FORMULATION AND CHARACTERIZATION OF MICROBALLOONS OF NORFLOXACIN

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ABSTRACT

The present study involves preparation and evaluation of floating microballoons of norfloxacin for improving the bioavailability by prolongation of gastric residence time. Norfloxacin, a sparingly water soluble drug, was selected and microballoons were prepared by emulsion solvent diffusion method using Eudragit L-100 and Eudragit RS-100 in ethyl alcohol and dichloromethane organic solvent system. The formation of a sphere and hollow within the sphere was confirmed through SEM studies. The percentage of drug entrapment and recovery was found to be 75-80%. The micromeritic properties indicated better flowability and packability of the spheres. The Buoyancy test showed good floatability of norfloxacin microballoons in the simulated gastric fluid for more than 12 h. *In vitro* dissolution profile showed prolonged release of drug from the formulations. Thus microballoons of norfloxacin with acrylic polymers prepared by emulsion solvent diffusion proves to be an ideal novel floating dosage form that is adaptable to any intragastric condition for controlled drug delivery and enhanced bioavailability.

Keywords: norfloxacin, hollow microspheres, acrylic polymers, evaluation

INTRODUCTION:

For oral sustained or prolonged-release dosage forms, multiple units are more advantageous than single units because they disperse widely and uniformly along the gastrointestinal tract and could lessen intra- and inter-subject variability. Gastric-retentive systems, multiple units, may have the advantage of avoiding all- or –nothing emptying, and increase the probability that some of the dosage form will remain in the stomach [1]. Approaches devising multiple unit floating systems include multiple unit HBS, polycarbonate microspheres [2], alginate beads [3], charged ion exchange resins with bicarbonate [4,5,6], air compartment multiple unit systems, coated granules with a dual effervescent layer [7] and emulsion solvent diffusion [8,9,10].

There are various approaches in delivering substances to the target site in a controlled release fashion via oral route. One such approach is using polymeric hollow microsphere as carrier for drugs. Hollow microspheres are known as the microballoonsdue to their low-density core [11]. Microballoons based drug delivery systems have received considerable attention in recent years. The most important characteristics of microballoons are microphase separation morphology, which endows it with a controllable variability in degradation rate and also drug release.[12,13]

Multiple unit systems such as microballoons capable of floating on the gastric fluid have the advantage that they are not subjected to "all or nothing" gastric emptying nature of single unit systems. Drug loaded polymeric microballoons and ion-exchange beads capable of floating on the gastric fluids have therefore been examined as FDF.

Norfloxacin is a potent antibacterial agent having very broad spectrum of its activity. It acts by inhibiting DNA Gyrase and hence it is specific bacterial DNA Gyrase blocker, thus it inhibits the synthesis of DNA in bacteria leading to its rapid lyses[14]. Owing to the variable transit time in gastro intestinal tract of all dosage forms, it could not be ascertained to localize a dosage form at the site of maximum absorption of a drug. So it was proposed to prepare floating microballoons of norfloxacin to localize the drug at its site of maximum absorption.

For the development of floating microballoons of norfloxacin, a combination of polymer Eudragit RS 100 and Eudragit L 100 was selected. These polymers are comes under the category of polymethacrylates. Anionic acrylic polymer Eudragit L 100 is insoluble in acid media i.e. resistant to gastric fluid, and dissolves only in the neutral to weakly alkaline medium of the small intestine. Permeable acrylic polymer Eudragit RS 100 is water insoluble over the entire pH range, but swells in digestive fluids independently of pH. In the swollen state it is permeable to water and dissolved actives[15].

In this study, an emulsion solvent diffusion/evaporation technique was used to prepare a floating controlled-release system for norfloxacin and the influence of several factors on various physical characteristics, including the particle size, drug loading , dissolution and floating properties of the resulting microspheres, were investigated.

MATERIAL AND METHOD:

MATERIAL: The gift sample of Norfloxacin was obtained from Aurochem Pharma. Pvt. Ltd. Mumbai. Eudragit L-100 and Eudragit RS-100 were obtained as a gift sample from pharmachem, Gujrat. Rest of the chemicals was of analytical grade.

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METHOD:

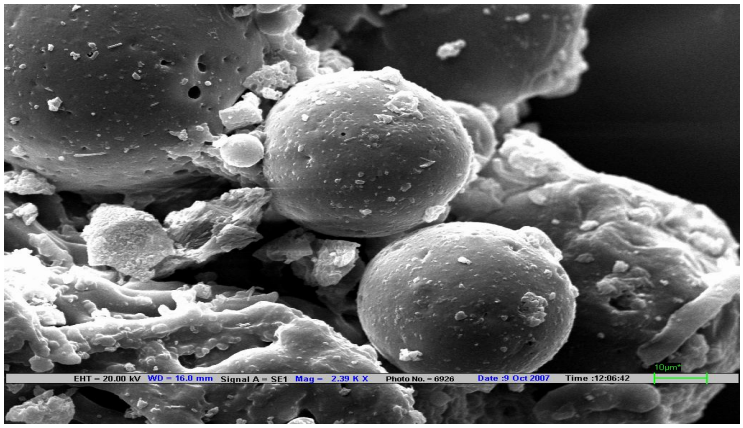
Microballoons with an internal hollow structure were prepared by solvent diffusion-evaporation method[16]. Equal quantities of two polymers i.e. Eudragit L-100 and Eudragit RS-100 were dissolved in ethanol, followed by the addition of isopropanol and dichloromethane. Then drug was homogeneously dispersed in this polymer solution. This polymer solution was slowly introduced into poly-vinyl alcohol (PVA) aqueous solution with stirring using a mechanical stirrer equipped with a propeller. The solution was stirred for 1 hour and microballoons were collected by filtration and washed 3 times with distilled water, dried at 40°C and kept in desiccators[17].

CHARACTERIZATION OF NORFLOXACIN MICROBALLOONS[18, 19, 20]

1. Morphology:

The surface morphology of microballoons selected on the basis of optical microscopy was visualized by scanning electron microscopy. The samples for SEM were prepared by lightly sprinkling the microballoons powder on a double adhesive tape which stuck to an aluminum stub. The stubs were then coated with gold to a thickness of about 300°A using a sputter coater. These samples were than randomly scanned and photomicrographs were taken which are shown in Fig. 1.

Figure 1: SEM of floating microballoons (2.39 K X)



2. Percent yield of microballoons

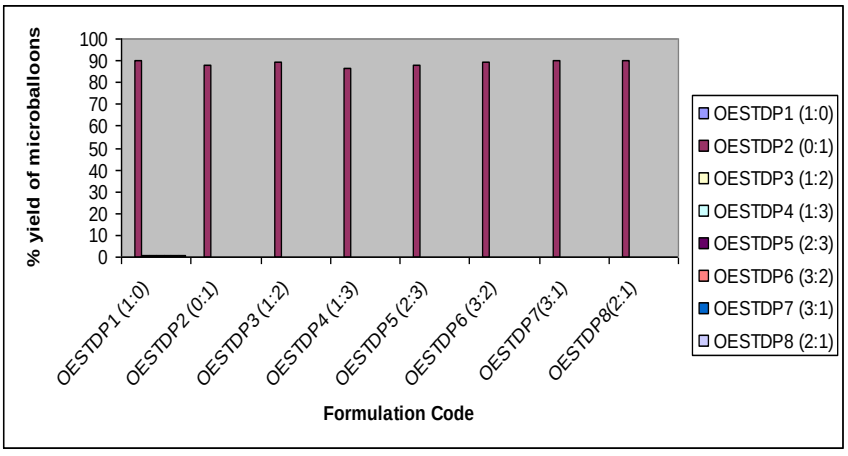
The prepared microballoons were collected and weighed. The weight of microballoons was divided by the total weight of all the non-volatile components used for the preparation of the microballoons.

% yield = weight of microballoons collected / wt. of all non-volatile components used for the preparation x 100

Table 1: Effect of polymer: polymer ratio (Eudragit L 100: Eudragit RS 100)

S.No.	Formulation Code	Eudragit L 100: Eudragit RS 100	% yield
1	**$OESTDP_1$**	1:0	90.1
2	**$OESTDP_2$**	0:1	88.2
3	**$OESTDP_3$**	1:2	89.2
4	**$OESTDP_4$**	1:3	86.3
5	**$OESTDP_5$**	2:3	87.7
6	**$OESTDP_6$**	3:2	89.6
7	**$OESTDP_7$**	3:1	90.0
8	**$OESTDP_8$**	2:1	89.8

Figure 2: % yield of microspheres at different polymer: polymer ratio (Eudragit L100: Eudragit RS 100)



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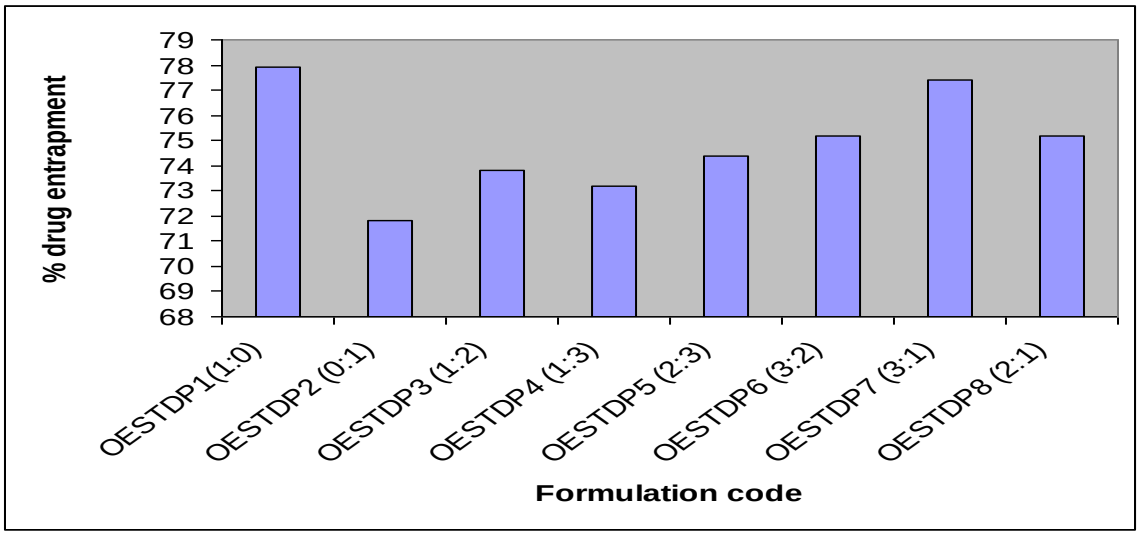
3. **Percentage drug loading efficiency:** The prepared microballoons were digested in minimum quantity of ethanol (95%), and then diluted with acetate buffer (pH 4.6) up to 10 ml. The digested homogenate was centrifuged at 3000 rpm for 3 minutes and the supernatant after suitable dilution was assayed for norfloxacin spectrophotometrically. The percentage drug entrapment is calculated from the equation given below.

% Drug entrapped = Amount of drug in the microballoons (actual content)/ Amount of drug used in formulation (theoretical content) x 100

Table 2: Drug entrapment values at different polymer ratio (Eudragit L 100: Eudragit RS100)

S. No.	Formulation Code	Eudragit L 100 : Eudragit RS 100	% entrapped drug
1	$OESTDP_1$	1:0	77.9
2	$OESTDP_2$	0:1	71.8
3	$OESTDP_3$	1:2	73.8
4	$OESTDP_4$	1:3	73.2
5	$OESTDP_5$	2:3	74.4
6	$OESTDP_6$	3:2	75.2
7	$OESTDP_7$	3:1	77.4
8	$OESTDP_8$	2:1	75.2

Figure 3: % drug entrapment at different polymer: polymer ratio (Eudragit L100: Eudragit RS100)



4. **Determination of physical parameters:** Prepared microballoons were evaluated for their physical properties like density, porosity and angle of repose.

Table 3: Density and porosity of different formulations

S. No.	Formulation Code	Density	% Porosity	Angle of repose (°)
1	$OESTDP_1$	0.719	47.8	29.4
2	$OESTDP_2$	0.834	60.5	32.0
3	$OESTDP_3$	0.802	57.9	31.2
4	$OESTDP_4$	0.825	59.6	31.6
5	$OESTDP_5$	0.787	56.2	30.8
6	$OESTDP_6$	0.742	51.3	30.5
7	$OESTDP_7$	0.726	48.9	29.7
8	$OESTDP_8$	0.738	50.4	30.1

1. In vitro floating behavior:

The floating test of the microballoons was carried out using the Dissolution test Apparatus method II specified in the USP XX[21]. The unloaded microballoons (800 mg) were spread over the surface of the simulated gastric fluid pH 1.2 (900 ml, 37 ± 0.5°C) which was agited by a paddle rotated at 100 rpm. Dissolution test solution SGF (pH 1.2) containing Tween 20 (0.02% w/v) was used as dispersion medium to simulate gastric fluid. After agitation for a previously determined interval, the microballoons that were floating and the ones that settled to the bottom of the flask were recovered separately.

After drying, the fraction of the microballoons was weighed; the % buoyancy of the microballoons was calculated by the following equation:

$$\text{Percent buoyancy} = Q_f / (Q_f + Qs) \times 100$$

Where, Qs is the weight of the settled microballoons, Q_f is weight of microballoons that were floating. The results are shown in Table 4 and graphically presented in Fig. 4.

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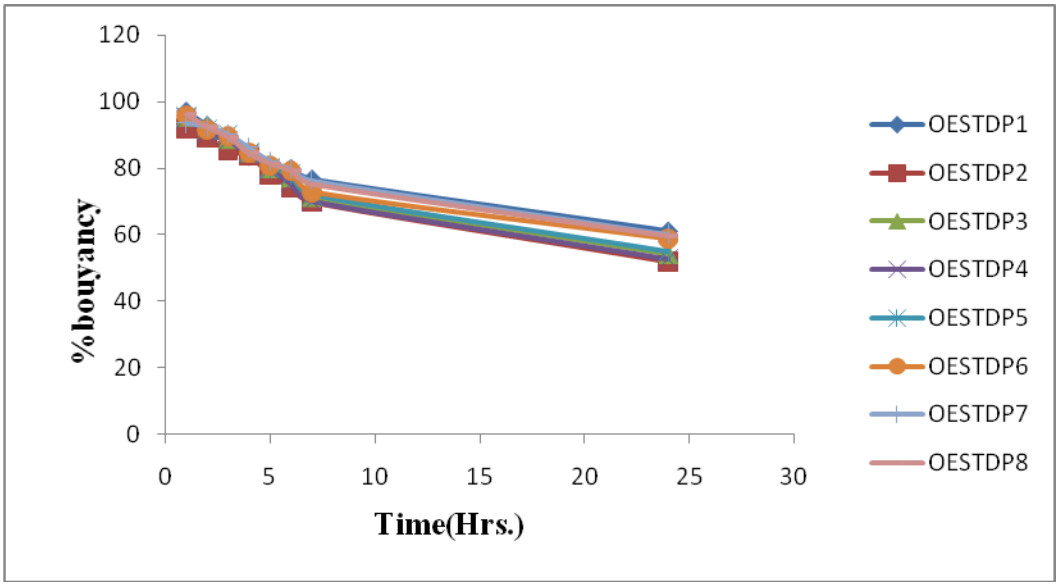
Table 4: Table 4: Percent buoyancy of different unloaded microballoons formulations in SGF (pH 1.2) at 37 ± 0.5°C

S.No.	Formulation Code	% Buoyancy at different time intervals (hour)							
		1	2	3	4	5	6	7	24
1	$OESTDP_1$	97.1	92.8	88.0	83.6	80.1	79.8	76.7	60.9
2	$OESTDP_2$	92.1	89.2	85.3	83.8	78.2	74.1	69.8	51.8
3	$OESTDP_3$	95.4	92.7	88.7	84.7	79.9	77.1	71.3	54.1
4	$OESTDP_4$	95.0	90.3	88.2	84.3	79.6	75.2	70.0	52.6
5	$OESTDP_5$	95.6	91.7	90.2	84.9	80.1	78.2	71.9	54.8
6	$OESTDP_6$	96.0	91.7	89.8	84.7	80.9	79.3	72.8	58.7
7	$OESTDP_7$	93.6	92.7	90.2	86.2	82.1	79.7	76.3	60.1
8	$OESTDP_8$	96.2	92.3	89.3	84.4	81.3	79.2	75.1	59.4

Figure 4: % buoyancy of different unloaded formulations in SGF at 37 ± 1°C



1. In vitro drug release:

The optimized nine formulations of norfloxacin microspheres e.g. $OESTDP_1$……$OESTDP_8$ were selected for the in vitro drug release studies. The drug release studies of microballoons were carried out in Dissolution Test Apparatus II USP XX by the paddle method. Microballoons equivalent to 800 mg of norfloxacin were gently spread over the surface of 900 ml of dissolution medium (SGF pH 1.2,) as specified in the Indian pharmacopoeia 2007.

The paddle was rotated at 100 rpm and the temperature of dissolution medium was thermostatically controlled at 37 ± 0.5°C. The samples were withdrawn at a suitable intervals of time from the dissolution vessel and were assayed after appropriate dilution spectrophotometrically at 278 nm in acidic medium for norfloxacin using Shimadzu 1700 (UV-Visible spectrophotometer)

Table 5: In vitro drug release profile of norfloxacin from optimized microballoons in SGF (pH 1.2) at λmax 278 nm

S. No.	Formulation Code	% cumulative drug release (hour)							
		1	2	3	4	5	6	7	24
1	$OESTDP_1$	6.1	8.2	9.8	10.3	11.1	11.6	12.2	21.3
2	$OESTDP_2$	11.6	25.9	37.8	46.2	54.3	61.3	64.4	93.2
3	$OESTDP_3$	7.6	16.9	25.7	36.8	43.9	51.4	54.8	91.3
4	$OESTDP_4$	8.0	20.2	32.9	41.3	48.7	56.2	60.1	92.3
5	$OESTDP_5$	7.4	15.8	23.2	30.1	37.3	42.6	46.4	90.3
6	$OESTDP_6$	6.8	13.6	18.4	23.1	29.0	32.1	36.2	76.9
7	$OESTDP_7$	6.6	11.8	14.9	20.1	22.8	26.0	29.7	56.2
8	$OESTDP_8$	6.7	12.3	15.2	20.8	24.7	28.6	31.5	65.9

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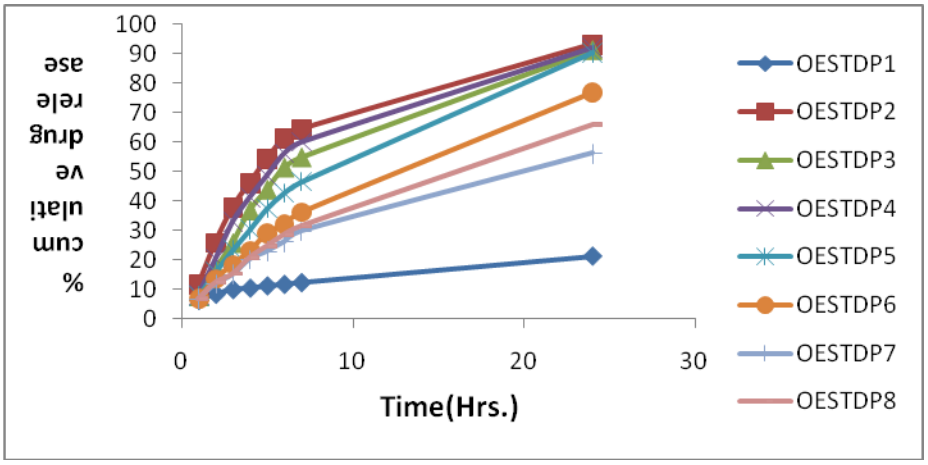
Figure 5: In vitro drug release profile of norfloxacin from optimized microballoons in SGF (pH 1.2) at λ_{max} 278 nm.



RESULTS AND DISCUSSION:

The floating microballoons were prepared by emulsion solvent diffusion evaporation method using combination of polymers (Eudragit L 100 and Eudragit RS 100). Formation of a stable o/w emulsion at the initial stage and the precipitation of the polymer at the surface of the dispersed droplet were the key factors in preparing desirable floating microballoons. The counter diffusion of ethanol and water through the interface between the emulsion droplet and the aqueous medium reduced the solubility of the polymer at the interface with the droplet inducing precipitation of the polymer on the surface of the emulsion droplet. The dispersed droplet of the emulsion was enclosed with a film like shell of the polymer. Based on the results from the o/w solvent diffusion method, the solvent composition of dichloromethane: ethanol: isopropanol (5: 8: 2) was considered and used in preparations.

Formulations are optimized for different process variables like Solvent ratio (dichloromethane: ethanol: isopropanol), drug-polymer ratio, Emulsifier concentration, temp. and stirring speed which are represented in the article as O,D,E,T and S respectively.

The scanning electron microphotograph clearly indicates that the microspheres are spherical in shape and there is a formation of hollow cavity in the sphere (Fig 1). It was clear that the solubility of the drug will determine the preferential location of the drug among the solvents used. Norfloxacin being water insoluble has a high entrapment in the microballoons. One more factor that has a high entrapment of drug was the proportion of Eudragit RS 100 in the polymer phase. As the proportion of Eudragit RS 100 was increased, the entrapment efficiency decreased owing to high porous nature of the polymer.

It was found that most of the microballoons were still floatable even after 24 hours of testing because of their low density and owing to the internal voids being completely conserved during the test. This finding indicated that the enteric property of the microballoons shell might be advantageous in prolonging the residence time of microballoons in the stomach, since dissolution and disruption of the microballoons could be prevented.

A combination of polymer was used for the current study to design a perfect gastro retentive delivery system which released most of the drug in upper part of gastrointestinal tract. As the amount of Eudragit RS 100 used in the preparation was increased the release of the drug was also increased. It may be concluded from this in vitro drug release study that the release rate can be controlled by varying the polymer: polymer ratio and the dosage form could be designed to give the release in a controlled fashion at the desired site. As for norfloxacin, the site of absorption is upper GI tract, the formulation $OESTDP_3$ and $OESTDP_5$ can serve the needs of a controlled release in upper GIT.

The data obtained from *in vitro* dissolution studies were fitted into Zero order, First order and Korsmeyer-Peppas models. Regression analysis suggests that the release of drug from microballoons followed non-Fickian diffusion mechanism.

CONCLUSION:

The microballoons of norfloxacin prepared by emulsion-solvent diffusion method exhibited excellent *in vitro* buoyancy and the drug release was sufficiently sustained with non-Fickian transport of drug from the microballoons. Hence the floating hollow microspheres of norfloxacin prepared with acrylic polymers may provide a convenient dosage form for achieving better floating behavior and drug release.

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