HOLLOW MICROSPHERES OF DICLOFENAC SODIUM – A GASTRORETENTIVE CONTROLLED DELIVERY SYSTEM

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ABSTRACT

Most of the floating systems have an inherent drawback of high variability in the GI transit time, invariably affecting the bioavailability of drug. To overcome it, a multiple unit floating system with extended GI transit time, capable of distributing widely throughout the GIT for effective enteric release of the drug has been sought. Microballoons loaded with drug in their outer polymer shells were prepared by novel emulsion solvent diffusion method.

The ethanol: dicloromethane solution of drug and Eudragit-S were poured into an aqueous solution of PVA that was thermally controlled at 40°C. The gas phase generated in the dispersed polymer droplet by the evaporation of solvent formed an internal cavity in the microsphere of the polymer with the drug.

The flowability of the resulting microballoons improved when compared to pure drug. The microballoons on floatation along with the surfactant, floated continuously for more than 12 hours in the acidic medium *in-vitro* conditions. The *in-vitro* drug release profile of the formulation in the simulated gastric buffer showed no drug release, which emphasizes the enteric release property and in simulated intestinal buffer, a slow and controlled drug release of 60 to 84% was obtained over a period of 8 hours. Drug release was significantly affected by increased drug to polymer concentration at pH 6.8. The formulation was found to be physically and chemically stable as per the ICH guidelines.

Keywords: Microballoons, multiple units, diclofenac sodium, Eudragit-S, microspheres, controlled delivery, gastro retentive.

INTRODUCTION

Most of the orally administered controlled release dosage forms that are coated with polymers or encapsulated to prolong the drug release results in poor bioavailability due to variable gastric residence time and incomplete drug release from devices. Very short residence time in the GIT leads to low bioavailability and low therapeutic efficacy of such dosage forms. To overcome these problems various attempts have been made to extend the GI transit time of the devices. One such approach is the floating dosage forms (Dubey, 2004). They have low density as compared to that of gastric fluids, due to which they float in the stomach contents for a longer period of time. But most of the floating systems have an inherent drawback of high variability in the GI transit time invariably affecting the bioavailability of drug. Thus to overcome the above problem, a multiple unit floating system with extended GI transit time capable of distributing widely throughout the GIT for effective enteric release of drug has been sought. In this study Hollow Microspheres (micro balloons) of Diclofenac sodium (Indian Pharmacopoeia, 1996) developed by a novel emulsion-solvent diffusion technique for controlled delivery, was evaluated for its physiochemical, micromeritic properties, invitro drug release profiles and stability studies.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as a gift sample from Eros Pharma, Bangalore. Eudragit-S 100 was obtained as a gift sample from Rohm Pharma, Germany. All the other reagents were of pharmaceutical grade and were used as received.

Preparation of microballoons

Weighed amount of Diclofenac sodium was mixed with Eudragit-S 100 (in ratios of 1:1, 1:2 and 1:3) in a solution of Dichloromethane and Ethanol (1:1) at room temperature. Glyceryl Monostearate was added as the emulsifying agent. The resulting drug-polymer solution was poured gradually into 200ml of water containing 0.75%w/v polyvinyl alcohol, maintained at constant temperature of 40°C and the preparation was stirred at 300rpm for one hour. The finely developed microballoons were then filtered, washed with water and dried overnight at 40°C (Shukla, 2002; Yasunori *et al.,* 2003). Table 1 gives the details of the various formulations.

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Table 1: Composition of Microballoon formulations

Ingredients	MB-1 (1:1)*	MB-2 (1:2)*	MB-3 (1:3)*
Diclofenac Sodium (g)	0.5	0.5	0.5
Eudragit S-100 (g)	0.5	1.0	1.5
Glyceryl Monostearate (g)	0.3	0.4	0.5
Dichloromethane (ml)	5	5	5
Ethanol (ml)	5	5	5

*Values in parentheses refer to the Drug: Polymer ratio.

Table 2: Micromeritic properties of formulation MB-2

Properties	Pure Drug (Diclofenac Sodium)	Formulation MB-2
Average Diameter of the particles	240µm	150µm
Particle size range	120-360µm	55µm-240µm
Angle of repose	32.6^o	19.4^o
Tapped density	0.926g/cm^3	0.564g/cm^3
Bulk density	0.928g/cm^3	0.7466g/cm^3
Uniformity index	--	1.21
Percentage drug entrapment	--	86%

Evaluation

a) Measurement of micromeritic properties

The average particle sizes, diameter of the resultant microballoons were determined by sieve analysis method. The flow properties and packing properties were investigated by measuring the angle of repose and tapped density. By measuring the true density and particle density, porosity of the microballoons was determined (Berthold, 1996).

b) Determination of mean particle size and particle size distribution

Particle size analysis of drug-loaded microspheres was carried out using optical microscopy using Olympus Microimage LITE-microscope (Aiedeh, 1997).

c) Uniformity index

It is calculated by the formula

UI = Dw/Dn

Where Dw is weight average diameter and Dn is number average diameter (Tomlinson, 1985).

d) Percentage drug entrapment

Percentage drug entrapment was determined by UV spectrophotometric method. Drug was extracted form the microballoons using 1N HCl and the absorbance was measured using UV-visible spectrophotometer at 254nm. The amount of Diclofenac sodium was estimated by specific gravity method.

PDE = (Practical drug loading/Theoretical drug loading) X 100

For all purposes it was assumed that the theoretical drug loading is 100%

Practical drug loading is calculated by assay.

e) Measurement of buoyancy:

Microballoons equivalent to 100mg was weighed and transferred to a beaker containing 300ml of 0.1N HCl, pH 1.2 at 37^{o}C (Singh UV, 1998). The mixture was stirred at 100rpm for a period of 6 hours using a stirrer and the floating times were recorded.

f) Invitro Drug Release Studies:

The *in vitro* release profiles of the formulations were carried out by USP-II method (paddle type). Microballoons equivalent to 100mg of drug was studied in simulated stomach buffer (pH 1.2) for a period of 2 hours and subsequently in simulated phosphate buffer (pH 6.8) maintained at 37^{o}C and 100rpm. The aliquot samples were withdrawn at frequent intervals, suitably diluted and assayed spectrophotometrically at 254nm (Niwa and Handa, 1989).

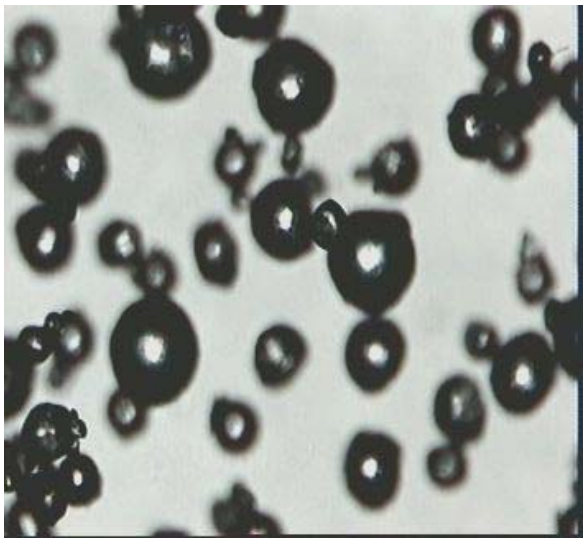
g) Stability studies

The stability studies of the selected formulations were performed as per ICH guidelines (for drug polymer ratio of 1:2) for a period of two months.

RESULTS AND DISCUSSION

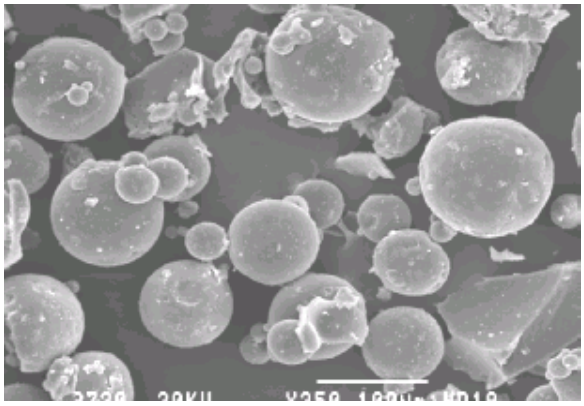
Based on the surface morphology, the microballoons of drug: polymer ratios 1:2 were selected for further characterization. The formations of hollow cavity within the microspheres as well as a porous surface structure are clearly evident in the optical and scanning electron microphotographs (figs. 1 and 2). The micromeritic studies revealed improved physical characteristics of the formulation MB-2 in terms of bulk density (0.746g/cm^3),angle of repose (19.4^o) and the particle size range (55µm -240µm) over the pure drug. The percentage of drug entrapped within the crust of the polymeric sphere was found be around 86%. The buoyancy test showed the floatation of the microballoons in the gastric buffer pH 1.2 containing Tween 20 (2%) as a surfactant upto 3 hours without any considerable drug release in the gastric buffer. The *In vitro* drug release from the formulation MB-2 was found to be maximum (90%) upto 8 hours. The formulation MB-2 was subjected to stability studies as per ICH guidelines for a period of 2 months and it was observed that the drug was intact within the formulation without any physical changes.

Before drying

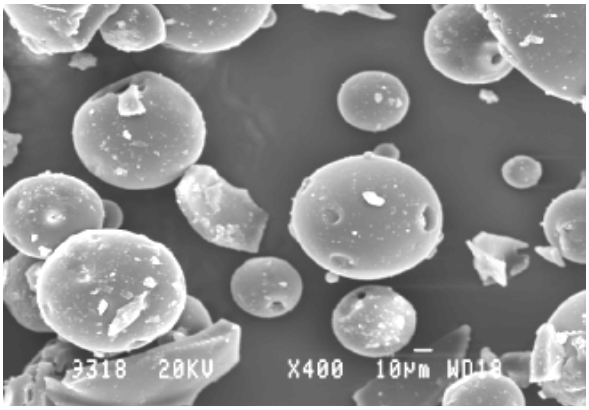


After drying

Fig. 1: Optical microphotographs of formulation MB-2



Before drying



After drying

F**ig. 2**: SEM photographs of formulation MB-2

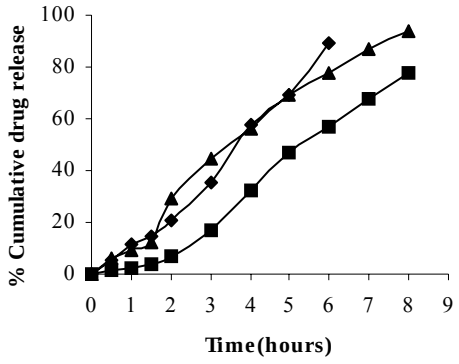


Fig. 3: *In vitro* release of Diclofenac sodium from MB-1 (-▪-) MB-2 (-♦-) and MB-3 (-▲-).

CONCLUSION

Microballoons of Diclofenac Sodium prepared with an acrylic polymer (Eudragit S 100) in different ratios by an emulsion-solvent diffusion method were optimized. The formulation MB-2, with a drug: polymer ratio (1:2) showed better physicochemical and micromeritic properties in comparison to original drug. The *in vitro* release profile clearly indicated that the dosage form was intact in the gastric pH for 2 hours and released the drug in a controlled manner in the intestinal pH upto 8 hours proved that the microballoons were an ideal device to prolong the residence time in stomach and to enhance the enteric bioavailability of drug. It was noticed that increase in the polymer concentration decreased the drug release from the microballoons due to increased thickness of the outer shells.

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