

## Research Article

# Formulation and Evaluation of Gastro-retentive Floating Multi-particulate System of Metoprolol Tartarate

G Vijaya Baskar<sup>1</sup>, N Narayanan<sup>1</sup>, Rajiv Gaikwad<sup>2</sup> and Samad Abdul<sup>2</sup>

<sup>1</sup>College of Pharmacy, Madras Medical College, Chennai-600003.Tamilnadu, <sup>2</sup>Bombay Veterinary College, Mumbai, India

## Abstract

**Purpose:** To develop a floating multiparticulate unit system for metoprolol tartarate, using a porous carrier, with an outcome for delayed gastric emptying.

**Methods:** Dried microparticles of metoprolol tartarate were prepared by solvent evaporation using Eudragit<sup>®</sup> RS-PO, polypropylene foam powder, and dichloromethane as release-rate modifying polymer, floating aid and solvent respectively. The surface topography of the particles was assessed by SEM while the physical state of the drug within the developed system was characterised by DSC and XRD. Drug release was investigated by in vitro dissolution test. Tc99m sulfur colloid radio-labelled microparticle formulation was administered to fasting rabbits and their transit behavior was monitored using gamma scintigraphy. The anterior and posterior images recorded were computed to determine the geometric mean counts, enabling quantitative estimation of gastric emptying rate.

**Results:** Dried free-flowing, white coloured microparticles were obtained. They were highly porous and also irregular in shape. The drug in the microparticles was partly amorphous, showing a decrease in crystallinity. In vitro drug release from the particles followed a biphasic pattern with zero-order kinetics. The multiparticulate system exhibited good floating ability with  $t_{1/2}$  of 300 min over the duration of the in vivo study (6 h).

**Conclusion:** The developed microparticles showed suitable release properties, were free-flowing and exhibited good floating ability in rabbit stomach. Therefore, the formulation is capable of being further processed into tablet and/or capsule dosage forms for oral administration as a gastro-retentive controlled delivery system.

**Keywords:** Metoprolol tartarate, Gastro-retention, Eudragit polymer, Polypropylene foam powder, Gamma scintigraphy, Microparticulate system, Zero order release.

Received: 25 June 2009

Revised accepted: 24 February 2010

---

\*Corresponding author: **E-mail:** [gghas@rediffmail.com](mailto:gghas@rediffmail.com); **Tel:** +91-9704759081

## INTRODUCTION

"Less dense porous materials (meso, micro, nano) have been evinced as controlled drug delivery matrices" due to a stable uniform porous structure, tunable pore size with narrow distribution and higher surface area, enabling adsorption of drugs and their release in a reproducible and predictable fashion [1]. Successful per-oral intragastric floating dosage forms a lower bulk density than gastric fluids and remain buoyant in stomach contents without affecting gastric emptying rate [2]. Multi-particulate unit systems are preferred to single-unit forms because of their consistent gastric emptying and predictable absorption - release profile, thus reducing the risk of dose-dumping and improved patient compliance [3].

For desired therapeutic efficacy, constant plasma concentration of a cardiovascular drug has to be maintained. Metoprolol tartarate, a  $\beta_1$  selective adrenergic blocker whose absorption rate is directly proportional to dose availability<sup>4</sup>, has a half-life of 3 to 4 h, and thus requiring multiple doses to attain constant plasma concentration. Polypropylene foam powder, Accurel® MP 1000<sup>5</sup>, acting like sponges, exhibits an open cell structure with interconnected pores. United States Food and Drug Administration (FDA) has approved polymethacrylates such as Eudragit RSPO as an additive in drug formulation<sup>6</sup>.

The objective was to develop a peroral intragastric floating dosage form with Metoprolol tartarate using a porous carrier.

## EXPERIMENTAL

Polypropylene foam powder (Accurel® MP 1000, Membrana GmbH, Obermburg, Germany), metoprolol tartarate (Amanath Pharmaceuticals, India), Eudragit RSPO (Rohm Pharma, GmbH, Darmstadt, Germany), ethanol (Hong Yang International Co, China) dichloromethane (SD Fine Chemicals, India), Tween 20 (Vin Biotech,

India) were among the materials used. Cold kits were supplied by the Board of Radiation and Isotope Technology (BRIT), Barc, India. Hydrochloric acid and sodium hydroxide pellets were of analytical grade. Polypropylene foam powder was sieved to a particle size range of 250 -315  $\mu\text{m}$  size prior to use.

### Preparation of microparticles

Microparticles were prepared by first dissolving Eudragit RSPO and metoprolol tartarate in an organic solvent, dichloromethane, as previously described [7]. The polypropylene foam powder was dispersed in the organic mixture and the resulting suspension poured in to a Teflon dish. The polypropylene foam particles acted like sponges with the ability to absorb the organic solution. After solvent evaporation at room temperature under ambient pressure, free-flowing microparticles were obtained. Four different formulations were prepared with the drug and carrier kept constant while varying the polymer content (see Table 1). The yield of microcapsules was assessed as in Eq 1.

$$\text{Yield}(\%) = \frac{W_m}{W_{dp}} \times 100 \dots\dots\dots (1)$$

where  $W_m$  and  $W_{dp}$  represent total weight of floating microparticles and drug + polymer, respectively.

**Table 1:** Yield and encapsulation efficiency of microparticle formulation containing 100 and 150 mg of drug and carrier, respectively (n = 3).

| Formulation batch code | Polymer (mg) | Yield (%) | Encapsulation efficiency (%) $\pm$ SD |
|------------------------|--------------|-----------|---------------------------------------|
| A                      | 150          | 97.0      | 92.0 $\pm$ 0.1                        |
| B                      | 250          | 97.5      | 95.0 $\pm$ 0.2                        |
| C                      | 400          | 97.0      | 98.0 $\pm$ 0.1                        |
| D                      | 75           | 98.0      | 88.0 $\pm$ 0.1                        |

### Drug content

A quantity (50 mg) of microparticles was soaked in 50 ml of ethanol followed by

agitation with a magnetic stirrer for 12 h and then filtered through a 0.45 µm filter paper. Drug concentration in the ethanol phase was determined spectrophotometrically (UV-1601, Shimadzu) at 276 nm. Encapsulation efficiency was computed from Eq 2.

$$E = Da/Dt \dots\dots\dots (2)$$

where E, Da, Dt represent encapsulation efficiency, drug content (actual), drug content (theoretical), respectively.

### Microparticle morphology

The microparticles were placed in a stub and then coated for 120 s, with platinum at 20 milli amperes and 8 Pa using a Jeol JFC - Autofine coater. The coated samples were then examined with a scanning electron microscope (JEOL, Japan, model JSM -6360)

### In vitro drug release

A quantity of floating microparticles, equivalent to 100 mg drug, was filled into a hard gelatin capsule (No. 0) and placed in a basket immersed in 900 ml of simulated gastric fluid (SGF) without pepsin maintained at  $37 \pm 1$  °C and rotated at a speed of 75 rpm in a United States Pharmacopoeia (USP) XXIII basket type dissolution apparatus (TDT-08L, Electrolab, India). Five millilitre samples were withdrawn at intervals over a period of 8 h, passed through a 0.45 µm filter and the filtrate analysed spectrophotometrically at 274nm. Sink conditions were maintained during the test. Drug release rate kinetics was assessed by fitting the release data into dissolution kinetic study models Zero order, First order, Higuchi, Korsmeyer-Peppas and Hixon-Crowell.

### Differential scanning calorimetry (DSC)

Netsch DSC 204 scanning calorimeter equipped with a thermal analysis data system was used to record thermograms for 5-15 mg samples of the materials and formulations in the temperature range of 20 to 200 °C and at

a heating rate of 10 K/min under a nitrogen atmosphere. The samples were sealed in aluminium crucibles, with the lid perforated, prior to the test. An empty aluminum crucible was used as the reference.

### X-ray powder diffraction (XRD)

Wide angle x-ray scattering measurements were carried out on a high resolution powder diffractometer (Rich Seifert JSO Debye flex 2002) with guinier geometry. X-ray diffraction patterns were recorded automatically at a scanning rate of 0.02 ° 2θ per sec over the range of 10° - 70°, 2θ. The average particle (grain) size was calculated from Scherer formula, shown in Eq 3 [8]

$$D = 0.9 \lambda / \beta \cos \theta \dots\dots\dots (3)$$

where λ is the wavelength of copper K<sub>α</sub> line (1.5406Å), θ is the diffraction angle, β is the full width at half maximum of the peak, and D is the average particle size.

### Radiolabelling with <sup>99m</sup>Tc-sulphur colloid

Radiolabelling of the microparticles was effected by direct labeling method [9], i.e., physical adsorption. Eudragit RSPO (250 mg) was dissolved in 3 ml of dichloromethane; 100 mg of metoprolol tartarate was added to it and stirred until a clear solution was formed; 40 MBq of cold kit of <sup>99m</sup>Tc - sulphur colloid solution was added and stirred vigorously for 15 min. The radioactive mixture was then adsorbed on to 150 mg polypropylene foam powder. Labeling efficiency was assessed by placing a drop of the aqueous dispersion on a pre-coated silica gel plate. After eluting the dried plate in normal saline in an ascending mode, the plate was examined for total radioactivity counts.

### Acquisition of images by gamma scintigraphy

Three healthy New Zealand white rabbits with no past history of gastro-intestinal (GI) disease were fasted for 12 h prior to the

commencement of the experiment. The study was approved by the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) and the Institutional Animal Ethics Committee (IAEC) at Veterinary Nuclear Medicine Centre, Bombay Veterinary College, Mumbai. The procedure followed was as previously described [10]. Labelled metoprolol tartarate containing 8mg of the drug in 40 mg of microparticles with 40 MBq radioactivity (an average of 33.33MBq dose of labeled drug) were fed orally to each rabbit. Anterior posterior static images were acquired in 128 x 128 matrix for 1 min at the following times: 30, 60, 120, 180, 240, 300, 360 and 480 min post feeding using a gamma camera (Millenium MPS M/S GE ) fitted with low energy general purpose (LEGP) collimator at an energy set at 140 kev at 20 % window . The recorded images from an online computer system (Genie Workstation) were examined (with the aid of Entegra workstation software) for gastric retention of the fed material. Post-scan animals were permitted to move freely but were not allowed to take any food or water for the entire study period. The percentage of retained gastric activity of labeled drug was calculated from the anterior and posterior images recorded. PRGA versus time curve was plotted (see Fig 3). A linear fit curve with slope values of - 0.99, -0.24 and 0.56 at 180, 300 and 360 minutes, respectively, was obtained with the aid of Excel program, and  $t_{1/2}$  was calculated manually from the curve for % retained. The acquired images were analysed as in Eq 4.

$$\text{Geometric mean} = A \times P \dots\dots\dots (4)$$

where A is the anterior image total count and P is the posterior image total count. Decay corrections of images were carried out and decay correction factor [11] for  $^{99m}\text{Tc}$  at 6 h, which was 0.500, was used to calculate percent retained gastric activity (PRGA) as in Eq 5.

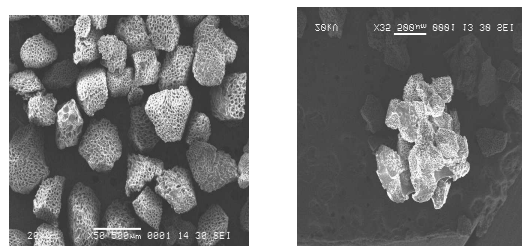
$$\text{PRGA} = \text{Dtg} / \text{Dt} \times 100 \dots\dots\dots (5)$$

where PRGA is the retained gastric activity (%), Dtg is the decay corrected geometric mean at a given time, and Dt is the decay corrected geometric mean at time, 0

## RESULTS

### Encapsulation efficiency

As shown in Table 1, encapsulation efficiencies were high in all cases (about 80 %). The original polypropylene foam powder is highly porous and irregular in shape (Fig 1).



**Fig 1:** SEM images of population of formulated microparticles (left) and agglomeration of microparticles prepared at high polymer: drug ratio (400:100, right) indicates that the microparticles exhibited irregular shape with their pores (open cell structure) partially covered by the polymer.

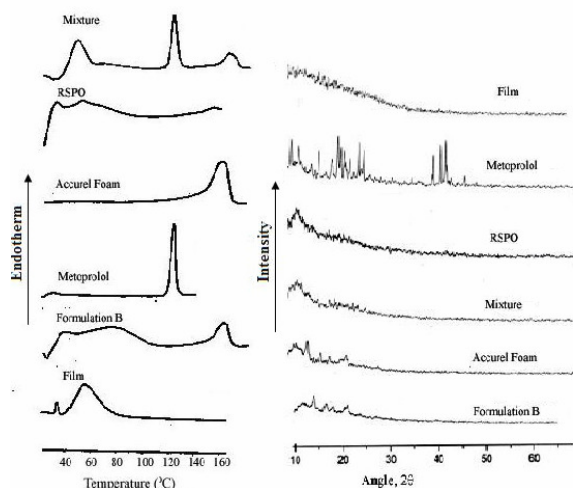
### Thermal analysis

DSC thermograms are shown in Fig 2. Endothermic peaks at 126.6, 163.6 and 58.6 °C, corresponding to metoprolol tartarate, polypropylene foam powder, Eudragit RSPO, were observed. The physical mixture of these components showed their individual characteristic peaks which indicated there was no interaction between the components. Microparticles showed polypropylene peak at 163.6° C while the film cast from an organic solution of Eudragit RSPO did not show any transition peak.

### X-ray diffraction

Diffractograms from XRD studies are shown in Fig 2. The mean crystal (grain) size of the

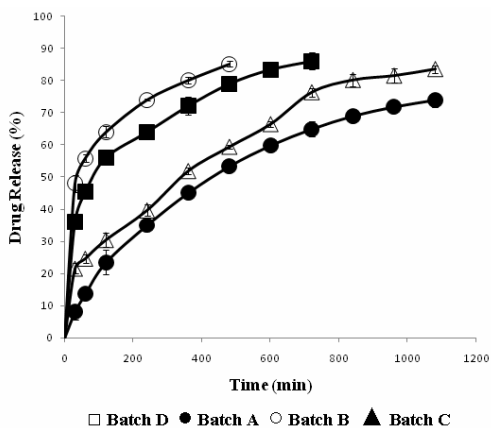
drug decreased from  $1.0087 \times 10^{-7}$  to  $0.3338 \times 10^{-7}$  micrometers.



**Fig 2:** DSC thermograms (left) and x-ray diffractograms (right) of microparticle formulation and formulation components.

### Drug release

The drug release data are shown in Fig 3. The pattern was mostly biphasic with an initial rapid drug release phase (burst effect) followed by a second slower drug release phase for all the formulations. At higher polymer concentrations, burst effect was minimal. The controlled release property of the polymer was confirmed by comparing the

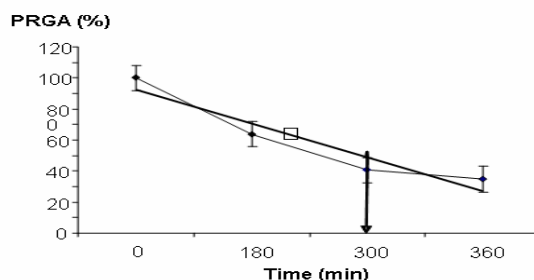


**Fig 3:** Dissolution characteristics of micro-particles

$T_{80\%}$  of microparticles (840 min) to that of the commercial formulation, Lopressor<sup>®</sup> SR tablets (710 min).

### Gastric imaging studies

Radiolabelling efficiency of the formulation was 65 %. There was good floating ability of the radiolabeled microparticles containing metoprolol tartarate *in vivo* over the period of study. The value of  $t_{1/2}$  was 300 min which was calculated using the linear trend line, as shown in Fig 4.



**Fig 4:** Mean retained gastric activity (PRGA, %) of labelled metoprolol tartarate. Note:  $\blacklozenge$  = mean PRGA;  $\square$  = Linear PRGA

### DISCUSSION

Encapsulation efficiency was high due to the formulation technique employed, which entailed the use of only an organic phase. The non-use of aqueous phase accounted for the minimal drug loss. Excessive heating temperature and decreased viscosity of the aqueous polymeric solution would have decelerated the rate of film formation over the polypropylene foam powder (aqueous solvent). This why drug entrapment also increased as the polymer proportion in the microparticles increased. The aggregation of the microparticles is attributed to the presence of excess polymer which also occluded the inner pores of the particles. DSC thermograms suggest that the drug in the microparticle was partly dissolved in the polymer and that it was partially amorphous. This is buttressed by the fact that the polypropylene free film did not show any endotherm that indicates melting of the drug

which would have meant that the drug was crystalline.

The XRD patterns also show that the drug in the microparticles is not crystalline or, at least, has decreased in crystallinity. The decrease in crystal size also suggests that the crystallinity of the drug fell thus favouring its slow release in the microparticle formulation [12]. At an enhanced polymer concentration, unlike at the lower polymer content, burst effect was not evident because the release medium could no longer gain access to the drug within the microparticles since the polymer completely covered the drug. All the formulations, except batch D which had the lowest polymer concentration, exhibited diffusion - controlled release since the release followed zero order kinetics.

Good floating behavior was due to the low apparent density of the microparticles which in turn can be attributed to the porous nature of the polypropylene foam powder that created a highly porous internal and external structure within the microparticles. With the polymer partially covering the pores, air is trapped within the microparticles, thus causing them to be buoyant in aqueous medium. Since the entrapped air is released slowly from the microparticles, the latter exhibited extended floating times.

## CONCLUSION

A multiparticulate unit floating dosage form based on microporous polypropylene has been formulated. Drug release from the formulation was biphasic and showed zero-order kinetics. Optimisation studies on the formulation have been planned which will facilitate further development into tablet and/or capsule dosage forms for oral gastro-retentive delivery.

## REFERENCES

1. Sher P, Ingavle G, Ponrathnam S, Pawar AP. Low density porous carrier Drug adsorption and release study by response surface methodology using different solvents. *Int J Pharm*, 2007; 331; 72- 83.
2. Sato Y, Kawashima Y, Takeuchi H, Yamamoto H. In vitro evaluation of floating and drug releasing behaviors of hollow microspheres (microballoons) prepared by the emulsion solvent diffusion method. *Eur J Pharm Biopharm*. 2004; 57; 235-43.
3. El-Kamel AH, Sokar MS, Al Gamal SS, Naggar VF. Preparation and valuation of ketoprofen floating oral delivery system. *Int J Pharm* 2001; 220; 13-21.
4. Jobin G, Cortot A, Godbillon J, Duval M, Schoeller JP, Hirtz J, Bemier JJ Investigation of drug absorption from the gastrointestinal tract of man: I. Metoprolol in the stomach, duodenum and jejunum. *Br J Clin Pharmacol*. 1985; 19: 97S-105S.
5. Streubel A, Siepmann J, Bodmeier R Floating microparticles based on low density oam powder *Int J Pharm* 2002; 241:279-292.
6. United States Patent 6706281. Melt-extrusion multiparticulates <http://www.freepatentsonline.com/6706281.html>. (Cited: 27 July 2007)
7. Streubel A, Siepmann J, Bodmeier R. Multiple unit gastro retentive drug delivery Systems: a new preparation method for low density micro particles. *J Microencapsul*. 2003; 20: 329-247.
8. Randall M. Handbook of mathematical relations in particulate materials processing, John Wiley & Sons, 2008; pp 28.
9. Welch MJ, Redvanly CS. Handbook of radiopharmaceuticals; radiochemistry and applications, John Wiley & Sons, 2003; pp 323-327.
10. Jain SK, Agrawal GP, Jain NK. Evaluation of Porous Carrier-based Floating Orlistat Microspheres for Gastric Delivery. *AAPS PharmSciTech*. 2006; 7: 90.
11. Early PJ, Sodee DB. Principles and Practice of Nuclear Medicine, 2nd edn, Mosby Press, 1995.
12. Pawa AP, Paradkar AR, Kadam SS, Mahadik KR. Crystallo-co-agglomeration: A novel technique to obtain ibuprofen-paracetamol agglomerates. *AAPS PharmSciTech*. 2004; 5: 1-8.