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Research Article

# Study of Eudragit Rs 100-Indomethacin Floating Microballoons Prepared by Solvent Evaporation Technique

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**ABSTRACT**

In this study, the floating microballoons of indomethacin were prepared by o/o solvent evaporation technique using Eudragit RS 100 as a wall polymer. Amongst different wall polymers, therapeutic agents and the anti-tacking agents, only, Eudragit RS 100: indomethacin: magnesium stearate system was able to float for a prolonged period of time. Thus, microballoons with this system were produced and evaluated for the impact of core: coat ratio, viscosity of liquid paraffin and stirring speed of external phase (EP). Increase in polymer concentration increased the particle size, drug loading, buoyancy, and decreased the porosity and drug release rate of microballoons. In contrast, increase in stirring speed and viscosity of EP decreased the particle size, buoyancy, drug loading, and increased the porosity and drug release rates of microballons. Microballoons particle sized ranged from 164 to 247 µm. Microballoons prepared with polymer: drug ratio of 2:1 released 28.31% drug at the end of 10 h. Drug release from most of the formulations followed Hixson-Crowell kinetic equation. Results revealed that Eudragit RS 100 can form floating microballoons with indomethacin conceivably by the formation of network between the quaternary ammonium groups of Eudragit RS 100 and Cl of indomethacin. Such microballoons, owing to their floating propensity, are promising candidates for sustained drug release.



## INTRODUCTION

Eudragits® are the class of biocompatible copolymers synthesized from acrylic and methacrylic acid esters [1]. These polymers are well tolerated by the skin and have been widely used in pharmaceutical dosage forms, most commonly in the preparation of matrix tablets [2-4] and in tablet coatings [5,6]. They have also been used successfully for the microencapsulation of numerous therapeutic substances [7-11].

Indomethacin is a nonsteroidal anti-inflammatory drug commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation. Chemically, it is 2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid.

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It is known that the quaternary ammonium groups of Eudragits® may form an ionic network with certain functional groups of therapeutic substances [12]. Such type of ionic network in-between the sulphate groups of heparin and the quaternary ammonium groups of Eudragit RS 100 and RL 100 has been reported [13]. Such networks, during formation, may also trap the air domains making the entire system/phase porous or hollow. This phenomenon can be utilized to design the floating microparticles that can float on gastric fluid for a prolonged period of time. Earlier, an attempt has been made by scientists to formulate and characterize the floating microballoons of indomethacin [14]. However, their study was based on a principle of using water diffusible and non-diffusible solvents to create hollow microspheres. The study used combination of ethanol and dichloromethane on the presumption that ethanol diffused out of the embryonic microspheres, whereas, dichloromethane cannot diffuse out and retains

in the microspheres as a core material. On keeping these microspheres at 40°C, the vapours of dichloromethane generate and escape creating the hollow spheres. Also, this study used a combination of polymers (Eudragit S100 and Eudragit RS 100) without describing a need/rational for use of such combination. Presuming that the formation of network between quaternary ammonium of Eudragit RS 100 and certain functional groups of therapeutic substances can entrap air and form the buoyant particles, we prepared microparticles of Eudragit RS 100 with different therapeutic substances namely diltiazem hydrochloride, diclofenac sodium, ibuprofen and indomethacin and their floating propensity was assessed. Amongst these, only Eudragit RS 100-indomethacin system could float. To verify whether it was an ionic interaction of Eudragit Rs100-indomethacin or the property of polymer or drug itself that imparted floating to microparticles, microparticles of indomethacin with rosin (a natural oleoresin) were also produced and their floating ability was investigated. This system was unable to float, which suggests that the quaternary ammonium groups of Eudragit RS 100 forms ionic network conceivably with the $Cl^-$ of indomethacin resulting into floating microparticles. Since the microparticles were spherical and hollow (as observed in SEM), these were termed as microballoons. Conventional O/O solvent evaporation method was used to produce the microballoons and impact of viscosity of liquid paraffin, stirring speed of EP and the coat: core ratio on particle size, porosity, buoyancy, drug loading and *in vitro* drug release profile of microballoons was investigated.

## MATERIALS AND METHODS

### Materials

Eudragit RS 100 was received as a gift sample from Evonik Industries, Germany. Indomethacin was received as a gift sample from M/S Zim laboratory Ltd., Nagpur, India. Liquid paraffin and petroleum ether were purchased locally from Nagpur, India. All other chemicals were of analytical grade, procured locally and used.

### Viscosity measurement,

The viscosity of liquid paraffin was measured at 27±1°C using a Brookfield DVII + Viscosimeter (Brookfield Englabs, USA) with RV 4 spindle at 100 rpm for 30 min.

### Preparation of microballoons,

Microballoons were prepared by O/O emulsion solvent evaporation technique as per the literature [15]. In brief, Eudragit RS 100 and indomethacin were dissolved in 10 ml of acetone. To this, magnesium stearate (10 % w/w of polymer weight) was added and stirred for 5 minutes. This mixture was poured into 160 ml of liquid paraffin rotating at a speed of 2000 rpm in a 250 ml glass beaker. After three hours, 5 ml of petroleum ether (60-80) was added. Total time for the preparation of microballoons was 6 hours. After, 6 hours, microballoons were collected by vacuum filtration and washed two times with 12 ml of petroleum ether. These were stored in a desiccator maintained at 0 % relative humidity before study.

### *In vitro* buoyancy,

Microballoons (100 mg) were dispersed in JPXIII No. 1 solution composed of HCl and NaCl (300 ml, pH 1.2, 37°C) containing Tween 20 (0.02 % w/v). The mixture was stirred with a paddle at a speed of 100 rpm. After 10 h, the layer of buoyant particles was pipetted and the floating particles were separated out by filtration. The sinking particles were also separated by filtration. Both were dried overnight and the weight of each was noted. Buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles.

### Morphology and Particle size of microballoons,

The morphology of EC microcapsules was observed by scanning electron microscopy (SEM) (JEOL, JXA-840A, Japan). A sample of few microballoons was also cut randomly by a surgical blade to capture the inside view of microballoons by SEM. The microcapsules were examined by an optical microscopy (Leica LaborLux Leitz S bright field microscope, Germany)) and the mean particle diameter was determined by measuring about 100 particles using 1-mm stage micrometer.

### Loading efficiency,

Dried microballoons (50 mg) were dissolved in acetone (0.5 ml) and extracted several times in JPXIII No. 1 solution (900 ml, pH 1.2, 37°C) containing Tween 20 (0.02 % w/v). The samples after suitable dilutions were analyzed for indomethacin content by UV spectrophotometer (Shimadzu, 1601, Japan) at 319 nm. The drug loading efficiencies were calculated as:

$$\text{Loading efficiency (\%)} = \frac{\text{Practical yield}}{\text{Therotical yield}} \times 100$$

**Porosity determination,**

True densities of microballoons and drug were determined pycnometrically by employing n-hexane as a displacement fluid. Bulk and tap densities were determined by the conventional method in duplicate. Porosity (%) was calculated as:

$$\text{\% Porosity} = \left[1 - \left(\frac{\text{Tap density}}{\text{True density}}\right)\right] \times 100$$

***In vitro* drug release,**

*In vitro* drug release profile was studied using USP XXIV dissolution test apparatus II (paddle type). About 50 mg of microballoons were taken in a muslin cloth and tied on the paddle adjusted to 100 rpm. JPXIII No. 1 solution (900 ml, pH 1.2, 37°C) containing Tween 20 (0.02 % w/v) was used as a dissolution medium throughout the study. Hourly, 5 ml of sample was withdrawn and analyzed by UV-Spectrophotometer at 319 nm for indomethacin content. Drug release profile was read for 10 hours.

**Drug release kinetics,**

To study the exact mechanism of drug release from microballoons, dissolution data was computed in the light of different kinetic equations [16]. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the systems where drug release rate depends on its concentration. Higuchi Eq. (3) describes the drug release by diffusion from an insoluble matrix. The Hixson-Crowell Eq. (4) describes systems through which drug releases with the changes in surface dimensions and Baker-Lonsdale Eq. (5) describes drug release from the spherical matrix.

$$Qt = K_o t \quad \text{.... (1)}$$

$$\text{In } Qt = \text{In Qo} - K_1.t \quad \text{.... (2)}$$

$$Qt = K_H.\sqrt{t} \quad \text{.... (3)}$$

$$\sqrt[3]{Qo} - \sqrt[3]{Qt} = K_{HC}.t \quad \text{.... (4)}$$

$$3/2\,[1-(1-Qt)^{2/3}] - Qt = K_{BC}.t \quad \text{.... (5)}$$

Where, $Qt$ is the amount of drug released in time $t$. Qo is the initial amount of drug released. $K_o$, $K_1$, $K_H$, $K_{HC}$ and $K_{BC}$ are the release rate constants for Zero order, First order, Higuchi, Hixson-Crowell and Baker-Lonsdale rate equations.

**RESULTS AND DISCUSSION**

The quaternary ammonium groups of Eudragit have propensity to form an ionic network with certain functional groups of the therapeutic substances. During formation of such network, air can be entrapped that may produce the floating microparticles. This principle was used in present study to develop the floating microballoons of indomethacin. Since the solvent evaporation technique has been widely used for microencapsulation, Eudragit microballoons containing indomethacin were prepared by the O/O emulsion solvent evaporation technique. Different organic solvents to prepare internal phase (IP), IP: EP ratios and anti-tacking agents were evaluated and optimized during the initial set up of formulation. Six different anti-tacking agents namely span 40, span 80, glyceryl monostearate, talc, tween 20 and magnesium stearate were initially evaluated; only magnesium stearate was found efficient to yield the spherical, discrete and free flowing microballoons. Therefore, it was used in all subsequent formulations in an optimized concentration of 10 % w/w of total polymer weight. To alter the viscosity of liquid paraffin, heavy and light liquid paraffin were combined in different ratios to get the EP of 80, 130 and 180 cps. Effect of coat: core ratio, stirring speed and the viscosity of liquid paraffin was investigated in terms of particle size, % porosity, drug loadings and *in vitro* drug release profiles of microballoons.

The SEM revealed that microballoons of the study were discrete, well spherical and had hollow cavities within, which imparted buoyancy to the particles for a prolonged period of time (Fig. 1).

**Effect of polymer concentration, stirring speed and viscosity of liquid paraffin on microballoons particle size**

An increase in polymer concentration of IP increased the particle size of microballoons (Table 1). This was because an increase in polymer concentration increased the viscosity of IP. Due to high viscosity of IP, it appears that the radial, axial and tangential flows that exist in rotating EP could not break IP in more number of droplets, which eventually increased the size of microballoons [15]. Furthermore, an increase in viscosity of the droplets of IP facilitates the droplet coalescence increasing the resulting microballoons size.

**Table 1:** Effect of coat: core ratio on particle size, buoyancy, porosity and drug loading of microballoons

| Formulation | Coat: core ratio | Particle Size (µm) | Buoyancy (%) | Porosity (%) | Drug Loading (%) |
|---|---|---|---|---|---|
| F1 | 2:1 | 247±46 | 96.3±2.1 | 36±4 | 92±4 |
| F2 | 1:1 | 210±40 | 91.8±2.6 | 48±6 | 88±6 |
| F3 | 1:2 | 183±34 | 89.5±4.3 | 52±5 | 92±5 |
| F4 | 1:3 | 164±27 | 81.7±6.2 | 59±4 | 76±8 |

Mean ± S.D in parenthesis

**Table 2:** Effect of stirring speed on particle size, buyoancy, porosity and drug loading efficiency of Eudragit microballoons

| Stirring speed (rpm) | Particle Size (µm) | Buoyancy (%) | Porosity (%) | Drug Loading (%) |
|---|---|---|---|---|
| 600 | 260±48 | 98.2±2.8 | 43±3 | 90±2 |
| 1000 | 210±40 | 91.8±2.6 | 48±6 | 88±6 |
| 1400 | 180±30 | 85.6±5.7 | 54±4 | 72±8 |

Mean ± S.D in parenthesis. The core: coat ratio of 1:1 was constant in three batches

**Table 3:** Effect of viscosity of liquid paraffin on particle size, buoyancy, porosity and drug loading efficiency of eudragit microballoons

| Viscosity of liquid paraffin (cps) | Particle Size (µm) | Buoyancy (%) | Porosity (%) | Drug Loading (%) |
|---|---|---|---|---|
| 80 | 280±27 | 95.3±3.1 | 43±2 | 93±2 |
| 130 | 237±39 | 93.4±2.9 | 45±3 | 90±2 |
| 180 | 210±40 | 91.8±2.6 | 48±6 | 88±6 |

Mean ± S.D in parenthesis. Different viscosities were obtained by the combination of heavy and light liquid paraffin. The core: coat ratio of 1:1 was constant in three batches

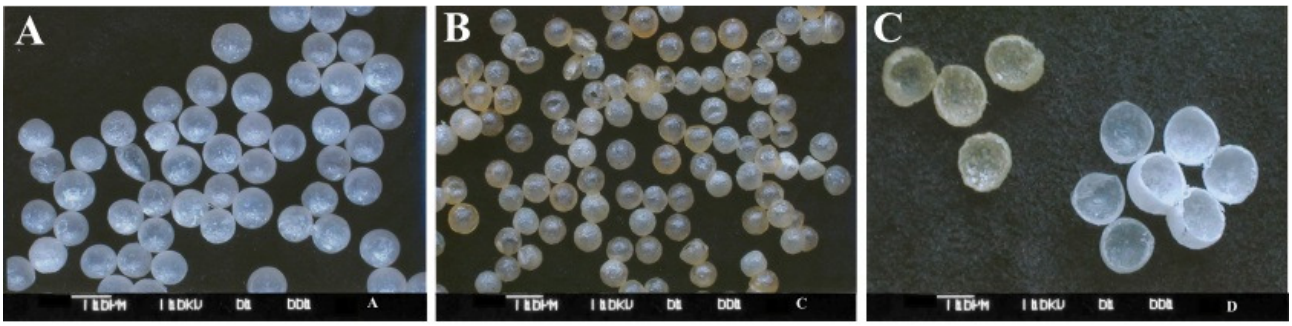


**Figure 1:** SEM image of indomethacin microballoons with (A) coat: core ratio of 2:1, (B) coat: core ratio of 1:3 and (C) inside view.

Increase in stirring speed decreased the particle size of microballoons (Table 2). This may be due to the fact that high stirring speed, due to high shear forces, breaks IP into more number of droplets reducing the size of final microballoons. Anti-tacking agent has certain potential to stabilize the droplets of IP rotating in EP. But at high stirring speed, it seems that the shear forces dominated the droplet stabilizing potential of anti-tacking agent, and thus dispersed IP in more number of droplets producing fine emulsion and eventually the smaller microballoons.

Decrease in viscosity of EP increased the microballoons size (Table 3). The droplets (of IP) coalescence would be affected by the viscosity of EP; lower the viscosity higher would be the

coalescence [15]. Therefore, it may be stated that in a high viscous EP, anti-tacking agent and viscosity of IP in combination have dominated the radial, axial and tangential flows and thus prevented the droplet coalescence producing the smaller microballoons.

**Effect of polymer concentration, stirring speed and viscosity of liquid paraffin on microballoons porosity**

It was observed that the porosity (%) of mciroballoons was decreased with increasing polymer concentration in IP (Table 1). This was in agreement with the general assumption about solvent evaporation technique that the microparticle porosity decreases with increasing polymer concentration in IP. The solvent evaporation rate primarily governs the porosity of microaprticles. Higher solvent evaporation rate produces more porous microaprticles. Increase in polymer concentration of IP yielded bigger microballoons and thus diminished the total surface area available for the solvent evaporation. This relatively slows down the solvent evaporation rate and thus produces microballoons with less porosity.

Increase in stirring speed increased the porosity of microballoons (Table 2). This may be attributed to decrease in particle size of microballoons with an increase in stirring speed. The smaller size microballoons provide more surface area for solvent evaporation and thus become porous.

Decrease in the viscosity of EP decreased the porosity of microballoons. Again, this was because decrease in the viscosity of EP increased the size of microballoons providing less surface area for solvent evaporation and thus lowered the porosity of microballoons.

**Buoyancy**

As can be seen from Table 1, there was a direct co-relation between the buoyancy and porosity of microballoons. Effect of various formulation variables on the porosity of microballoons has been discussed earlier in the text. In, particular, increase in polymer concentration of IP increased the particle size of microballoons and thus produced less porous microballoons, which were more buoyant that the microballoons having higher porosity. Increase in stirring speed of EP decreased the microballoons size and thus their buoyancy. Decrease in the viscosity of EP increased the microballoons size and thus their buoyancy.

**Drug loading,**

Microballoons drug loading was significantly affected by the polymer concentration of IP; increase in polymer concentration increased the % drug loading (Table 1). This may be due to the fact that the amount of uncoated drug decreases with an increase in polymer concentration in IP. Also, the high polymer concentration in IP produces relatively larger particles that provide less surface area for drug diffusion into the EP during microballoons formation. Increase in the stirring speed decreased the particle size of microballoons. The smaller balloons provide larger surface area for drug loss to the medium and thus achieve lower drug loadings. Similarly, an increase in viscosity of EP decreased the balloons size and subsequently the % drug loadings.

**Drug release**

The microballoons with the coat: core ratio of 2:1, 1:1, 1:2 and 1:3 showed 28.31, 42.31, 53.45 and 63.21 % drug release, respectively at the end of 10 h (Figure 2). This clearly suggests that an increase in polymer concentration of IP decreases the drug release rates. It has been documented that the drugs that form an ionic network with the quaternary ammonium groups of Eudragit usually exists in entrapped and electrostatically bound state in microparticles. The strength of such electrostatic binding increases with increase in amount of quaternary ammonium groups in Eudragit. Because of this, scientist have noticed slow heparin release from Eudragit RS 100 microspheres as compared to Eudragit RL 100 as the former has more number of quaternary ammonium groups in its backbone [13]. In view of this, it can also be stated that an increase in Eudragit RS 100 concentration of IP might have provided more sites for drug binding and retarded the drug release. Furthermore, increase in the amount of drug in microballoons markedly increased the drug release rate. This supports above theory that the amount of quaternary ammonium groups of Eudragit RS 100 primarily governs the drug release on the basis of the binding sites; more the binding sites slower is the drug release. Furthermore, the slow drug release with an increase in Eudragit concentration may also be attributed to the large size of microballoons. Bigger microballoons have low porosity and less surface area for drug escape. Release profile of all indomethacin microballoons suggests the absence of unbound drug in microballoons, as there was no burst effect found in any formulation (Fig. 2).

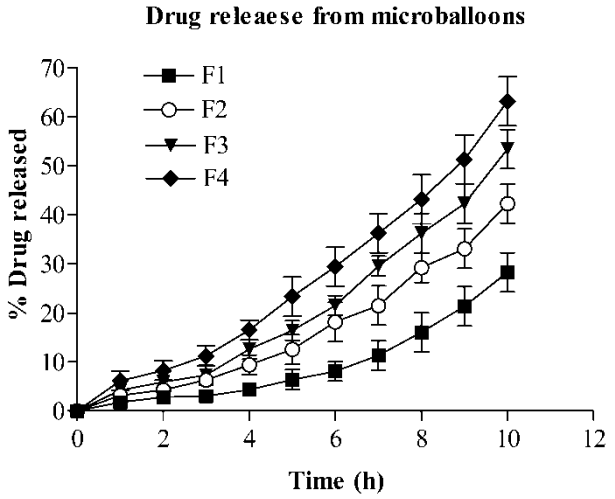


**Figure 2:** Drug release profile of Eudragit RS 100: indomethacin microballoons of different coat: core ratios.

### Release kinetics

The non-linearity of the % drug released versus time plots of indomethacin microballoons suggests that these formulations did not release drug by the zero order kinetics. This can be confirmed by the poor correlation coefficient values (Table 4). The correlation coefficient data suggest that microballoons prepared with Eudragit: drug ratio of 2:1 released drug by first order kinetics indicating that the drug release was dependent on the amount of drug at high polymer concentration. The drug release data from all other batches followed Hixson-Crowell kinetic equation, which indicates that drug release happened with the diminishing surface area of the microballoons [16]. Therefore, it may be stated that the drug release was progressed first with the regular loss of electrostatically bound and then the entrapped drug.

**Table 4:** Correlation coefficients according to different kinetic models

| Kinetic model | r* for Coat core ratio | | | |
|---|---|---|---|---|
| | 2:1 | 1:1 | 1:2 | 1:3 |
| First order | 0.997 | 0.991 | 0.991 | 0.990 |
| Baker-Lonsdale | 0.822 | 0.881 | 0.879 | 0.889 |
| Hixson-Crowell | 0.990 | 0.998 | 0.997 | 0.998 |
| Zero order | 0.937 | 0.976 | 0.976 | 0.985 |
| Higuchi | 0.882 | 0.935 | 0.936 | 0.950 |

*r = Correlation coefficient for linearity according to different kinetic equations used to describe the drug release from the floating indomethacin microballoons

## CONCLUSION

In this study, floating microballoons of indomethacin using Eudragit RS 100 were prepared by O/O emulsion solvent evaporation technique. Different combinations of wall polymer and therapeutic substances were evaluated and it was found that Eudragit RS 100: indomethacin system was able to float for a prolonged period of time. Different anti-tacking agents were investigated and only magnesium stearate was found efficient amongst them to produce the discrete and spherical microballoons of indomethacin. Increase in polymer concentration increased the particle size, drug loading, buoyancy, and decreased the porosity and drug release rate of microballoons. In contrast, increase in stirring speed and viscosity of EP had an opposite impact. Microballoons prepared with polymer: drug ratio of 2:1 released 28.31% drug at the end of 10 h. Drug release from most of the formulations followed Hixson-Crowell kinetic equation. This study revealed that Eudragit RS 100: indomethacin floating microballoons can be successfully prepared by conventional solvent evaporation technique for a sustained drug release.

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