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# Formulation and Development of Floating and Mucoadhesive Microspheres of Clarithromycin

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The basic objective of this comparative study between gastro retentive floating microspheres and mucoadhesive microspheres of drugs Clarithromycin. Floating microspheres and mucoadhesive microspheres loaded with Clarithromycin in their outer polymer shells were prepared by emulsification solvent evaporation method. Using different grades of hydroxyl propyl methylcellulose (HPMC) such as HPMC K15M, HPMC K100M, carbopol 934, carbopol 940 and ethyl cellulose (EC). The prepared microspheres were characterized by polymer compatibility, percentage yield, buoyancy percentage, drug entrapment efficiency and in vitro drug release. An optimized formulation investigated for morphology and particle size analysis by scanning electron microscopy. Clarithromycin has low bioavailability i.e. 50-60% due to its first pass metabolism. Floating and mucoadhesive microspheres have been accepted as a process to achieve controlled drug delivery by prolonging the residence time of the dosage form at the site of absorption, thereby improving and enhancing the bioavailability of drug.

*Keyword:* Clarithromycin, Floating Microspheres, Mucoadhesive Microspheres, Gastro Retentive Drug Delivery.

## 1. Introduction

The basic objective of this study formulation and evaluation of gastro retentive floating microspheres and mucoadhesive microspheres of drugs Clarithromycin. As well as comparative study between floating and Mucoadhesive microspheres evaluation parameter.

Gastroretentive 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. Gastro retention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients[1].

Floating systems 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. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This result sin an increased GRT and a better control of the fluctuations in plasma drug concentration[2].

Mucoadhesion, an interfacial phenomenon, is based on two materials, one of which is mucus layer of mucosal tissue to which the drug is held together by means of interfacial forces for prolonged period of time. Mucoadhesive drug delivery systems promises several advantages

that arise from localization at a given target site, prolonged residence time at the site of drug absorption and an intensified contact with the mucosa increasing the drug concentration gradient[3].

Clarithromycin (CLR) is a macrolide antibiotic with broad spectrum of activity. It is given in the treatment of respiratory tract infections and in the skin and soft tissue infections. CLR may be given to eradicate *H. pylori* in treatment regimens for peptic ulcer diseases. CLR is rapidly absorbed from the gastrointestinal tract and undergoes first pass metabolism. The bioavailability of the drug is about 55%. The terminal half life of CLR is reportedly about 3-4 hours. Thus CLR has all the requisites of gastro retentive drug delivery system[4].

## 2. Materials and Methods

### 2.1 Materials

Clarithromycin, carbopol 934, carbopol940, HPMC K15M, HPMC K100M was purchased from Balaji drug supplier surat, Gujarat, India. All other ingredients were used analytical grade from my college's laboratory.

## 3. Methods

### 3.1 Preparation of Floating Microspheres of Clarithromycin

The technique of floating microspheres preparation is based on emulsification solvent evaporation method in which the polymer ethylcellulose was dissolved in 50ml of acetone at different concentrations with stirring. HPMC K15M, HPMC K100M, Sodium bicarbonate, citric acid and clarithromycin of different concentrations were added to the above polymer solution and the total mixture was blended for 1h. Then this suspension was slowly added to the 200 ml light liquid paraffin which containing 2.0% Span 80 and stirred at a rate of 1000 rpm using Remi mechanical stirrer equipped with a three bladed propeller at room temperature for 1h. After 1hr of emulsification, acetone was evaporated gradually with the help of a rotary flash evaporator at 40 $^0$C until the microspheres were formed. The formed microspheres were washed with petroleum ether (40-60 $^0$C) and dried at room temperature[5]. Six formulations had been prepared by this method; the various formulation variables considered for optimization were shown in the table 1.

**Table 1:** Formula for preparation of floating microspheres of Clarithromycin

| Formulation code | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 |
|---|---|---|---|---|---|---|
| Clarithromycin | 200 | 200 | 200 | 200 | 200 | 200 |
| HPMC K15M | 150 | --- | 150 | --- | 150 | --- |
| HPMC K100M | --- | 150 | --- | 150 | --- | 150 |
| Ethyl cellulose | 150 | 200 | 150 | 200 | 150 | 200 |
| Sodium bicarbonate | 75 | 75 | 75 | 75 | 75 | 75 |
| Citric acid | 25 | 25 | 25 | 25 | 25 | 25 |
| Span 80 | 2 | 2 | 2 | 2 | 2 | 2 |
| Liquid paraffin | 200 | 200 | 200 | 200 | 200 | 200 |
| Time | 45 | 60 | 45 | 60 | 45 | 60 |
| RPM | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |

### 3.2 Preparation of Mucoadhesive Microspheres of Clarithromycin

The microspheres were prepared by non-aqueous emulsification solvent evaporation method. Drug and Polymer i.e. Clarithromycin and Carbopol 940P Carbopol 934 & HPMC (Hydroxy propyl methyl cellulose) K100 M, HPMC K15M were mixed in Ethanol & Dichloromethane. The slurry was introduced in to 200 ml of Liquid Paraffin while being stirred at 1000 rpm by mechanical stirrer for 45 min to allow the solvent to evaporate completely and the microspheres were collected by filtration. The microspheres were washed repeatedly with Petroleum ether 40-60 $^0$C until free from oil. The collected microspheres were dried for 1hr at room temperature[6]. Six formulations had been prepared by this method; the various formulation variables considered for optimisation were shown in the table 2.

**Table 2:** Formula for preparation of Mucoadhesive microspheres of Clarithromycin

| Formulation code | CM1 | CM2 | CM3 | CM4 | CM5 | CM6 |
|---|---|---|---|---|---|---|
| Clarithromycin | 200 | 200 | 200 | 200 | 200 | 200 |
| Carbopol 934 | 200 | --- | 200 | --- | 200 | --- |
| Carbopol 940 | --- | 200 | --- | 200 | --- | 200 |
| HPMC K15M | 100 | --- | 100 | --- | 100 | --- |
| HPMC K100M | --- | 100 | --- | 100 | --- | 100 |
| Dichloromethane | 15 | 15 | 15 | 15 | 15 | 15 |
| Ethanol | 15 | 15 | 15 | 15 | 15 | 15 |
| Liquid paraffin | 200 | 200 | 200 | 200 | 200 | 200 |
| RPM | 1000 | 1000 | 1000 | 1000 | 1000 | 1000 |
| Time | 45 | 60 | 45 | 60 | 45 | 60 |

## 4. Evaluation of Floating Microspheres

### 4.1 Yield of Microspheres

The prepared microspheres were collected and weighed. The measured weight divided by the total amount of all non-volatile components, which were used for the preparation of the microspheres[7].

$$Practical\ yield = \frac{Actual\ weight\ of\ product}{Weight\ of\ excipient\ \&\ drug} \times 100$$

### 4.2 Particle Size

The size was measured using an optical microscope under regular polarized light, and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer[8].

### 4.3 Scanning Electron Microscopy (SEM)

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 aluminum stub. The stubs were then coated with gold to a thickness of about 300Aº under an argon atmosphere using a gold sputter module in a high vacuum evaporator. The coated samples were then randomly scanned and photomicrographs were taken with a scanning electron microscope[8,9].

### 4.4 Drug Entrapment Efficiency

Microspheres equivalent to 50 mg of the drug were taken for evaluation. The amount of drug entrapped was estimated by crushing the microspheres and extracting with aliquots of 0.1N HCl and small quantity of methanol repeatedly. The extract was transferred to a 100 ml volumetric flask and the volume was made up using 0.1N HCl. The solution was filtered and the absorbance was measured after suitable dilution with 0.1N HCl spectrophotometrically at 231 nm against appropriate blank[10,11]. The amount of drug entrapped in the microspheres was calculated by using the following formula:

$$\%Drug\ entrapment\ efficiency = \frac{Amount\ of\ drug}{Theoretically\ expected\ drug\ loaded} \times 100$$

### 4.5 *In vitro* Buoyancy

An *in vitro* floating study was carried out using 0.1N HCl containing 0.02% tween-80 as a dispersing medium. Microspheres were spread over the surface of 900 ml of dispersing medium at 37±0.5 ºC. A paddle rotating at 100 rpm agitated the medium. Each fraction of microspheres floating on the surface and those settled down were collected at a predetermined time point. The collected samples were weighed after drying[12].

### 4.6 *In vitro* Dissolution Studies

The in vitro release of drug from floating microspheres was carried out using paddle type Electrolab tablet dissolution tester USP XXIII. Drug loaded microspheres equivalent to 250 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 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[5,6].

## 5. Result & Discussion

### 5.1 Percentage Yield

The maximum percentage yield was found in CM6 batch and was noted to be 81.80% for drug Clarithromycin mucoadhesive Microsphere and for Clarithromycin floating microsphere it was found 75% of formulation CF4. It was found that average percentage yield of mucoadhesive microsphere was better than for Clarithromycin floating microsphere for all. Results were given in table 3 and 4.

### 5.2 Particle Size

The average particle size of the various batches of Clarithromycin floating microsphere had in the range of 175.5µm to 275.64µm and Clarithromycin mucoadhesive Microsphere had in the range of 150.43µm to 350.12µm. The particle size was increased as the stirring time and stirring speed was decreased.

### 5.3 Percent Drug Entrapment

The Percent Drug Entrapment of Clarithromycin mucoadhesive Microsphere had in the range 60% to 68% & Clarithromycin floating microsphere had in the range 63% to 72%.

So, The Percent Drug Entrapment of Clarithromycin mucoadhesive Microsphere was better than Clarithromycin floating microsphere. Results were given in table 3 and 4.

### 5.4 *In vitro* buoyancy

The result of the in Percent buoyancy of Clarithromycin floating microsphere had in the range of 58% to 75 %. Formulation CF1 has 75% highest Percent buoyancy is shown in table no. 3

### 5.5 Scanning Electron Microscopy (SEM)

The morphology of the microspheres was examined by SEM the view of the microspheres showed a spherical shape with a smooth surface morphology. The mean particle size increase with increase polymer concentration. The mean diameter clarithromycin loaded floating microspheres was found to be 4.33 to 259.6µm & the mean diameter clarithromycin loaded floating microspheres was found to be 3.33 to 357.6µm.

**Table 3:** Evaluation of Clarithromycin Floating Microspheres

| Formulation code | Percentage Yield (%) | Particle size range (µm) | Drug entrapment efficiency (%) | Percentage buoyancy |
|---|---|---|---|---|
| CF1 | 68.33 | 175.5 | 65 | 75 |
| CF2 | 62.5 | 225.5 | 59 | 58 |
| CF3 | 58.33 | 195.23 | 62 | 68 |
| CF4 | 75 | 235.42 | 68 | 60 |
| CF5 | 50 | 275.64 | 60 | 62 |
| CF6 | 61.66 | 250.5 | 63 | 63 |

**Table 4:** Evaluation of Clarithromycin Mucoadhesive Microspheres

| Formulation code | Percentage yield (%) | Particle size range (µm) | Drug entrapment efficiency (%) |
|---|---|---|---|
| CM1 | 74.40 | 150.43 | 65 |
| CM2 | 70 | 200.03 | 63 |
| CM3 | 76 | 280.56 | 69 |
| CM4 | 81.20 | 270.42 | 72 |
| CM5 | 70 | 310.25 | 62 |
| CM6 | 81.80 | 350.12 | 70 |

### 5.6 *In-Vitro* Dissolution

Drug Release profile of batches of Clarithromycin mucoadhesive Microsphere CM1-CM6 was found 59.04%, 73.33, 69.7, 67.02, 66.07, and 61.48 % respectively. And Clarithromycin floating microsphere's Drug Release profile of the batch CF1-CF6 was found 59.04%, 63.09, 64.93, 58.86, 70.12, and 56.4. CM2 formulation of Clarithromycin mucoadhesive Microsphere shows highest release of drug among the all batches. And in Clarithromycin floating microsphere's CF4 shows highest release of drug. So Drug Release profile of Clarithromycin mucoadhesive was fond better than Microsphere floating microsphere.

**Table 5:** Percentage cumulative release of Drug Clarithromycin floating Microspheres

| Time (hr) | CF1 | CF2 | CF3 | CF4 | CF5 | CF6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 11.68 | 7.46 | 10.13 | 6.13 | 9.53 | 4.7 |
| 2 | 15.31 | 11.97 | 11.97 | 10.97 | 15.64 | 8.22 |
| 4 | 22.11 | 20.26 | 23.12 | 24.49 | 24.08 | 16.81 |
| 6 | 29.64 | 29.09 | 32.08 | 30.68 | 33.06 | 24.18 |
| 8 | 37.16 | 36.87 | 40.81 | 42.12 | 47.66 | 32.88 |
| 10 | 48.25 | 47.48 | 56.41 | 57.89 | 58.62 | 47.96 |
| 12 | 59.04 | 63.07 | 64.95 | 58.87 | 70.12 | 56.4 |

**Table 6:** Percentage cumulative release of Drug Clarithromycin mucoadhesive Microspheres.

| Time (hr) | CM1 | CM2 | CM3 | CM4 | CM5 | CM6 |
|---|---|---|---|---|---|---|
| 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 1 | 15.49 | 18.47 | 22.64 | 20.14 | 9.53 | 11.5 |
| 2 | 19.23 | 23.1 | 26.38 | 23.34 | 12.86 | 15.12 |
| 4 | 26.1 | 30.1 | 36.83 | 30.87 | 19.49 | 22.53 |
| 6 | 33.18 | 41.22 | 44.5 | 37.77 | 30.5 | 30.68 |
| 8 | 40.92 | 51.59 | 51.89 | 44.86 | 44.86 | 44.38 |
| 10 | 48.25 | 62.55 | 62.55 | 51.89 | 55.7 | 55.74 |
| 12 | 59.04 | 73.33 | 69.7 | 67.02 | 66.07 | 61.48 |

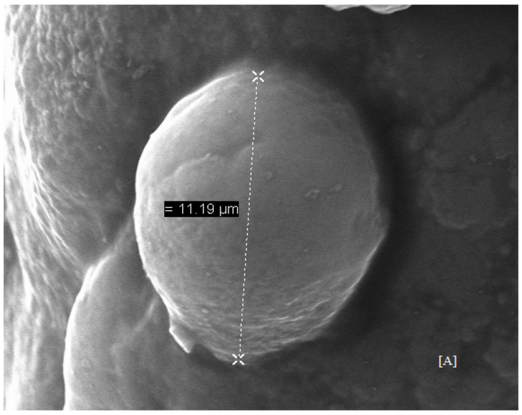


**Fig 1:** (A) SEM of Optimized batch CF5 of Floating Microspheres

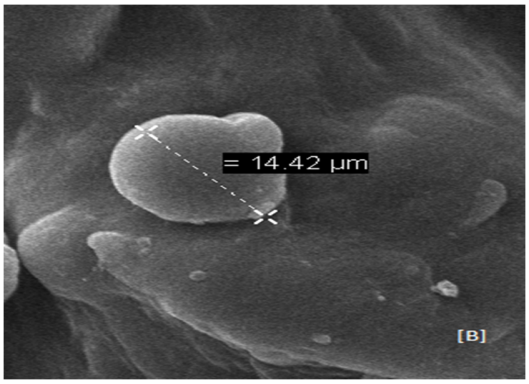


**Fig. no.2** (B) SEM of optimized batch CM2 of mucoadhesive microspheres.

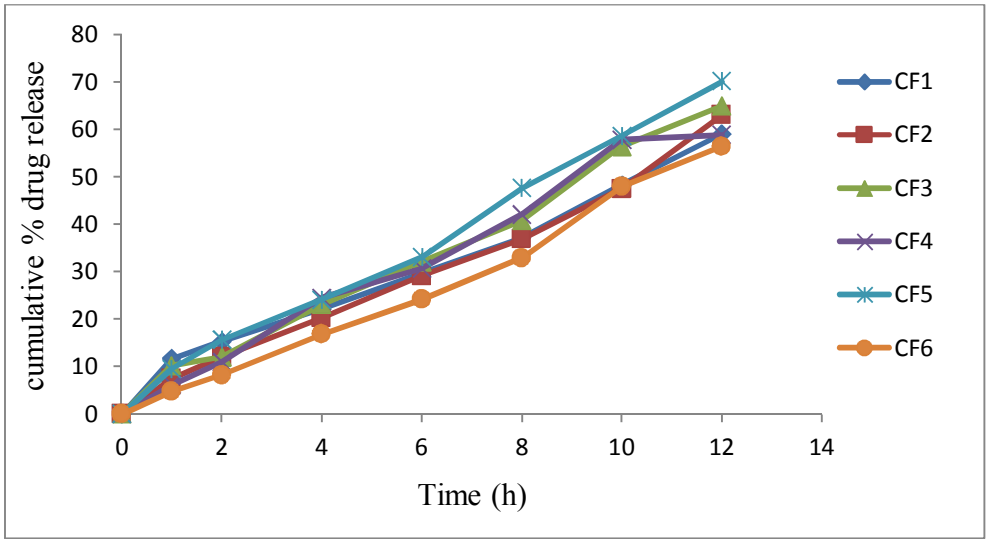


**Fig 3:** Drug release pattern of batches CF1 to CF6 of Clarithromycin Floating Microspheres

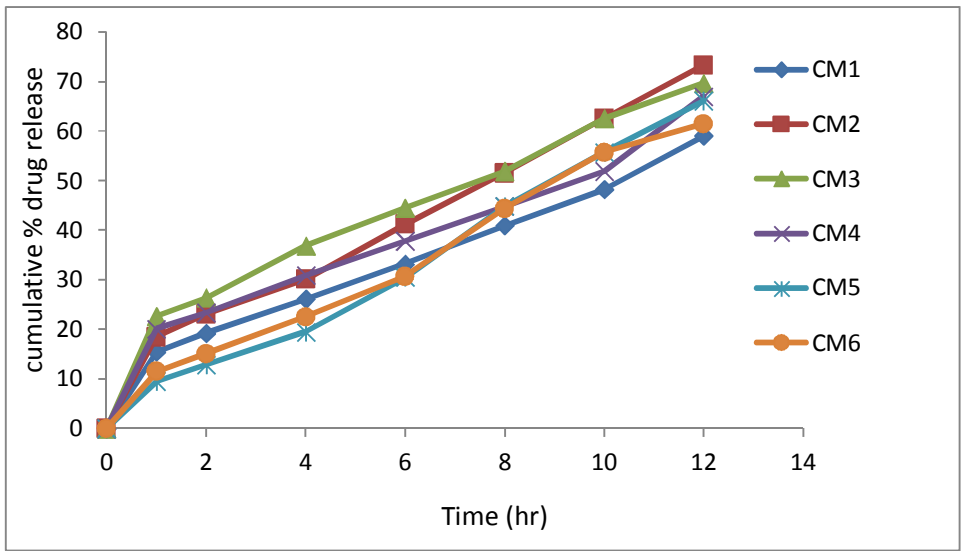


**Fig 4:** Drug release pattern of batches CM1 to CM6 of Clarithromycin Mucoadhesive Microspheres

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