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RESEARCH ARTICLE

NOVEL DRUG DELIVERY SYSTEM

# FORMULATION AND EVALUATION OF FLOATING DRUG DELIVERY SYSTEM

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## ABSTRACT

Floating matrix tablets are designed to prolong the gastric residence time after oral administration at a particular site. It is useful for achieving controlled plasma level as well as improving bioavailability. With this objective, floating dosage form containing clarithromycin as drug was designed for the treatment of *Helicobacter pylori* infection. Tablets containing hydroxyl propyl methylcellulose (HPMC) drug and different additives were compressed using wet granulation. The study showed that tablet composition and mechanical strength have great influence on the floating properties and drug release. Incorporation of gas-generating agent together with polymer improved drug release, besides optimal floating lag time lass than 30 sec; total floating time less than 6 hrs. The optimized formulation was obtained using 150mg of HPMC K4M gave floating lag time less than 30 sec with a total floating time grater than 6 hrs.

## KEY WORD

Floating tablets, Hydroxyl propyl methylcellulose K4M, Clarithromycin, Gastro retentive delivery systems

## INTRODUCTION

Oral delivery of the drug is by far the most preferable route of drug delivery due to the ease of administration, patient compliance and flexibility in the formulations. From immediate release to site-specific delivery, oral dosage form has really progressed. It is evident from the recent scientific and patented literature that an increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time exist today in academic and industrial research groups. Various attempts have been made to develop Gastro retentive delivery systems. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low-density systems. This technology benefits drugs that have a narrow window of absorption in the stomach and upper GI tract. Gastro retentive systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients.

***Helicobacter pylori*** is a prevalent human specific pathogen, which is now believed to be the causative bacterium for chronic gastritis, peptic ulcer and adenocarcinoma, one of the most common forms of cancer in humans 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. Clarithromycin is an advanced generation macrolide antibiotic used in treatment of *H.pylori* and respiratory infection. If the concentration of antibiotic is maintained above MIC, drug resistance can be reduced. Clarithromycin exhibits concentration dependent pharmacodynamics, where peak concentration / MIC ratio of approximately ten. Therefore, high drug level should be achieved by using gastric floating drug delivery system. Short elimination half-life of clarithromycin (3-6 h) makes it a useful candidate for controlled release dosage form and stability in the acidic environment is useful for gastro-retentive drug delivery system. [1]

***Requirements for Gastric Retention****:*

Physiological factors in the stomach, it must be noted that, to achieve gastric retention, the dosage form must satisfy certain requirements. One of the key issues is that the dosage form must be able to withstand the forces caused by peristaltic waves in the stomach and the constant contractions and grinding and churning mechanisms. To function as a gastric retention device, it must resist premature gastric emptying. Furthermore, once its purpose has been served, the device should be removed from the stomach with ease.[2]

***GI MOTILLITY PATTERN***

- Phase I (basal phase) - lasts from 40 to 60 minutes with rare contractions.
- Phase II (preburst phase) -lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
- Phase III (burst phase) - lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
- Phase IV - lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.
- After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state. This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate.[3] Scintigraphic studies determining gastric emptying rates revealed that orally administered controlled release dosage forms are subjected to basically 2 complications, that of short gastric residence time and unpredictable gastric emptying rate.

***Approaches to Gastric Retention:-***

Various approaches have been paused to increase the duration of oral dosage form in the stomach, including floating systems, swelling and expanding system, modified shape system, high density systems and other delayed gastric emptying devices. (Magnetic systems, super porous – biodegradable hydrogel systems).

- Hydrodynamically balanced systems (HBS) [4]
- Raft systems [5]
- Swelling type [6]
- Bioadhesive or mucoadhesive systems
- Modified shape systems
- High density formulations[7]

***Floating Drug Delivery Systems (FDDS):-***

Floating systems, first described by Davis in 1968, have bulk density lower than that of the gastric fluid, and thus remain buoyant in stomach for prolong period. Floating drug delivery systems are classified depending on the use of 2 formulation variables: EFFERVESCENT and NON-EFFERVESCENT SYSTEMS.

**A. *Effervescent Floating Dosage Forms:-***

***1) Volatile liquid containing systems:***

The GRT of a drug delivery system can be sustained by incorporating an inflatable chamber, which contains a liquid e.g. ether, cyclopentane, that gasifies at body temperature to cause the inflatation of the chamber in the stomach. The device may also consist of a bioerodible plug made up of PVA, Polyethylene, etc. that gradually dissolves causing the inflatable chamber to release gas and collapse after a predetermined time to permit the spontaneous ejection of the inflatable systems from the stomach. (Figure__A and B) [8] developed floating capsules composed of a plurality of granules that have different residence times in the stomach and consist of an inner foamable layer of gas-generating agents.

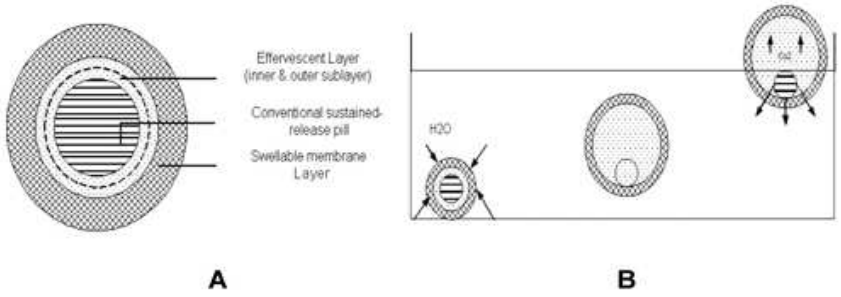



**Fig.no. 1**
***(A) Multiple-unit oral floating drug delivery system. (B) Working principle of effervescent floating drug delivery system.***

This layer was further divided into 2 sublayers, the outer containing sodium bicarbonate and the inner containing tartaric acid. This layer was surrounded by an expansive polymeric film (composed of poly vinyl acetate [PVA] and shellac), which allowed gastric juice to pass through, and was found to swell by foam produced by the action between the gastric juices and the gas-generating agents. It was shown that the swellable membrane layer played an important role in *maintaining the buoyancy of the pills for an extended period of time.*

***2) Gas-generating Systems:***
These buoyant delivery systems utilize effervescent reactions between carbonate/bicarbonate salts and citric/tartaric acid to liberate $CO_2$, which gets entrapped in the gellified hydrocolloid layer of the systems thus decreasing its specific gravity and making it to float over chyme. [9, 10]

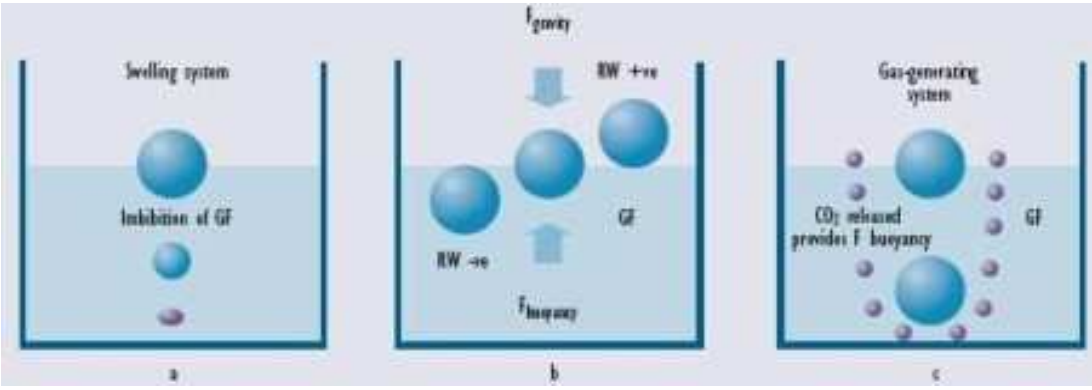



**Fig. no - 2**
***The Mechanism of Floating System***

**B. *Non-effervescent systems:***

1. ***Colloidal gel barrier systems***

Hydrodymamically balance system (HBS™) was first design by Sheth and Tossounian in 1975.Such systems contains drug with gel forming hydrocolloids meant to remain buoyant on stomach contents. This system incorporate a high level of one or more gel forming highly swellable cellulose type hydrocolloids.e.g.HEC, HPMC, NaCMC, Polysacchacarides and matrix forming polymer such as polycarbophil, polyacrylates and polystyrene, incorporated either in tablets or in capsule. On coming in contact with gastric fluid, the hydrocolloid in the system hydrates and forms a colloidal gel barrier around the gel surface. The air trapped by the swollen polymer maintains a density less than unity and confers buoyancy to this dosage forms. [11]

2. ***Microporous Compartment System***

This technology is based on the encapsulation of drug reservoir inside a Microporous compartment with aperture along its top and bottom wall. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of the gastric mucosal surface with the undissolved drug. In stomach the floatation chamber containing entrapped air causes the delivery system to float over the gastric contents. Gastric fluid enters through the apertures, dissolves the drug, and carries the dissolve drug for continuous transport across the intestine for absorption.

3. ***Alginate beads***

Multiple unit floating dosage forms have been developed from freeze-dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping a sodium alginate solution in to aqueous solutions of calcium chloride, causing precipitation of calcium alginate. The beads are then separated snap and frozen in liquid nitrogen, and freeze dried at -40°C for 24 hours, leading to the formation of porous system, which can maintain a floating fource over 12 hours.

4. ***Hollow microspheres***

Hollow microspheres (microballons), loaded with ibuprofen in their outer polymer shells were prepared by a novel emulsion-solvent diffusion method. The ehanol: dichloromethane solution of the drug and an enteric acrylic polymer was poured in to an agitated aqueous solution of PVA that was thermally controlled at 40°C.The gas phase generated in dispersed polymer droplet by evaporation of dichloromethane formed in internal cavity in microspheres of the polymer with drug. The microballons floated continuously over the surface of acidic dissolution media containing surfactant for greater than 12 hours in vitro.

***Application of Floating Drug Delivery System*** [12]

- Recent study indicated that the administration of Diltiazem floating tablets twice a day may be more effective compared to normal tablets compared to normal tablets in controlling the B.B of hypertensive patients.
- Modapar® HBS containing L-Dopa and Benserazide, here the drug was absorbed over a period of 6-8 hours and maintained substantial plasma concentration for Parkinsonian patients. Cytotech®- containing Misoprostol, a synthetic prostaglandin –EL analogue, for prevention of gastric ulcer caused by non-steroidal anti-inflammatory drugs (NSAIDS).
- As it provides high concentration of drug within gastric mucosa, it is used to eradicate *H.pylori* (a causative organism for chronic gastritis and peptic ulcers).
- 5-fluorouracil has been successfully evaluated in the patients with stomach neoplasm.
- Developing HBS dosage form for tacrin provide better delivery systems and reduced its GI side effects.

- Treatment of gastric and duodenal ulcer.

***Merits***[13]

- The delivery of drugs with narrow absorption window in the small intestinal region.
- Longer residence time in stomach could be advantageous for local action in the upper part of the small intestinal. i.e. treatment of peptic ulcer.
- Improved bioavailability is expected for drugs that are absorbed readily upon release in the GI tract. These drugs can be delivered ideally by slow release from the stomach.
- Improvement of bioavailability and therapeutic efficacy of the drugs and possible reduction of dose e.g. Furosemide
- Maintenance of constant therapeutic levels over a prolonged period and thus reduction in fluctuation in therapeutic levels minimizing the risk of resistance especially in case of antibiotics. e.g. b-lactam antibiotics (penicillins and cephalosporins)
- Retention of drug delivery systems in the stomach prolongs overall.
- Gastrointestinal transit time thereby increasing bioavailability of sustained release delivery systems intended for once-a-day administration. e.g. Ofloxacin

***Demerits***

- There is certain situation where gastric retention is not desirable. Aspirin & NSAID are known to cause G.I. lesions & slow release of such drug in stomach is unwanted.
- Those that have multiple absorption sites in the gastrointestinal tract
- Those that is not stable at gastric pH.
- Those which gets degraded due to gastric enzymes.

## MATERIALS AND METHODS

Hydroxypropyl methyl cellulose K4M was obtained as gifts from. Colorcon Asia Pvt. Ltd., (Mumbai, India). Clarithromycin was buy from a local market. Potassium chloride, Hydrochloric acid, Sodium bicarbonate (30%), Citric acid (5%), Magnesium stearate, Talc All other chemicals were used of analytical grade.

## METHODS

***1) FOR PREPARATION OF TABLET***

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 60ºC. Dried granules were sieved through # 20/44 sieves and mixed with sodium bicarbonate used as gas generating agent and lubricated with magnesium stearate and talc just 4-5 min before compression. Lubricated granules were compressed into tablets using Krishna Minipress-I rotary tablet machine to obtain tablets of desired specifications.

**Table1**
***Formulation table***

| Active ingredient (mg) | F1 | F2 | F3 |
|---|---|---|---|
| **Clarithromycin** | 250 | 250 | 250 |
| **HPMC K4M** | 50 | 100 | 150 |
| **Na.bicarbonate** | 100 | 100 | 100 |
| **Citric acid** | 25 | 25 | 25 |
| **Mg.stearate** | 2 | 2 | 2 |
| **Talc** | 4 | 4 | 4 |

***2) FOR FINDING FLOATING LAG TIME***

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 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 floatation i.e. as long the dosage form remains buoyant is called **Total Floating Time (TFT).**

**Fig .no. 3**
***Tablet Preparation***

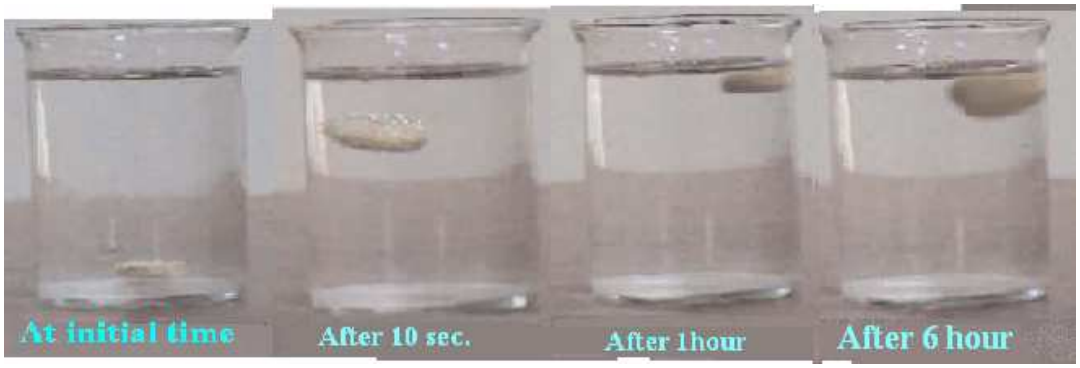



**Fig .no. 4**
***Floating Lag Time***

3) ***METHOD FOR DETERMINING THE CALIBERATION CURV OF METOPROLOL TARTARATE*** [14]

10mg of clarithromycin tartarate was dissolved in 100ml of the solvent to obtain the working standard of 100µg/ml. aliquots of 1ml to 3.5 ml from the stock solution representing 10 to 35µg/ml of drug were transferred to 10ml volumetric flask and the volume was adjusted to 10ml with the solvent. Absorbance of the above solution were taken at λ= 288nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 10 to 35 µg/ml indicating, its compliance with Beer's law.

4) ***METHOD FOR IN VITRO DRUG RELEASE STUDIES***[15]

The *in vitro* release study for all the formulations were carried out by USP Dissolution Test Apparatus Type-II. The temperature of the dissolution medium (0.1 M HCl, 900 ml) was maintained at $37^0C \pm 1^0C$ with a stirring rate of 50 rpm ,then 5ml of dissolution medium was taken out at intervals of 1,2,3&4 hours. Exactly 5ml of fresh buffer was added to the dissolution vessel after each withdrawal, to maintain a constant volume. Then the withdrawal samples were analyzed by using a U.V spectrophotometer.

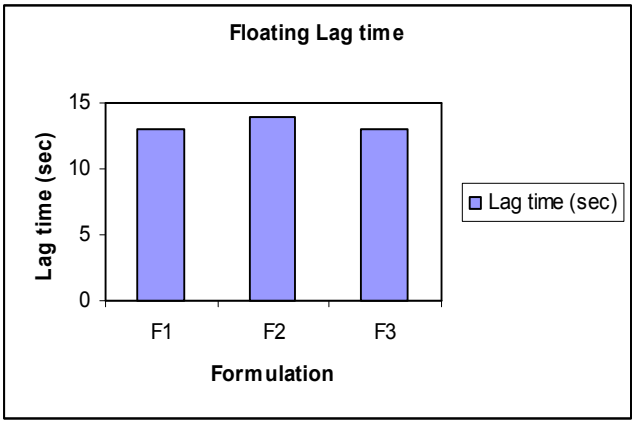
## RESULTS

### 1) TABLET EVALUTION TESTS

| Parameters | F1 | F2 | F3 |
|---|---|---|---|
| Friability | 0.81% | 0.80% | 0.78% |
| Hardness | 4.5 kg/cm$^2$ | 4.5 kg/cm$^2$ | 4.4 kg/cm$^2$ |
| Weight variation | 3.85% | 4.02% | 3.90% |

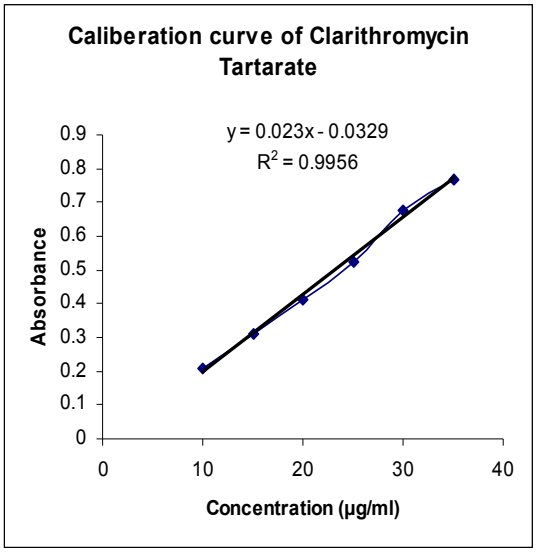
### 2) FLOATING LAG TIME

| Formulation | Lag time (sec) |
|---|---|
| F1 | 13 |
| F2 | 14 |
| F3 | 13 |



**3) Caliberation curve of Clarithromycin tartarate**

| Sr.No. | Concentration (µg/ml) | Absorbance |
|---|---|---|
| 1 | 10 | 0.208 |
| 2 | 15 | 0.312 |
| 3 | 20 | 0.41 |
| 4 | 25 | 0.526 |
| 5 | 30 | 0.676 |
| 6 | 35 | 0.771 |




## DISCUSSION

***In Vitro* Disolussion Study**

From above observations it can be concluded that as the concentration of the sustained release polymer increases the release rate of the drug from the formulation decreases without any impact on the floating lag time of the formulations.

## CONCLUSION

From the data obtained, it can be concluded that hydro dynamically balanced tablet of an antibacterial drug clarithromycin can be formulated as an approach to increase gastric residence time and thereby improve its bioavailability. Formulation F3 prolonged the release (82.56% up to 6 hrs) of the drug as compared to other prepared formulation. Thus the objective of formulating a floating dosage form of clarithromycin has been achieved.

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