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Original Article

# EUDRAGIT® RL100 MICROSPHERES AS DELAYED-RELEASE SYSTEM FOR IBUPROFEN: *IN VITRO* EVALUATION

**APARNA DATTA*, ABHRA DAS, RAJKUMAR GHOSH**

**Department of Pharmaceutical Technology, NSHM Knowledge Campus, Kolkata Group of Institutions, Kolkata 700053, West Bengal, India**
***Email: adatta75@gmail.com**

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**ABSTRACT**

**Objective:** The objective of this study was to encapsulate ibuprofen in microspheres made of Eudragit® RL100 as the polymer and evaluate it *in vitro*.

**Methods:** Microspheres were prepared by the solvent evaporation method. Significant parameters in the evaluation of microencapsulation are yield, particle size, encapsulation efficiency, swelling index, uniformity factor and buoyancy. The *in vitro* release studies were carried out in phosphate buffer solution pH 7.4 at 37±1 °C.

**Results:** Microspheres containing higher ratio of polymer had higher yields as high as 89.25%. The external diameter ranged from 300 to 550 µ, with geometric mean close to 420 µ. Evidently, the formulation containing higher concentration of Eudragit® RL100 had a larger diameter, indicating greater cross-linking and a larger sphere, signifying a higher loading capacity. The loading efficiency was above 81%, while the swelling index was found to be between 29% to 36%, with buoyancy factor of 74.53% for the superior batch. The results suggest that ibuprofen was successfully and efficiently encapsulated. The release rates of drug-loaded microspheres are related to the amount of polymer, thus, to get extended drug release while reducing the ill effects of the drug in the stomach. *In vitro* release was compared with marketed product, divulging better data for the indigenously prepared samples.

**Conclusion:** Data obtained by matching the *in vitro* release for the superior microspheres, so prepared and one of the commercial products showed the indigenous preparation of ibuprofen microspheres to be a better performer in the simulated gastric environment of phosphate buffer solution pH 7.4 at 37±1 °C.

**Keywords:** Eudragit® RL100, Ibuprofen, Microspheres, Solvent evaporation method, Encapsulation


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## INTRODUCTION

Smart drug administration is gradually replacing traditional drug administration for therapeutic agents that cause stomach irritation. Dosage forms that adheres to the stomach surface or float in the gastrointestinal (GI) environment are the alternatives that allow them to stay at the site for prolonged period and release the drug over a long duration of time while also reducing stomach irritation [1-5]. This permits the drug to be delivered to target site at a predetermined rate and concentration while reducing side effects to a minimum. Among the various approaches in delivering therapeutic ingredients to the target site in a sustained and controlled release fashion, microspheres hold a distinct place as carriers for drugs. The therapeutic agents can be absorbed across the mucous membrane in the stomach region and reach directly into the circulatory system.

Ibuprofen, an NSAID (non-steroidal anti-inflammatory drug), has and analgesic and mild antipyretic action. However, Ibuprofen has short half-life of 1-3 h, allowing quick elimination and hence selected as a model drug [6]. Peptic ulceration, GIT (gastrointestinal tract) discomfort and GI bleeding are all serious side effects of ibuprofen. This can be corrected by maintaining a low and constant level of the drug in the blood by administering site-specific drug delivery of ibuprofen [7, 8].

Eudragit® RL100 (EU-RL), a positively charged polymer displays unique property of pH-independent changes [9], enabling it to remain intact during pH variations in stomach. In addition, EU-RL exhibits several other features like low density (allowing it to remain buoyant in gastric fluid), high permeability and intrinsic swell ability, thereby contributing to increased bioavailability of the encompassed drug [10].

The present work deals with the encapsulation of ibuprofen in microspheres made of Eudragit® RL100 as the polymer. Because of the unique and most suitable features of Eudragit® RL100, this work is one of its kind where no other polymers are used in the making of the microcapsules. The shape and the swelling index were significant enough to give the formulation the required entrapment efficiency and eventual release of the drug in a simulated gastric environment. The sole role of the floating ability of the micro balloons were well within the acceptable limits giving it an elevated drug discharge relative to one of the similar marketed products.

## MATERIALS AND METHODS

### Material

Ibuprofen, the active agent and Polyvinyl Alcohol (PVA), as a cross linking agent were procured from Balaji Drugs, India, whereas, Eudragit ® RL100, a cationic polymer, was obtained from Yarrow Pharma, India. Ethanol was used as a solvent and was bought from Changshu Hongsheng Fine Chemical Co. Ltd., China. Dichloromethane (DCM) was obtained from RANKEM, India. Glycerol Monostearate, an emulsifying agent was obtained from Loba Chemie Pvt. Ltd., India. Merck, India supplied isopropyl alcohol EMPARTA®. All the chemicals were of analytical grade and was used without further purification.

### Preparation of the microspheres

Solvent evaporation technique was adapted for the preparation of the microspheres [11]. Briefly, the required amount of Eudragit® RL100 was added to 10 ml of the equi-volume ratio of dichloromethane and ethanol (internal phase) to prepare the polymer solution at room temperature. At 200 to 350 rpm, 200 mg of Ibuprofen was added in this polymeric solution under magnetic stirrer to form the drug-polymer solutions. A measured quantity of Glyceryl monostearate was added into the drug polymer solution as an emulsifying agent, while still under continuous stirring according

to table 1. 1.5% w/v PVA (external phase) was added in a 100 ml of distilled water to form a continuous aqueous phase. Further, this drug polymer solution was poured slowly via 22G needle into 100 ml of water containing 1.5 % w/v PVA, which was maintained at a temperature of 35 ºC to 43 ºC to get spherical beads. These beads were kept in contact with PVA solution for 60 min and then removed from PVA solution by straining with Whatman® cellulose filter papers. The microparticles were washed with distilled water, centrifuged, dried and stored under a vacuum at room temperature. The obtained microspheres were subjected to further studies. The formulations were prepared under different names, F1 through F8, varying the polymer ratio, according to table 1.

**Table 1: Formulae of ibuprofen microspheres**

| S. No. | Formulation | Drug (mg) (Ibuprofen) | Eudragit® RL100 (mg) | Drug: polymer ratio |
|---|---|---|---|---|
| 1 | F1 | 200 | 50 | 4:1 |
| 2 | F2 | 200 | 75 | 8:3 |
| 3 | F3 | 200 | 100 | 2:1 |
| 4 | F4 | 200 | 150 | 4:3 |
| 5 | F5 | 200 | 200 | 1: 1 |
| 6 | F6 | 200 | 400 | 1: 2 |
| 7 | F7 | 200 | 600 | 1: 3 |
| 8 | F8 | 200 | 800 | 1: 4 |

For all the formulations, Glycerol monostearate, as an emulsifying agent, was kept constant. Polyvinyl alcohol, as a crosslinking agent, was not altered. Dichloromethane was used as a solvent along with the major ingredients mentioned in table 1.

**Uniformity index**

Uniformity index was calculated by using the formula

$$UI = DW/Dn$$

Where DW is the weight, average diameter and *Dn* of particles studied [12].

**Swelling index studies**

The swelling behaviour of a dosage unit was measured by studying its weight gain [13]. The swelling index of microspheres was determined by placing the microspheres in the basket of a dissolution apparatus (USP type, Rotating Basket) using 0.1N HCl as the dissolution medium at 37±0.5 °C. Every 30 min, up to 6 h, microspheres were withdrawn, blotted with tissue paper to remove the excess water and weighed using an electronic balance (BL-220H, Schimadzu, Japan). The experiment was performed in triplicate, every time. Swelling index was calculated by using the following formula:

Swelling index = (Wet wt. of microspheres–Dry wt. of microspheres)/Dry wt. of microspheres

**Measurement of buoyancy**

Microballoons equivalent to 100 mg were weighed and transferred to a beaker containing 300 ml of 0.1N HCL, pH 1.2 at 37 ºC. Then the mixture was stirred at 100 rpm for a period of 6 h using a stirrer and the floating time was recorded [14]. This was called as buoyancy time.

**Loading efficiency**

For determining loading efficiency (LE), approximately 10 mg of microspheres were weighed and dissolved in 10 ml of ethanol. The solution was diluted to give a concentration of 20 µl of ibuprofen. The absorbance was measured at 310 nm using a UV/Vis spectrophotometer (UV 1800, Shimadzu, Japan), and a calibration curve was used to calculate the actual amount of drug [15].

**Morphology of the microspheres**

The microspheres were visually examined using an optical microscope (Magnus, MLX-B Plus, Olympus Opto Systems, India Pvt. Ltd.), after calibrating the eyepiece reticle with a stage micrometre. A homogenous aqueous dispersion of microspheres was used to determine the particle size [16]. The mean was calculated and plotted from the optimized batch. Magnification of 10x in the eye piece and 10x in the objective lens was applied to sufficient micro balloons from each batch to minimize error and the mean calculated.

**Stability studies**

Short-term stability studies were carried out following International Conference on Harmonization (ICH) guidelines [17]. The best formulation, F8 was stored at 40±2 °C/75±5% relative humidity (RH) in closed high-density polyethylene bottles for a period of 45 d in a stability chamber and tested for any alterations after the predetermined period of short-term stability test.

***In vitro* drug release**

*In vitro* drug release was carried out in phosphate buffer solution, pH 7.4 at 37±1 °C dissolution apparatus (DS 8000, Lab India), maintaining 1000 rpm for 6 h. Approximately 10 mg of microspheres were placed in the dialysis bag (grade 60) and threaded onto the meshed basket of the USP Type I dissolution apparatus [18]. To simulate the GIT environment, a buffer shifting approach was employed along with a rotational speed of 100 rpm. 5 ml solution sample was taken at predefined intervals up to 360 min. The withdrawn volume was replaced with fresh media in an equal volume. The collected samples were passed through a membrane filter and diluted to a sufficient concentration with the same dissolution media, and absorbance was measured at 310 nm using a UV spectrophotometer. A standard calibration curve was used to quantify the cumulative percent of drug release.

**RESULTS AND DISCUSSION**

**Microsphere yield and morphology**

The microspheres were prepared by the solvent evaporation method, with constant stirring. The first four formulations, namely F1 to F4, resulted in very low yields, owing to the incomplete formation of the microspheres, and were treated as preliminary batches. As the percentage of the polymer was much less than 50% of the drug content, the rigidity of the spheres was appreciably low and this resulted in the immature breakage of the micro-balloons even before the formation and subsequent washing. Hence, these batches were not considered for further studies. Batches, F5 to F8, that had the least polymer ratio, the same as that of the drug, and above, showed appreciable outcomes and were assessed further. Spherical white, free-flowing microspheres were formed using the solvent evaporation method. The percentage yield varied from 61.9% to 89.25%±5%, with the highest yield obtained with higher polymer content. The results confirm that an increase in polymer ratio increases product yield [27]. Prepared microspheres were viewed under the light optical microscope for the optimized batch. Majority of the microspheres looked spherical in shape with regular outlines. Few microspheres (less than 5%) were fused or aggregated. Micrographs were taken and they are shown in fig. 1. The external diameter ranged from 300 to 550 µ, with geometric mean close to 420±5 microns. The size distribution of microspheres was generally fine at the speed used with the geometric mean of ~ 420 µ and a geometric standard deviation of 1.38 calculated from 50% undersized and 18% oversized particles.

**Loading efficiency**

Depending on the drug-to-polymer ratio, the entrapment efficiency of the drug varied to a large extent, as evident from table 2. The

analysis of drug content varied from 69.2–81.4±5%. The percentage yield was the least for the lowest ratio of the polymer and appreciably increased with the rising ratio for those batches that were evaluated in terms of *in vitro* release studies and encapsulation efficiency. It was found that an increased amount of polymer leads to good encapsulation efficiency [15], table 2. This is probably attributed to the fact that a higher concentration of the polymer gave the structures more firmness so that they did not break up during the process of preparation and wash. Also, the particle diameter linearly increased when the polymer quantity was increased. This could have been because of the reason that with the lesser diffusion rate of non-solvent to the polymer solution, the larger size of microcapsules was easily obtained [21, 22].

Additionally, the loading efficiency augmented gradually because of the reason that cross-linking due to the polymer gave room for the drug to get encapsulated into the microscopic balls [23-25].

**Swelling index and buoyancy**

The swelling index of all the formulations was evaluated and it was seen that for F5 through F8, this value was noteworthy and ranged from 29.34% to around 36% for F8. Accordingly, buoyancy was recorded as high as almost 75±2% for the same formulation, table 2. This was attributed to the presence of the maximum amount of the, polymer, which helped in gelling and permitting swelling of the matrix, thereby increasing the buoyancy factor [26]. Therefore, F8 was chosen for the *in vitro* assay.

**Stability studies**

Short-term stability studies displayed that F8 was found to be quite stable pertaining to physical attributes and *in vitro* drug discharge pattern during the study period. There was no change in the size of the microspheres and the cumulative release of these microspheres was 88. 4±5% at the end of six hours of study in phosphate buffer solution, pH 7.4 at 37±1 °C for 3 consecutive studies.

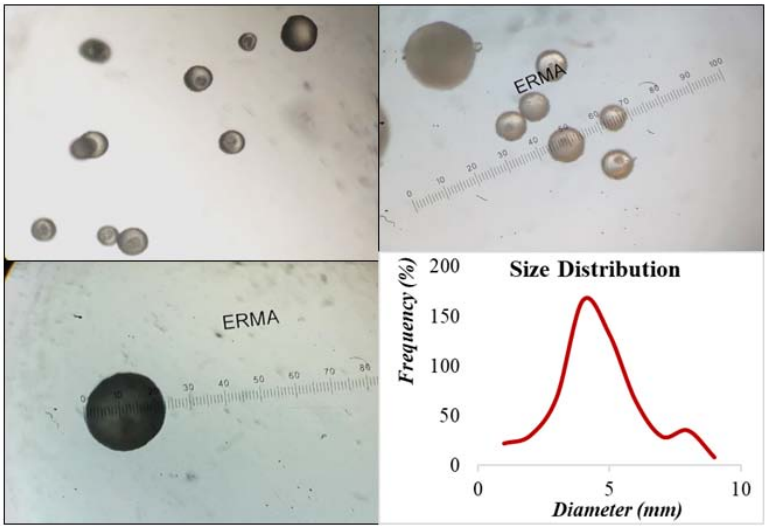


**Fig. 1**: **Microscopic images of Ibuprofen Eudragit® RL100 microspheres, [n = 5] (a) microspheres under microscope (b) uniformity of size of the particles (c) measurement of the diameter of microparticles (d) size distribution, signifying uniformity**

**Table 2: Microsphere formulations, loading efficiency and particle diameter**

| Formulation | Drug: polymer ratio | *Percentage yield (%) | *Loading efficiency (%) | *Particle diameter (µm) | % Swelling index* | *Buoyancy (%) |
|---|---|---|---|---|---|---|
| F5 | 1: 1 | 61.9±3.9 | 69.21±1.49 | 185.59±0.1 | 29.34±2.33 | 54.55±2 |
| F6 | 1: 2 | 65.6±3.1 | 74.56±1.22 | 277.42±0.1 | 30.66±1.30 | 61.43±2 |
| F7 | 1: 3 | 71.2±2.4 | 77.12±1.31 | 296.28±0.2 | 32.18±1.22 | 67.23±2.3 |
| F8 | 1: 4 | 89.25±1.9 | 81.36±1.08 | 338.20±0.1 | 35.91±2.13 | 74.53±2 |

*Data is given in mean±SD, n=5

***In vitro* drug release**

The release profiles of ibuprofen microspheres for the batches F5, F6, F7, and F8 are shown in fig. 2 and indicate that the proportion of polymers greatly influenced the drug release. Formulations F7 and F8, which had a greater amount of polymer, showed a linear initial drug release followed by a prolonged ibuprofen release until six hours of analysis. Fig. 2 highlights the highest percentage of ibuprofen released of 88.6±5 % from F8 and the lowest release of around 12.0±5 % from the same formulation at the 15$^{th}$ minute. An aspect that might have influenced the discharge of ibuprofen is the drug crystals adhering to the outer surface in addition to the porosity of the particles of the microspheres owing to the presence of higher percentage of polymer in that formulation [27]. The linear initial release of the drug is often desirable in the case of extended drug-release microspheres. Optimization of process conditions for the preparation of microspheres and also the development of more complex systems can be modulated further based on the requirements. The porosity of these microspheres probably facilitated the penetration of the dissolution medium and, consequently, facilitated the ibuprofen dissolution. It has been previously reported that Eudragit ® RL100 microspheres could promote the fast release of ibuprofen due to its porosity [28]. Additionally, the gelling and swelling capacity of the polymer allowed the drug to remain in the networked trap and later slow release of the same, enabling gradual release over time [29, 30]. Thus, it was concluded that formulation F8 was the most appropriate to prolong the ibuprofen *in vitro* release for the oral route.

An assessment of the prepared sample F8 was made with a similar product available in the drug stores, with respect to *in vitro* dissolution for the same span of time under identical conditions. The findings are plotted in fig. 3. The outcomes demonstrated that there was better release capacity of F8 under identical conditions and hence was superior

to the existing product found in the market, thereby concluding that the prepared microspheres were of superior quality and proposing for further *in vivo* and long-term stability tests. The overall comparison with the marketed sample indicated F8 to be better, with an average of above 88±5 % at the end of 6 h under similar conditions, compared to the existing product available on the market.

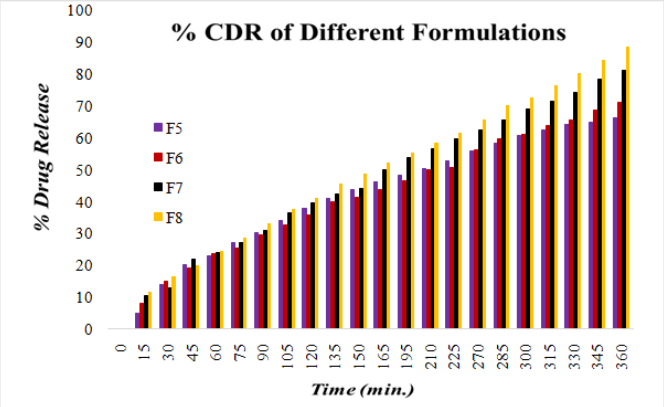


**Fig. 2**: **Comparative release profiles for all batches (F5 to F8) of ibuprofen microspheres, [N = 3] for *in vitro* drug dissolution (from each formulation) and the test was done for each formulation in triplicate. Data is given in mean**

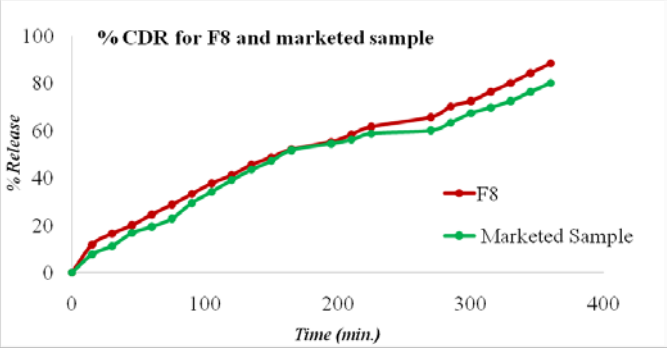


**Fig. 3: Comparative release profiles from F8 and marketed sample [N = 3] for *in vitro* drug dissolution and the test was done for each formulation in triplicate. Data is given in mean**

## CONCLUSION

In the current study, ibuprofen-loaded Eudragit® RL100 microspheres were found to be an effective method in providing the extended-release of ibuprofen for up to six hours. Sustained-release microballoons were prepared with Eudragit ® RL100 which was proven to be advantageous in the context of enhancing ibuprofen dissolution characteristics in simulated gastric medium. Microspheres prepared with Eudragit® RL100 as a delayed-release system for Ibuprofen displayed satisfactory physical properties, swelling index, buoyancy lag time and exhibited the required *in vitro* release pattern that agrees with the purpose set for this study. Further, a comparison of the release study of the optimized batch with a marketed product with similar composition revealed better cumulative drug release in a similar gastric environment when studied for 6 h and is proposed for further *in vivo* and long-term stability tests.

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## AUTHORS CONTRIBUTIONS

All authors discussed the outcomes and contributed to the final manuscript. AD conceptualized and drafted the manuscript prior to correction and finalization of the same. A Das performed all the experimental work, while R Ghosh did the data collection, plotting and revision of the manuscript.

## CONFLICT OF INTERESTS

Declared none

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