.

Table-1: Activity score of Clarithromycin

S No	Activity target	Activity Score
1	GPCR ligand	-0.64
2	Ion channel modulator	-1.51
3	Kinase inhibitor	-1.42
4	Nuclear receptor ligand	-1.31
5	Protease inhibitor	-0.29

Table-2: Different batches of Floating Tablets of Clarithromycin Prepared.

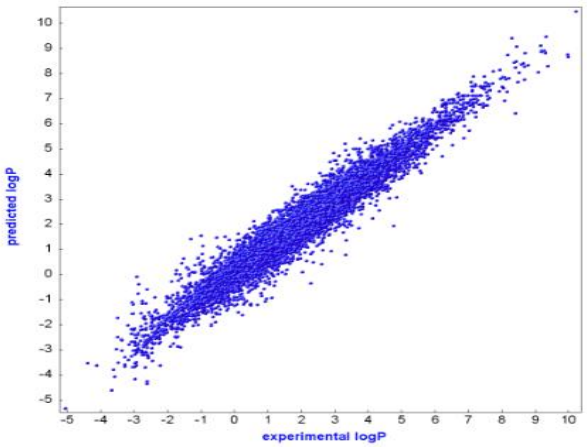
Formulation code	Drug (%w/w)	**Hydroxy propyl methyl cellulose** K4M (%w/w)	**Hydroxy propyl methyl cellulose** 90 SH (%w/w)	Sodium bicarbonate (%w/w)	Mg stearate (%w/w)	Talc (%w/w)
F1	62.5	23	3	10	0.5	1
F2	62.5	13	13	10	0.5	1
F3	62.5	19.5	6.5	10	0.5	1
F4	62.5	25	1	10	0.5	1
F5	62.5	23	3	10	0.5	1
F6	62.5	13	13	10	0.5	1
F7	62.5	1	25	10	0.5	1

Table-3 Pre compression Evaluation parameters of Floating Tablets of Clarithromycin

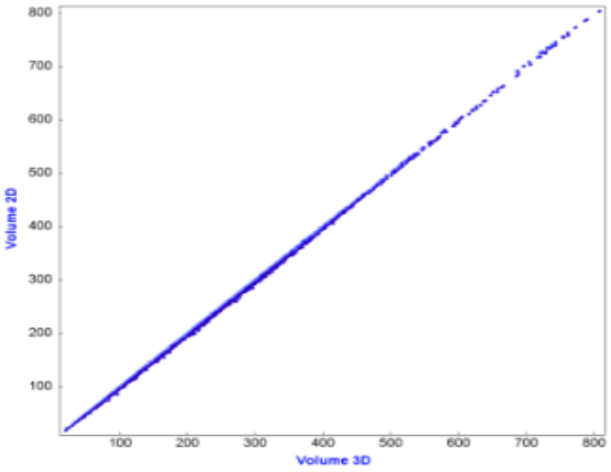
	Angle of repose(θ)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausner ratio (HR)	Carrs Index (Ic
Granules	24.62± 0.37	0.575± 0.04	0.68± 0.06	1.18	0.15

Table-4 Post compression Evaluation Parameters of Floating Tablets of Clarithromycin

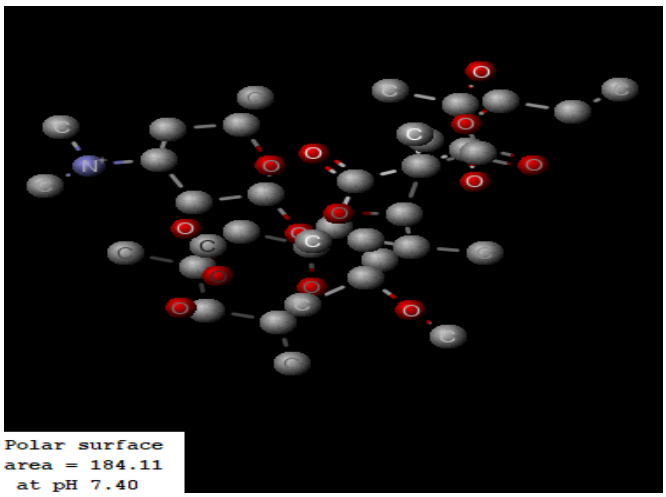
Formulation code	**Friability (%)**	**Hardness (kg/cm^2)**	**Floating Lag time(sec)**	**Total Floating time (hrs)**
F1	0.76	4.6	32	9
F2	0.88	4.2	35	10
F3	0.65	6.3	37	8
F4	1.03	3.9	28	9
F5	0.67	5.4	24	9
F6	0.78	5.3	29	10
F7	0.42	6.1	23	10



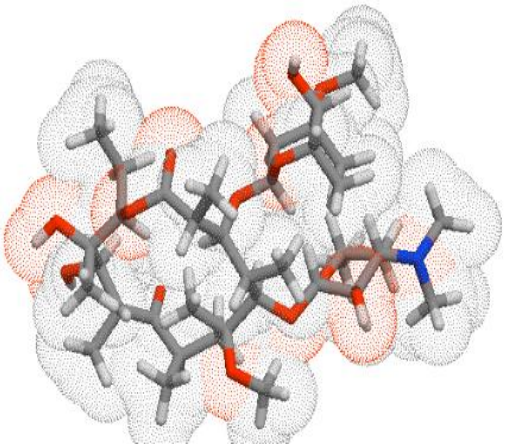
(**a**) Log P value ,r^2 = 0.944, r = 0.972, stdev = 0.428



(**b**) Volume = 1.000, r = 1.000, stdev = 0.994



(**c**) Polar surface area of Clarithromycin



(**d**) 3D Structure of Clarithromycin

Figure-1 Different biopharmaceutical properties of Clarithromycin along with Dot structure {(a), (b),(c),(d)}

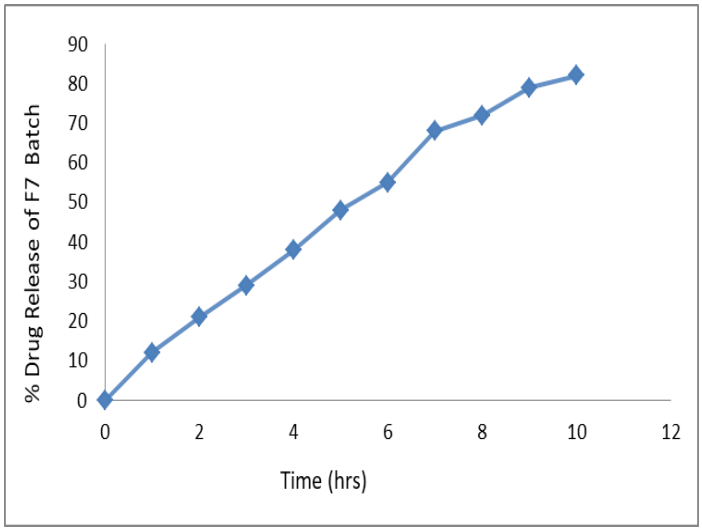


Figure -2 *In vitro* Drug release profile of the best batch of Floating Tablet of Clarithromycin

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