AMERICAN JOURNAL OF PHARMTECH RESEARCH

**Journal home page:** http://www.ajptr.com/

# Design and Development of Floating Microsphere of Clarithromycin as Gastroretentive Drug Delivery System.

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## ABSTRACT

In the present study, an attempt has been made to prepare floating microspheres of clarithromycin designed as gastroretentive dosage form for the treatment of *Heliobacter pylori.* The floating microspheres were prepared using different polymers like HPMC- ethyl cellulose, HPMC, eudragit S-100, eudragit L-100, by solvent evaporation/diffusion methods which offer advantage of short processing time, lack of exposure of the ingredients to high temperature and gives high encapsulation efficiency. Formulations were characterized for their particle size, practical yield, entrapment efficiency, *in vitro* buoyancy, scanning electron microscopy (SEM) and *in vitro* drug release. Scanning electron microscopy shows that spherical microspheres with porous surface were formed. The optical microscopic studies revealed that the practical yield was more than 61.78% with a particle size range of 105.61-292.40 µm. The percent entrapment efficiency is about 62.68% and more in larger particle as compared to smaller particle. The percent buoyancy was more than 74.10% up to 12 hours. The particle size, percent yield, percent drug entrapment and percent was increased significantly with increase in polymer concentration. The *in vitro* release was significantly decreased with in polymer concentration. Hence it can be inferred that the floating microsphere of clarithromycin as a gastroretentive dosage form may prolong drug release thereby improving bioavailability and enhance opportunity of drug absorption in stomach to prevent degradation of drug under alkaline pH.

**Keywords:** Clarithromycin, HPMC, SEM, *In- vitro* buoyancy, bioavailability.

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Received 03 June 2013, Accepted 03 July 2013

Please cite this article in press as: Mane KJ *et al* Design and Development of Floating Microsphere of Clarithromycin as Gastroretentive Drug Delivery System . American Journal of PharmTech Research 2013.

## INTRODUCTION

In the field of pharmaceutical technology; great efforts are being directed towards the refabrication of existing drug molecules in a fashion, capable of solving problem related to poor water solubility, poor bioavailability, dosing problem, stability, toxicity, etc. This trend of working has lead to development of new drug delivery system. Even today, conventional drug delivery systems are primary pharmaceutical products commonly seen in prescriptions and 'over the counter' market place. They provide prompt release of the drug but in order to achieve as well as maintain drug concentration within therapeutically achieved range, it is often necessary to administer it several times a day. Conventional drug therapy results in significant fluctuations of drug concentration in systemic circulation causing either lethal effect or no therapeutic action.[1] Basic goal of drug therapy is to provide therapeutic amount of drug to proper site in body to promptly achieve and then maintain desired drug concentration. This idealized objective points to two aspects most important to the drug delivery, namely spatial placement and temporal delivery of drug. Spatial placement relates to targeting a drug to specific organ or tissue while temporal delivery refers to controlling rate of drug delivery to that specific organ or tissue[2].

Despite tremendous advancement in drug delivery, oral route remains preferred route for administration.[3] Oral controlled release dosage forms have been developed over past three decades. These drug delivery system have a great potential of solving problems associated with conventional multiple dosing system like strict adherence to timely dosing, flip flop plasma concentration, associated side effects due to systemic accumulation of drug. Thus, there are numerous advantages such as improved efficacy, reduced toxicity, improved patient compliance and convenience, reduction in health care cost, etc.[4] However, this approach is be filled with several physiological difficulties such as inability to restrain and locate controlled drug delivery system within the desired region of GIT, due to variable gastric emptying and motility. Furthermore the relative brief gastric emptying time in humans which normally averages 2-3 hrs through major absorption zone i.e. stomach and upper part of intestine can result in incomplete drug release from drug delivery system leading to low bioavailability and thus reduced efficacy of administered dose.[5] Efforts to improve oral drug bioavailability have grown in parallel with pharmaceutical industry. As the number and chemical diversity of drugs has increased, new strategies are required to develop orally active therapeutics. The past two decades have been characterized by an increased understanding of causes of low bioavailability and great deal of innovation in oral delivery technologies, marked by an unprecedented growth of drug delivery

industry.[6] It is evident from the recent scientific and patent literature that an increased interest in novel dosage forms that are retained in stomach for prolonged and predictable period of time exists today in academic and industrial research groups. One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in GIT is to control gastric residence time.[7] Control of placement of drug delivery system in specific region of GIT offers advantage for variety of important drugs characterized by narrow absorption window in GIT or drugs with stability problem. These considerations have lead to development of unique oral controlled release dosage form with gastro retentive properties i.e. dosage form could be retained in the stomach for several hours and release the drug there in a controlled and prolonged manner, so that drug could be supplied continuously to its absorption site in the upper GIT.[5] To comprehend the considerations taken in design of gastro retentive dosage forms and to evaluate their performance, the relevant anatomy and physiology of GIT must be fully understood.[8] The GIT is essentially a tube about 9 mts long that runs through middle of body from mouth to anus and include throat(pharynx), esophagus, stomach, small intestine(consisting of duodenum, jejunum and ileum) and large intestine(consisting of cecum, appendix, colon and retum). In the living person it is shorter because the muscles along walls of GIT organs are in state of tone (sustained contraction). Wavelike contractions of smooth muscle in wall of GIT propel the food along the tract from esophagus to anus.[9]

## MATERIALS AND METHOD:

Clarithromycin obtained gift sample from Cipla Pvt. Ltd. Mumbai, Ethylcellulose, HPMCK4M, Ethanol, Dichloromethane, Hydrochloric acid, Polyvinyl alcohol, Tween-80, Tween-20, Acetone, SD Fine Che Ltd, Mumbai. Eudragit S 100 & L 100, Deggusa India Pvt. Ltd Mumbai.

**METHOD OF PREPARATION: [10-13]**

**Emulsion solvent evaporation:**

The drug and polymer in different proportions are weighed (as shown in table 4) the polymer was co dissolved into previously cooled mixture of ethanol: dichloromethane at room temperature. The mixture was stir vigorously to form uniform drug polymer dispersion. The above organic phase was slowly added to 100 ml distilled water containing 0.01% tween 80 by maintain the temperature at 15 – 20°C and emulsified by stirring at 200 rpm for 15 min. Microspheres formed were filtered, washed with water and sieved between 50 and 30 mesh size, and dried overnight for 40°C.

**Emulsion Solvent Diffusion:[14]**

Weighed amount of clarithromycin was mixed with Eudragit S 100 / Eudragit L 100 drug:polymer ratio (1:1, 1:2, 1:3) in a solution of ethanol :dichloromethane ( 1:1 ) at room temperature. The resulting drug polymer solution was poured slowly using glass tube into 200 ml of water containing 0.75 % w/v polyvinyl alcohol, maintained at constant temperature of $40^0$ c and preparation was stirred at 300 rpm for 1 hr. The finely developed floating microspheres were then filtered, washed with water and sieved between 50 and 30 mesh size and dried overnight at $40^0$ c. The formulation table of floating microspheres of Clarithromycin showed in Table 1.

**Table 1. Formulation table of floating microspheres of Clarithromycin F1 to F 6**

| Ingredients | Formulation code | | | | | |
|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 |
| Clarithromycin (mg) | 500 | 500 | 500 | 500 | 500 | 500 |
| HPMC K4M (gm) | 1.50 | 1.50 | - | - | - | - |
| Ethylcellulose (gm) | 0.50 | 1.00 | - | - | - | - |
| Eudragit S 100 (gm) | - | - | 0.50 | 1.00 | - | - |
| Eudragit L 100 (gm) | - | - | - | - | 0.50 | 1.00 |
| Dichloromethane (ml) | 20 | 20 | 20 | 20 | 20 | 20 |
| Ethanol (ml) | 20 | 20 | 20 | 20 | 20 | 20 |

## CHARACTERIZATION OF FLOATING MICROSPHERE:

### Scanning Electron Microscopy:[10-12]

The external and internal morphology of the microspheres were studied by scanning electron microscopy (SEM). The sample for SEM was prepared by lightly sprinkling the powder on a double adhesive tape stuck to an alminum stub. The stubs were then coated with gold to a thickness of about $300A^0$ under an argon atmosphere using a gold sputter module in a high vaccum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope (Joel JSM-1600, Tokyo, Japan). SEM photographs are shown in figure 1.

## EVALUATION OF FLOATING MICROSPHERES

### Micromeretic properties:[13, 14]

The microspheres were characterized by their micromeritic properties such as particle size, bulk density, tapped density, compressibility index. Hauser's ratio and angle of repose.

### Particle size:[15]

he particle size was measured by microscopic technique. In this method suspension of floating microspheres was prepared using castor oil. A drop of suspension was mounted on a slide and observed under optical microscope about 600 particles were measured with the help of the eye piece micrometer. All the microspheres in a field was counted.

### Bulk density:[16,17]

In this method floating microspheres are transferred to a measuring cylinder and is tapped manually till a constant volume is obtained. This volume is bulk volume and it includes true volume of the powder and the void space among the microspheres.

Bulk density = Mass of microspheres / Bulk Volume

**Tapped density:**[18, 19]

In this method floating microspheres were transferred to a measuring cylinder & tapped for 100 times. After tapping volume of microspheres was visually examined. The ratio of mass of microspheres to volume of microspheres after tapping gives tapped density floating microspheres.

Tapped density = Mass of microspheres/ Volume of Microspheres after tapping

Percent Compressibility index was determined by using the formula,

$$\% \text{ Compressibility index} = 1 - V/V_0 \times 100$$

Here V and Vo are the volumes of the sample after and before the standard tapping, respectively.

**Hauser's Ratio:**[20]

Hauser's ratio of microspheres was determined by comparing tapped density to bulk density using the equation

Hauser's ratio = Bulk density / tapped density

**Angle of Repose:**[19]

Angle of repose ($\theta$) of the microspheres, which measures the resistance to particle flow, was determined by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blends. Accurately weighed microspheres were allowed to pass through the funnel freely on to the surface. The height and radius of the powder conc was measured and angle of repose was calculated using the following equation

$$\theta = \tan^{-1} h/r$$

Where,

θ - Angle of repose

h - Height of granules above the flat surface

r - Radius of the circle formed by the granule heap.

**Yield of Floating Microspheres:**[18]

The prepared floating microspheres were collected and weighed. The measured weight was divided by total amount of all non-volatile components which were used for the preparation of microspheres.

% Yield = Actual weight of product / Total Weight of excipents and drugs X 100

***In-Vitro* Buoyancy:**[20]

Floating microspheres were dispersed in 900ml of 0.1 N hydrochloric acid solution containing 0.02% tween 80 to simulate gastric fluid at 37°. The mixture was stirred with a paddle at 100 rpm and after 12 hr, the layer of buoyant microspheres ($W_f$) was pipetted and separated by filtration simultaneously sinking microsphere ($W_{s)}$ was also separated. Both microspheres type were dried at 40°C overnight. Each weight was measured and buoyancy was determined by the weight ratio of the floating microspheres to the sum of floating and sinking microspheres.

$$\text{Buoyancy \%} = Wf/ Wf+ Ws \text{ X } 100$$

Where,

$W_f$ and $W_s$ are the weights of the floating and settled microspheres, respectively. All the determinations were made in triplicate.

**Incorporation efficiency:** [19]

Floating microspheres were dissolved in a minimum amount of methanol and drug was extracted into 0.1 N hydrochloric acid by evaporating methanol. The solution was filtered through whatman filter paper, diluted suitably and analyzed for drug content spectrophotometrically at 762 nm using 0.1N hydrochloric acid as blank.

***In-Vitro* Drug release:** [20]

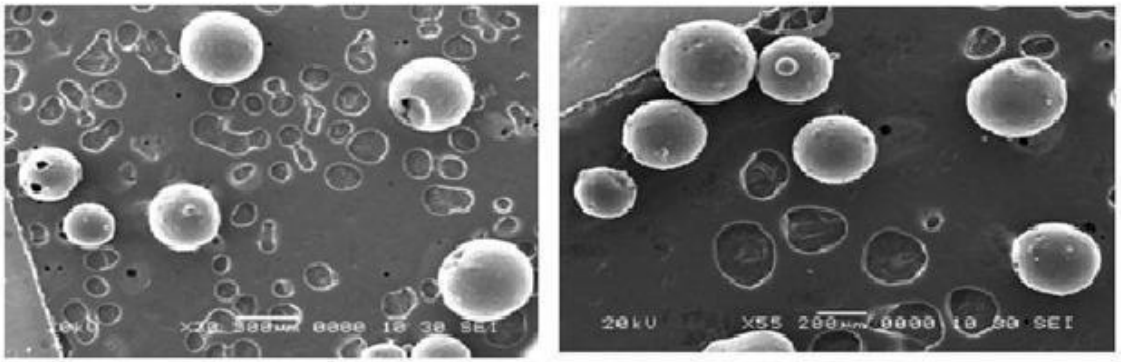
The *In-Vitro* release of drug from floating microspheres was carried out using paddle type Electro lab tablet dissolution tester USP XXIII. Drug loaded microspheres equivalent to 500 mg of drug was introduced into 900 ml of the dissolution medium (0.1N HCl) maintained 37±0.5ºC with paddle rotating at 100 rpm. Aliquots were withdrawn at regular interval and analyzed spectrophotometrically using Shimadzu-1700 UV-visible spectrophotometer. The dissolution studies were carried out in triplicate in 0.1N HCl for 12 hours. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5ml with same dissolution medium. The released data obtained was fitted into various mathematical models as under to know which mathematical model is best fitting the obtained release profile**.** The amount of drug released was analysed at 762 nm using shimadzu UV visible spectrophotometer.

## RESULTS AND DISCUSSION:

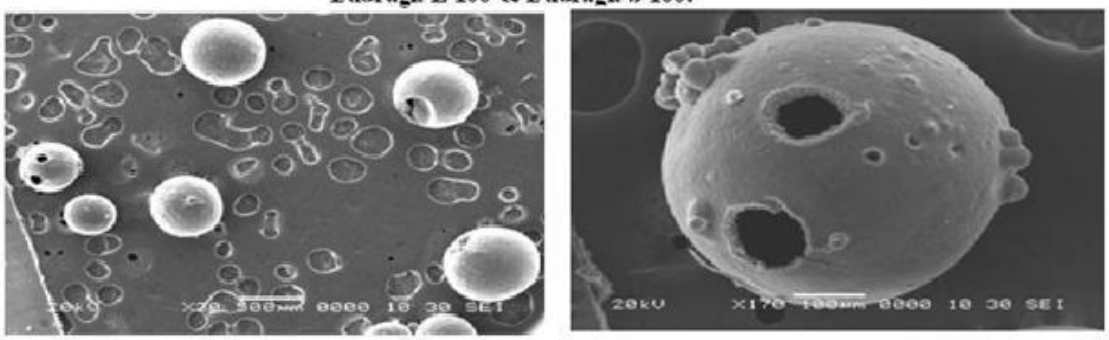
The aim of present study was to develop floating microspheres of clarithromycin for treatment of H. pylori by emulsion solvent evaporation and emulsion solvent diffusion method by using HPMC K4M, Ethyl cellulose and eudragit S-100, eudragit L-100 as polymers.

Floating microspheres of clarithromycin using Eudragit S -100 and Eudragit L -100 as polymer

prepared by emulsion solvent diffusion method as shown in table1. In this method, the organic solvent ethanol gets diffused out of dispersed droplets with controlled rate in presence of dichloromethane. The acrylic polymer Eudragit instantly solidified as thin film at the interface between aqueous and organic phase where clarithromycin get encapsulated in core-coat of polymer. Morphology of microspheres was examined by scanning electron microscopy. The view of the microspheres showed a hollow spherical structure with a smooth surface morphology Figure 1.



Scanning electron microphotographs of clarithromycin loaded floating microsphere of Eudragit L-100 & Eudragit S-100.



Scanning electron microphotographs of clarithromycin loaded floating microsphere of HPMC

**Figure 1. SEM Electron microphotographs of clarithromycin loaded floating microsphere of Eudragit L-100 & S-100 and HPMC.**

The Micromeritic properties of floating microspheres of Clarithromycin are given in table 2. *In-Vitro* drug release studies of clarithromycin from floating microspheres were performed in 0.1 N HCL for 12 hours using USP Type I dissolution test apparatus. *In-Vitro* release of clarithromycin was good at end of 12 hr from all the formulation. The Practical yield, *In-Vitro* buoyancy and entrapment efficiency of floating microspheres of Clarithromycin are given in table 3. The drug was get released from the microspheres by entry of dissolution medium through porous surface and that there was no polymer dissolution or chain relaxation due to non-swelling nature of

polymers , except for the HPMC K4M-EC microspheres where HPMC K4M get swelled in aqueous medium. No burst effect was observed from any of prepared microspheres.

**Table 2. Micromeritic properties of floating microspheres of Clarithromycin**

| Formulation | Mean Particle Size | Compressibility index (%) | Tapped density (gm/cm³) | True density ( g/cm³) | Angle of repose |
|---|---|---|---|---|---|
| F1 | 270.75 ± 2.52 | 15.41 ± 0.02 | 0.4435± 0.01 | 0.741± 0.04 | 19.35 ± 1.71 |
| F2 | 292.40 ± 2.51 | 18.51 ± 0.01 | 0.4942 ± 0.02 | 0.749± 0.05 | 22.65 ± 3.89 |
| F3 | 127.30± 15.27 | 23.52 ± 0.05 | 0.6847 ± 0.07 | 0.699± 0.01 | 15.81 ± 1.43 |
| F4 | 162.35± 11.01 | 22.29 ± 0.02 | 0.6730 ± 0.03 | 0.725± 0.03 | 19.05 ± 2.42 |
| F5 | 105.61± 21.12 | 25.11 ± 0.04 | 0.6350 ± 0.05 | 0.743± 0.01 | 17.71 ± 1.59 |
| F6 | 125.65± 19.60 | 21.45 ± 0.03 | 0.6940 ± 0.05 | 0.755± 0.03 | 18.07 ± 1.68 |

The *In-Vitro* release of clarithromycin significantly decreased with increase in polymer concentration in each type of preparation. The increased density of polymer matrix at higher concentration results in an increased diffusional path length. This may decrease overall drug release from the polymer matrix. Furthermore, smaller microspheres were formed at lower polymer concentration and have large surface area exposed to dissolution medium giving rise to faster drug release. The *In-Vitro* release from each formulation follows the following order**:** for HPMC**:** EC microspheres F1 > F2 ; for eudragit s-100 microspheres F3 > F4 ; for Eudragit L-100 microspheres F5> F6.

**Table 3. Practical yield, *In-Vitro* buoyancy and entrapment efficiency, cumulative percent release of floating microspheres of Clarithromycin**

| Formulation code | Practical yield (mean±SD) (%) | *In-Vitro* buoyancy (mean±SD) (%) | Drug entrapment efficiency (mean±SD) (%) | Cumulative Percent Drug Released |
|---|---|---|---|---|
| F1 | 65.20 ± 0.64 | 74.10 ± 1.52 | 80.30± 2.72 | 84.150 |
| F2 | 73.15 ± 0.69 | 78.70 ± 2.07 | 85.70± 2.84 | 81.156 |
| F3 | 62.55± 0.72 | 82.55 ± 2.08 | 65.35± 1.58 | 78.760 |
| F4 | 78.70± 2.00 | 86.16 ± 1.00 | 85.21± 2.02 | 75.765 |
| F5 | 61.78± 2.05 | 78.25 ± 4.04 | 62.68± 0.98 | 79.359 |
| F6 | 74.49± 1.51 | 86.76 ± 1.52 | 80.85± 2.34 | 76.664 |

## CONCLUSION:

The data obtained from the study of "Development and evaluation of floating microspheres of Clarithromycin reveals concluded that Clarithromycin loaded floating microspheres can be prepared using HPMC K4M-EC, cellulose eudragit L-100 and eudragit S-100 porous polymers by solvent evaporation/ diffusion method. The practical yield was significantly increases as the amount of polymer was increased in each preparation method. The particle size increased significantly as the amount of polymer increased. From the result it was observed that drug**:**

polymer ratio influence the particle size, *In-Vitro* buoyancy as well as drug release pattern of floating microsphere. Hence, the multiple-unit floating systems of clarithromycin are expected to provide clinician with a new choice of safe and more bioavailable formulation in the management of bacterial infections. The study reveals satisfactory results with a further scope of pharmacokinetic and pharmacodynamic evaluation.

## ACKNOWLEDGMENTS:

Authors thank Cipla Pvt Ltd. Mumbai for providing a gift sample of clarithromycin. The authors are also thankful **to** Dr. M. G. Purohith, Emeritus Professor, Luqman College of Pharmacy, and Gulbarga for their valuable suggestions in carrying out this research work. The authors are also thankful to Dr. M. A. Mujeeb, Chairman, Luqman College of Pharmacy, Gulbarga, providing the facilities to carry out the research work.

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