The Pharma Research
Year: 2009, Vol: 01

# FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF OFLOXACIN

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## ABSTRACT

The objective of the study was to develop floatable hollow microspheres of ofloxacin designed to increase its residence time in the stomach without contact with the mucosa having potential for intragastric sustained drug delivery. Floating microspheres were prepared using emulsion-solvent diffusion method, which involved co-dissolution of drug and Eudragit RS-100 & Eudragit S-100 in various ratios in ethanol: dichloromethane mixture (1:1 v/v), which was finely dispersed in the aqueous medium. *Invitro* testing revealed that the hollow microspheres floated continuously over the surface for more than 24 hours. The drug release profiles from floating microspheres reflected their enteric behavior.

**Keywords:** ofloxacin, hollow microspheres, Eudragit RS 100, Eudragit S 100

## 1. INTRODUCTION

Increased gastric retention of drug delivery system in certain situations may be desirable to improve the bioavailability and the therapeutic efficacy of the drugs. Drugs that are absorbed easily in the proximal part of the gastro intestinal (GI) tract, and having short half-life are estimated quickly from the blood circulation. To overcome these problems, orally administered drugs are generally film coated or microencapsulated to prolong the drug release period and drug action.

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However most of these forms have several physiological problems such as GI transit time, short residence time and incomplete drug release from devices, which leads to low bioavailability.

To overcome this problem, several attempts have been made recently to extend GI transit time of the devices. One such method is floating drug delivery systems. These devices have specific density that is lower than that of the gastric fluids. Most of the floating system is the high variability of the GI transit time. Therefore, a multiple-unit floating system has been worked upon.

In the present study, hollow microspheres of Ofloxacin were developed using Drug: Eudragit RS100: Eudragit S 100 in various ratios by emulsion solvent diffusion method. These hollow microspheres were tested for physicochemical properties along

with Invitro floating and the drug release behavior. The best Drug: Eudragit RS 100: Eudragit S 100 was also studied.

## 2. Materials and Methods:

Ofloxacin was a gift sample from Sun Pharmaceuticals Pvt. Ltd., Baroda, Eudragit RS 100 and Eudragit S 100 (Rohm Pharma Gmbh, Germany), PVA-120 (Sigma chemical Company, USA) AND Ethanol commercially available grade was obtained from Hayman Laboratories Ltd. England. All the other chemicals were of analytical grade and were used without further purification.

### Preparation of floating hollow microspheres:

The outline of the procedure for the preparation of microspheres of ofloxacin was the same as the method described previously by Kawashima et al. The method involves the co-dissolution of ofloxacin (100 mg), Eudragit RS 100 and Eudragit S 100 polymers in various ratios $R_1$ (1:1:1), $R_2$ (1:2:2), $R_3$ (1:3:3) in 10 ml Ethanol: Dichloromethane mixture (1:1 v/v) which is finely dispersed in a 200 ml aqueous medium (water) which contained 0.75% w/v PVA-120. This system was stirred with propeller type agitator at 500 rpm, which resulted in the formation of o/w type of emulsion.

The finely dispersed droplets of polymeric solution of the drug were solidified in the aqueous phase via diffusion of the solvent. Dichloromethane that evaporated from the solidified droplets was removed using an aspirator, leaving the cavity of microspheres filled with water. After agitating the system for 60 minutes, the microspheres were filtered, washed with water and dried in oven at 120°C for 2 hours. During the drying process, a hollow cavity was formed resulting in hollow microspheres.

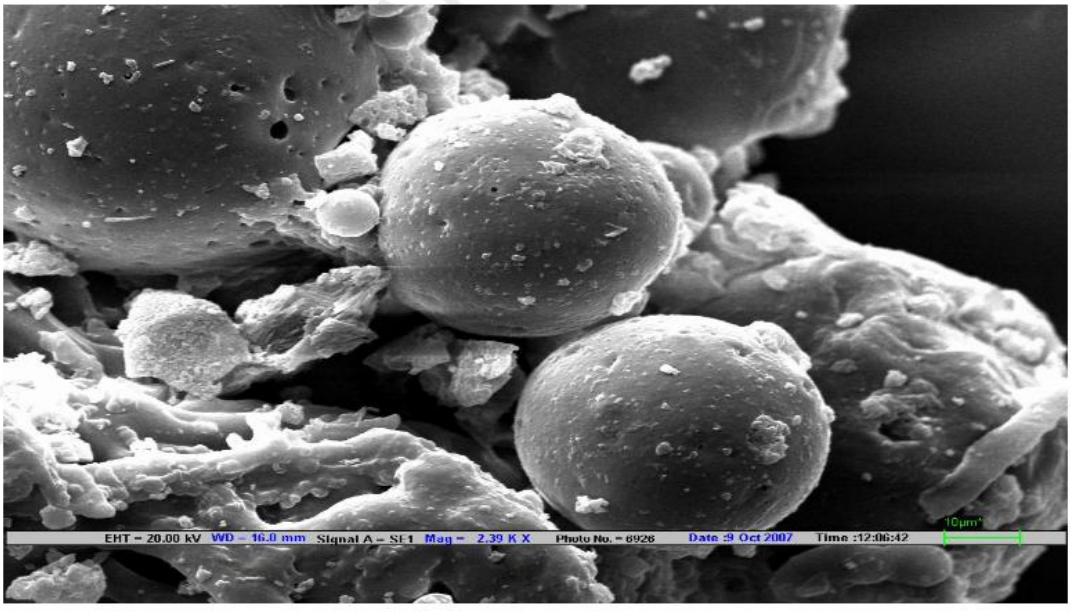


Figure 1. Scanning Electron microscope (SEM) image of floating ofloxacin Microspheres

**Evaluation of hollow microspheres**

**1. Determination of drug entrapment capacity**

UV spectroscopic method was used to determine the presence of drug in the microspheres. Microspheres (100 mg) were crushed in a mortar pestle. 500 ml of 0.1 N HCl was added slowly and mixed well. The solution was filtered using 0.45µm membrane filter. The filtrate was made to 900 ml with 0.1 N HCl and subjected to UV analysis (Shimadzu UV-VIS 1700) in triplicate at 291 nm. The entrapment was determined using the following relationship:

**Drug Entrapment Capacity (%) = (AQ/TQ) x 100**

Where AQ is the actual quantity of the drug present in the matrix and TQ is the 100% theoretical quantity of the drug in the matrix.

**2. Measurement of micromeritic properties of the microspheres**

The surface morphology and internal texture of the microspheres were observed by a scanning electron microscope-SEM (JSM-T330 A. Japan). The sieve analysis was conducted to determine the average diameter. The flow and packing properties were investigated by measuring the contact angle and tapped density as shown in Table 2.

**Table 1: Formulation Code, Ratio, Drug Entrapment, Percentage Loss of Drug in the Microspheres of Ofloxacin**

| Formulation Code | Drug to carrier Ratio | Drug Entrapment (% w/w) | % Loss of Drug |
|---|---|---|---|
| $R_1$ | 1:1:1 | 95.31 | 5.12 |
| $R_2$ | 1:2:2 | 92.23 | 7.86 |
| $R_3$ | 1:3:3 | 86.78 | 14.95 |

Average of three determinations R is the Drug: Eudragit RS 100: Eudragit S 100

**3. Determination of flow property of the microspheres**

The microspheres were put into an acid solution (0.1 N HCl) with Tween 20 (0.02%) and stirred with a magnetic stirrer continuously for more than 12 hours. The process was maintained at 37±0.5°C throughout the test.

**Table 2. Formulation Code, Ratio, Average Particle Size Range, Angle of Repose, Tapped Density for ofloxacin Microspheres**

| Formulation Code | Average Particle Size | Angle of Repose | Tapped Density ($g/cm^3$) |
|---|---|---|---|
| $R_1$ | 240-280 | 25°93' | 0.162 |
| | 280-440 | 33°66' | 0.171 |
| | 440-900 | 59°21 | 0.125 |
| $R_2$ | 240-280 | 30°16' | 0.178 |
| | 280-440 | 38°72' | 0.185 |
| | 440-900 | 66°10' | 0.168 |
| $R_3$ | 240-280 | 33°43' | 0.184 |
| | 280-440 | 37°89' | 0.164 |
| | 440-900 | 68°97' | 0.189 |

**Invitro release studies**

The release characteristics of ofloxacin microspheres were carried out using paddle method as specified in USP XXI. The microspheres were spread over the dissolution medium in 900 ml of 0.1 N HCl, pH 1.5 and then phosphate buffer pH 7.2 at 100 rpm foe 12 hours. The medium was maintained at 37±0.5°C. Perfect sink conditions prevailed during the drug dissolution test. The samples were withdrawn at suitable intervals from the dissolution vessel and assayed spectrophotometrically at 291 nm in triplicate.

**Table 3. % cumulative drug release at different time intervals**

| S. No. | Formulation Code | % cumulative drug release (hour ) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 24 |
| 1 | $R_1$ | **11.6** | **25.9** | **37.8** | **46.2** | **54.3** | **61.3** | **64.4** | **93.2** |
| 2 | $R_2$ | **10.6** | **22.3** | **33.5** | **41.7** | **45.6** | **54.6** | **59.9** | **88.6** |
| 3 | $R_3$ | **9.4** | **21.8** | **32.6** | **40.7** | **44.5** | **52.7** | **58.6** | **86.5** |

**Result and Discussion:**

The drug entrapment capacity for the microspheres of ofloxacin was found to be in the descending order of $R_1>R_2>R_3$ (95.31>92.23>86.78). This order suggested that as the polymer amount increased in the formulation, the entrapment of the drug in the microspheres is decreased. This phenomenon may be due to the fact that as the concentration of the polymer increases, the matrix becomes more and more thicker and finer resulting in the drug of particle size range not being entrapped as revealed with the increased percentage loss of the drug undergoing entrapment, which suggests that as regards to the aim of the study, the Drug: Eudragit RS 100: Eudragit S 100 ratio of 1:1:1 was a good ratio.

The SEM of surface of microspheres and its cross section indicated a perfect sphere without pore on the surface.

The micromeritic properties suggested that the microspheres can be handled easily and filled in capsules (Table 1). Therefore, capsules filled with microspheres are a good choice for Gastro Retentive Drug Delivery System. Here again, the formulation drug: Eudragit RS 100: Eudragit S 100 ratio of 1:1:1 was found to have best micromeritic properties.

The floating test of the microspheres of ofloxacin revealed that all the formulations underwent floating of 24 hours and more, especially as the concentration of the enteric polymer increased, the floating time also increased.

Invitro release studies of microspheres of ofloxacin showed that the formulation $R_1$ was higher as compared to $R_2$ and $R_3$. The drug release studies when subjected to Higuchi treatment (cumulative % release Vs sq. time) suggested a perfect Fickian diffusion ($r>0.999$). The release profile showed near perfect linearity ($r=0.9999$) when the data was plotted between log-log plot of amount dissolved Vs time (Weibull analysis). The diffusion mechanism was further authenticated when Peppas plot (cumulative % of drug remaining Vs time) was plotted ($n=0.4949$).

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**Source of support: Nil, Conflict of interest: None Declared**