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## Morphological study of eudragit microballoons by using scanning electron microscopy

Nilesh Gorde<sup>1,\*</sup>, Mohan Kale<sup>2</sup>, Sandeep Waghulde<sup>3</sup>, Pravin Naik<sup>4</sup>, Pritam Juvatkar<sup>5</sup>

<sup>1</sup>Assistant Professor, Dept. of Pharmaceutics, Rahul Dharkar college of Pharmacy & Research Institute (Affiliated to University of Mumbai), Karjat (Dist: Raigad) Maharashtra, India.

<sup>2</sup>Principal & Professor, Dept. of Pharmacology, Rahul Dharkar college of Pharmacy & Research Institute (Affiliated to University of Mumbai), Karjat (Dist: Raigad) Maharashtra, India.

<sup>3</sup>Assistant Professor, Dept. of Pharmaceutical Chemistry, Rahul Dharkar College of Pharmacy & Research Institute (Affiliated to University of Mumbai), Karjat (Dist: Raigad) Maharashtra, India.

<sup>4</sup>Assistant Professor, Dept. of Pharmaceutical Chemistry, Rahul Dharkar college of Pharmacy & Research Institute (Affiliated to University of Mumbai), Karjat (Dist: Raigad) Maharashtra, india.

<sup>5</sup>Assistant Professor, Dept. of Pharmacognosy, Rahul Dharkar college of Pharmacy & Research Institute (Affiliated to University of Mumbai), Karjat (Dist: Raigad) Maharashtra, India.

\*Corresponding Author: Email: [nileshgorde83@gmail.com](mailto:nileshgorde83@gmail.com)

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### Abstract

The aim of this research work was to formulate microballoons as a potential for use as controlled-release drug delivery systems. Microballoons, loaded with drug in their outer polymer shells, prepare by the emulsion solvent diffusion method using enteric acrylic polymers Eudragit RL100 and Eudragit RS100; dissolve in a mixture of dichloromethane and ethanol. Microballoons (MB), a multiple unit dosage forms possessing a spherical cavity enclosed within a hard polymer shell have been develops as a dosage form characterize by excellent buoyancy in the stomach. This gastrointestinal transit-controlled preparation is design to float on surface of gastric juice, which has a specific gravity less than 1. Dichloromethane evaporation appears to be especially related to cavity formation and ethanol relates to the wall of microsphere. Thicker wall-thickness and larger particle size obtained at higher concentration of ethanol and have an increased diffusional pathlength when exposed to dissolution medium giving rise to decrease drug release.

## 1. INTRODUCTION

Microballoons (MB), a multiple unit dosage forms holding a spherical cavity surrounded by a hard polymer shell has been develop as a dosage form illustrate by excellent buoyancy in the stomach. This preparation is intend to float on surface of gastric juice, which has a specific gravity less than 1. Microballoons, loaded with drug in their outer polymer shells, develop by the emulsion solvent diffusion method by means of various polymers; dissolve in a mixture of dichloromethane and ethanol. Cavity formation in microspheres is particularly associated to evaporation of Dichloromethane. Microballoons with a drug dispersed or dissolved throughout particle matrix have the potential for controlled release of drugs and floats constantly over the surface of acidic dissolution media for > 12 h in vitro. Since the microballoons floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and constant plasma drug concentration. The entrapped substance is dispersed throughout the microsphere made up of polymeric, waxy or other protective materials that are biodegradable synthetic polymers and modified natural products such as starches, proteins, gums, fats, and waxes. The natural polymers include albumin and gelatin. The synthetic polymers include polylactic acid and polyglycolic acid<sup>1-7</sup>.

### 1.1 Selection of polymer<sup>4-6,8,9</sup>

In the present study, the floating microballoons developed using Eudragit RS100 in combination with the permeable Eudragit RL100. Polymers were selected to form the floating microballoons since they have been approved by FDA and are widely used in the pharmaceutical industry. Since Eudragit RL freely permeable to water and RS slightly permeable to water, desired drug release can be obtained by mixing two types together.

Eudragit RL and RS, also referred as ammoniomethacrylate copolymer in the USP NF 20 monograph, are copolymers synthesized from acrylic acid and methacrylic acid esters, with RL having 10% of functional quaternary ammonium groups and RS having 5% of functional quaternary ammonium groups. These groups are presents as a salt and gives rise to pH independent permeability of the polymers. Both polymers are water-insoluble, and films prepared from Eudragit RL are freely permeable to water, whereas, RS films are slightly permeable to water.

Polymethacrylates are primarily used in oral capsules and tablet formulation as film-coating agent. Depending on the type polymer used, films of different solubility characteristics can be produced. Polymethacrylates are also used as binder in both aqueous and organic wet granulation processes. Larger quantities (5-20%) of dry polymer are used to control the release of an active substance from a tablet matrix. In direct compression solid polymer is used in 10-50%.

### 1.2 Selection of solvent for microballoons preparation<sup>1</sup>

Ethanol and dichloromethane are used for solubilising internal organic phase for microballoons preparation. Ethanol has higher solubility in water. As soon as the internal organic phase was added to the aqueous medium, the ethanol diffused rapidly from the droplets of the polymer solution resulting in polymer precipitation by simultaneous diffusion of water inside the sphere. Due to the poor miscibility of dichloromethane in water, it could not effectively invade by the water. Therefore, the diffusion of dichloromethane began late, after the initial solidification, and formed a central hollow structure. The central cavity produced by the solvents was gradually filled with water due to the reduced internal pressure. Water escaped out of the cavity during the drying process ultimately forming microballoons which led to lowering of the density and enabling the microballoons to float.

## 2. MATERIALS AND METHODS

### 2.1 Materials

Eudragit® RS100 and Eudragit® RL100 (Rohm Pharma) was utilized as an enteric polymer soluble at pH > 7.0. Ethanol and dichloromethane purchased from Bengal chemical and pharmaceutical Ltd and sd. fine chemie. Pvt. Ltd respectively. Polyvinyl alcohol and all other chemical were of analytical grade.<sup>10-14</sup>

### 2.2 Methodology

Microballoons were prepared by the emulsion solvent diffusion method using Eudragit RS100 and Eudragit RL100. Polymer Eudragit RS100: Eudragit RL100 in varying concentration were dissolved in a mixture of ethanol and dichloromethane in different proportion at room temperature. The solution in the organic phase was poured into an aqueous solution of polyvinyl alcohol (0.75 w/v%, 200 ml) at 25°C. The resultant emulsion or suspension was stirred at 200 rpm employing a propeller type agitator for 1 h. Subsequently, the resulting microballoons were filtered, washed several times with water to remove the traces of polyvinyl alcohol and dried for 12 hr at 45°C.<sup>7,15-18</sup>

### 2.3 In vitro buoyancy studies

An in vitro buoyancy study was carried out using simulated gastric fluid USP containing 1% Tween 80 as a dispersing medium. Microspheres were spread over the surface of 500ml of dispersing medium at  $37 \pm 0.5^\circ\text{C}$ . 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.<sup>7, 8,19,20</sup>

$$\% \text{ Floating microspheres} = \frac{\text{Weight of floating microspheres}}{\text{Initial weight of floating microspheres}} \times 100$$

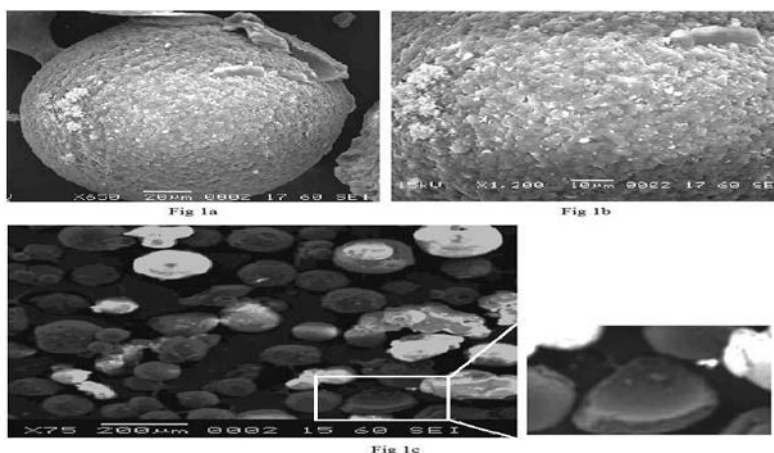
### 2.4 Scanning Electron Microscopy

Surface morphology and inner surface of a broken half of microballoons were examined by Scanning electron microscopy. Optimized microballoons were mounted on the SEM sample stab using a double-sided sticking tape and coated with gold under reduced pressure for 5 min using an Ion sputtering device. The gold coated microballoons were observed under the scanning electron microscope and photomicrographs of suitable magnifications were obtained.

## 3. RESULT AND DISCUSSION

### 3.1 Shape and surface characterization of optimized microspheres

The microballoons prepared in this study, as observed under scanning electron microscopy (Fig.1a and b), were spherical in shape with a rough outer surface. The entrapped dichloromethane diffused slowly out of the pocket giving a porous structure to the wall of the microspheres that could lead to the formation of rough outer surface. The porosity in a system of spheres is determined during microsphere hardening as the dichloromethane evaporates during preparation. As per various research sphere porosity can be controlled by changes in sphere preparation technique and differences in porosity do affect release kinetics. A highly porous matrix, released a drug at a considerably higher rate than its non-porous counterpart. Therefore, when preparing microspheres, it should be kept in mind that increasing the number of pores should increase the release rate. A photograph of a broken half of a microballoon (Fig.1c) showed that microballoons contained a central hollow core surrounded by a thick shell wall. Increased in wall thickness of microballoons (Fig.1c) increases resistance to the diffusion of the dissolution fluid that ultimately leads to decreased in density of the microballoons. This could be probably leads to increases resistance to the diffusion of the dissolution fluid that ultimately leads to increased buoyancy and decreased in the drug release.



**Fig 1: SEM photographs of Domperidone loaded Microballoons**

As the amount of Eudragit RL100 increased, buoyancy of the microballoons decreased with increased in drug release rate; this may be due to high affinity of Eudragit RL100 toward water, which promotes water penetration into microballoons, leading to increased density. In addition, the polymer might have been dragged further by the presence of more ethanol in the droplets, resulting in a thicker water/ethanol mixture zone. The thicker water/ethanol mixture zone resulted in a thicker wall thickness and a larger particle size that leads to decreased in drug release rate. The thick wall of the microspheres provides a larger volume for loading the drug. Eudragit RL100 contains more functional quaternary ammonium groups (10%) than RS100 (5%) gives the microspheres membrane a more open structure. Moreover Eudragit RL100 is strongly hydrophilic which promotes the penetration of the aqueous buffers and hence good leaching of the drug. So due to strong permeability and greater porosity of RL100 the release of drug was more as compared to the RS100.

#### 4. CONCLUSION

The present system, combining excellent buoyancy and release characteristic that could possibly be advantageous in terms of increased bioavailability of various drugs. Major advantages of the system include the ease of preparation and good buoyancy over more than 12 hours. Decreasing the concentration of dichloromethane could probably decrease the number of pores in the microballoons. Less porous surface should decrease the release rate and increase the buoyancy by reducing penetration of dissolution medium through the microballoons. Ethanol relates to the wall of microsphere. Thicker wall-thickness and larger particle size obtained at higher concentration of ethanol and have an increased diffusional pathlength when exposed to dissolution medium giving rise to decrease drug release. Thus microballoons prove to a potential candidate for delivery various drugs having absorption window in upper part of GIT.

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