Research Journal of Pharmaceutical, Biological and Chemical Sciences

Formulation and *In- vitro* evaluation of floating microbaloons of rosiglitazone maleate

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ABSTRACT

In recent years scientific and technological advancements have been made in the research and development of controlled release oral drug delivery systems by overcoming physiological disadvantages like short gastric residence time and unpredictable gastric emptying time, bioavailability etc, the present study involves the preparation and evaluation of floating microbaloons of Rosiglitazone maleate (RZM). The floating microspheres were prepared by solvent evaporation method using hydroxy propyl methyl cellulose (HPMC) and ethyl cellulose (EC) with different concentration of EC. The microbaloons were characterized for their shape and surface morphology by optical and scanning electron microscopy, drug loading, buoyancy time, infrared spectroscopy (IR) for the compatibility study. The micromeritic properties of microbaloons were found to be much improved. Effects of the stirring rate, polymer concentration during preparation on the size of microspheres and drug release were also observed. The prepared microspheres exhibited prolonged drug release (10 hrs) and remained buoyant for > 12 hrs. The mean particle size increased and the drug release rate decreased at higher polymer concentration. The release kinetics studies were fit into zero order and Fickian diffusion controlled mechanism was observed.

Keywords: Rosiglitazone maleate (RZM), Floating microbaloons, controlled release, HPMC, EC, gastric retention time.

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INTRODUCTION

A recent advancement in the pharmaceutical oral drug delivery is the most preferable route of drug delivery system due to the ease of administration, patient compliance and increased bioavailability. There is increased interest in novel dosage forms that are retained in the stomach for prolong and predictable period of time [1]. Gastric retentive delivery systems potentially allow increased penetration of the mucus layer and therefore increase drug concentration at the site of action. These systems can remain in the gastric region for several hours and hence significantly prolong the gastric residence time of drug. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment [2]. To provide the good floating behavior in the stomach, the density of the formulated product should be less than that of the gastric content [3].

Diabetes is the major cause of mortality and morbidity leading to cardiovascular and other related complications. The thiazolidinediones classes of drug consist of Rosiglitazone. This compound decrease insulin resistance in muscle and adipose tissue by activating the peroxisome proliferator-activated receptor (PPARγ) which increases production of proteins involved in glucose uptake. They also decrease hepatic glucose production by improving hepatic insulin sensitivity. RZM is an extremely selective and potent agonist of the peroxisome proliferator-activated receptor-gamma (PPARγ) [4].The aim of the work is to develop the floating microbaloons of RZM and it has the short biological is half life is 3 to 4 hr and it has two pKa values 6.8 and 6.2.

The RZM is degraded as the pH increases so it is necessary to dissolve in the less pH for the protection of the drug and to reduce the gastric disturbance and more over, the site of absorption of RZM is in the stomach pH. Hence it is aimed to formulate the Rosiglitazone Maleate as floating microbaloons to reduce frequency of dosing [5, 6].

MATERIALS AND METHODS

RZM was gift sample from the GlaxoSmithKline, ethyl cellulose was obtained from Signet chemicals and HPMC K15Mcps was from SD fine chemicals. Dichloromethane, ethanol and tween 20 were obtained from Loba chemical Mumbai. All other chemicals/reagents used were of analytical grade. A UV/Vis spectrophotometer (Shimadzu 1800pharma spec) was used for drug analysis.

PREPARATION OF MICROBALOONS

Microbaloons were prepared by the emulsion solvent evaporation technique. RZM, HPMC and EC were accurately dissolved in a mixture of ethanol and dichloromethane (DCM) in 1:1 ratio at room temperature. This solution was poured drop by drop into 250 mL water containing 0.02% Tween 80 maintained at a temperature of 30–40 °C and subsequently stirred

at ranging agitation speed for 20 min which results the formation of o/w type of emulsion and also to allow the volatile solvent to evaporate. The microbaloons formed were filtered, washed with water and dried in vacuum. The formulation design of RZM microbaloons were shown in the Table 1.

CHARACTERIZATION OF MICROBALOONS

DRUG POLYMER INTERACTION (FTIR) STUDY [7]

IR spectroscopy was performed by using Fourier transformed infrared spectrophotometer (840, Shimadzu, Japan). The pellets of drug and potassium bromide were prepared by compressing the powders at 20 psi for 10 min on KBr-press and the spectra were scanned in the wave number range of 4000- 600 cm^{-1}. FTIR study was carried on pure drug, physical mixture of drug and polymers, formulations and empty microspheres to confirm the compatibility of drug with other excipients used in the preparation of RZM microbaloons.

SCANNING ELECTRON MICROSCOPY (SEM) [8]

Scanning electron microscopy (SEM) studies were performed by JEOL JSM T-330A scanning microscope (Japan) to characterize the shape and Surface morphology of microbaloons of formed microbaloons. Microbaloons were mounted directly onto the sample stub and coated with platinum film. The sample holders were then coated with Platinum using a cold sputter coater. The samples were imaged using a 15 kV electron beam. The results of SEM is shown in Fig 1

PARTICLE SIZE DETERMINATION [9]

The particle sizes of the microbaloons was determined with an optical microscope under regular polarized light, and mean particle size was calculated by measuring 100 microbaloons with the help of a calibrated oculometer. It is shown as in Figure 2.

PERCENTAGE YIELD OF MICROBALOONS [10]

The prepared microspheres with a size range of 45.71- μm were collected and weighed. The measured actual weight was divided by the total amount of all non-volatile components which were used for the preparation of the microbaloons.

$$\% \text{ yield} = \frac{\text{actual weight of product}}{\text{total weight of excipient and drug}} \times 100$$

BUYOUNANCY PERCENTAGE [11]

Fifty milligrams of the floating microbaloons were placed in simulated gastric fluid pH 1.2, 100 ml containing 0.02 w/v% Tween 20. The mixture was stirred at 100 rpm in a magnetic stirrer. After 12 hr, the layer of buoyant microbaloons was pipette and separated by filtration. Particles in the sinking particulate layer were separated by filtration. Particles of both types were dried in a desiccator until constant weight. Both the fractions of microspheres were weighed and buoyancy was determined by the weight ratio of floating particles to the sum of floating and sinking particles. The floating microbaloons as shown in Figure3.

$$\text{Buoyancy(\%)} = \frac{Wf}{Wf + Ws} \times 100$$

Where Wf and Ws are the weights of the floating and settled microparticles, respectively.

DRUG ENTRAPMENT EFFICIENCY [12]

The drug content of RZM loaded microbaloons was determined by dispersing 20 mg microspheres in 20 ml of methanol, which was stirred with a magnetic bead for 8 hr to extract the drug. The samples were diluted and analyzed spectrophotometrically at 318.16 nm and the percentage drug entrapment was calculated.

Drug Entrapment Capacity (%) = (AQ/TQ) x 100

Where AQ is the actual quantity of the drug present in the matrix and TQ is the 100% theoretical quantity of the drug in the system.

***IN VITRO* RELEASE STUDY [13]**

The drug release rate from microbaloons was determined using USP XXIII basket type dissolution apparatus. Accurately weighed amount (100mg) of microbaloons were taken for dissolution study. The microbaloons were placed in a non reacting muslin cloth that had a smaller mesh size than the microspheres. The mesh was tied with a nylon thread to avoid the escape of any microbaloons. Simulated gastric pH 1.2 was used as the dissolution medium and maintained at 37^0C at a rotation speed of 100 rpm. Samples of 5 ml each were withdrawn at 1 hr, 2 hr, 4 hr, 6 hr, 8 hr, 10 hr and 12 hr intervals and analyzed spectrophotometrically at 318.16 nm to determine the concentration of drug present in the dissolution medium. The initial volume of the dissolution fluid was maintained by adding 5 ml of fresh dissolution fluid after each withdrawal.

KINETICS OF DRUG RELEASE

To examine the drug release kinetics and mechanism, the cumulative release data were fitted to models representing zero order (Q v/s t), first order [Log(Q_0-Q) v/s t], Higuchi's square root of time (Q v/s $t^{1/2}$) and Korsemeyer Peppas double log plot (log Q v/s log t) respectively, where Q is the cumulative percentage of drug released at time t and (Q_0-Q) is the cumulative percentage of drug remaining after time t. In short, the results obtained from *in vitro* cumulative percentage drug release Vs. Time (zero order rate kinetics) shown in figure 5

RESULTS AND DISCUSSION

The floating microbaloons were prepared by solvent evaporation method by using HPMC and EC polymer. The percent yield of prepared microbaloons was in the range 70.22% to 91.02 %.(table: 1).

The SEM photographs showed that the fabricated microspheres were spherical with a smooth surface and exhibited a range of sizes within each batch as shown in figure 1.

The mean particle size of the microbaloons significantly increased with increasing EC concentration and was in the range 45.71 µm to 122.30 µm. As the polymer concentration increases percentage drug entrapment efficiency of the microbaloons was increases in the range 72.28% to 86.67. As shown in figure 2.

The microbaloons floated for prolonged time over the surface of the dissolution medium without any apparent gelation. As the polymer concentration increases the buoyancy time increases. Percentage buoyancy of the microbaloons was in the range 65.87 to 81.80 after 12 hr. As shown in figure 3.

The *in-vitro* dissolution studies were carried out by using USP XXIII basket type dissolution apparatus. Weighed amount of drug loaded floating microspheres was introduced into 900 ml 0.1 N HC1, used as a dissolution medium, maintained at 37 ±0.5°C at a rotation speed of 100 rpm. The samples were withdrawn at predetermined time intervals. First two samples were withdrawn at 30 min. interval. As the polymer concentration increases the drug release decreases. The F1 shows 95.4% and F4 shows the 71.7% in controlled and predictable manner as shown in figure 4. The data obtained for *in vitro* release were fitted for the zero-order, first order and Higuchi-release models. The interpretation of the data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for the zero order model, as shown in figure 5. Indicating the diffusion to be the predominant mechanism of drug release. The release kinetics studies were fit into zero order and Fickian diffusion controlled mechanism was observed.

FIGURES AND TABLES

Fig 1: SEM photograph of RZM floating microbaloons.
Fig 2: Average particle size of RZM microbaloons.
Fig3: Floating microbaloons RZM microbaloons.
Fig 4: In vitro release study of RZM microbaloons.
Table 1: Formulation design of floating microbaloons of RZM.
Table 2: Formulation code, percentage yield, buoyancy time, Incorporation efficiency, particle size distribution.
Table 3: Drug content and In vitro drug release study of RZM microbaloons.
Table 4 Regression co-efficient (r2) values of different kinetic models and diffusion exponent (n) of Peppas model for RZM microbaloons.
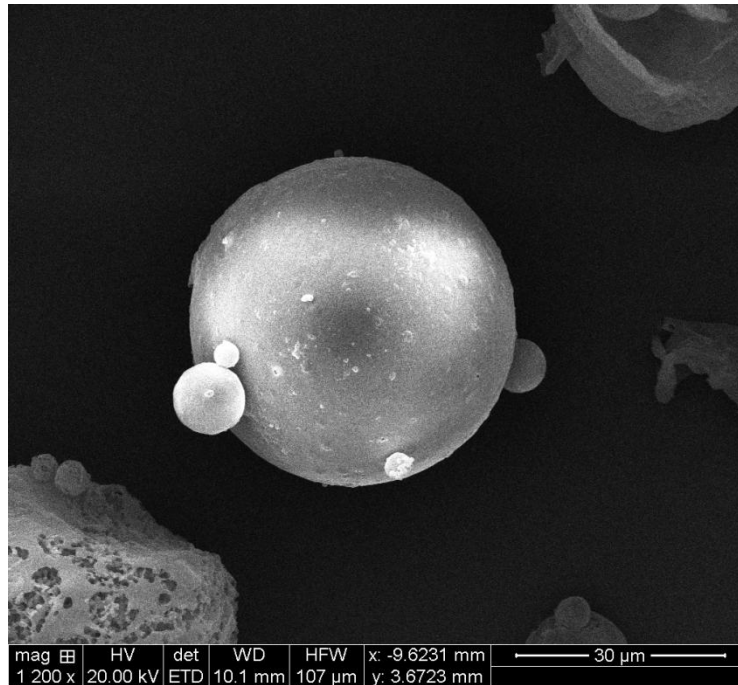

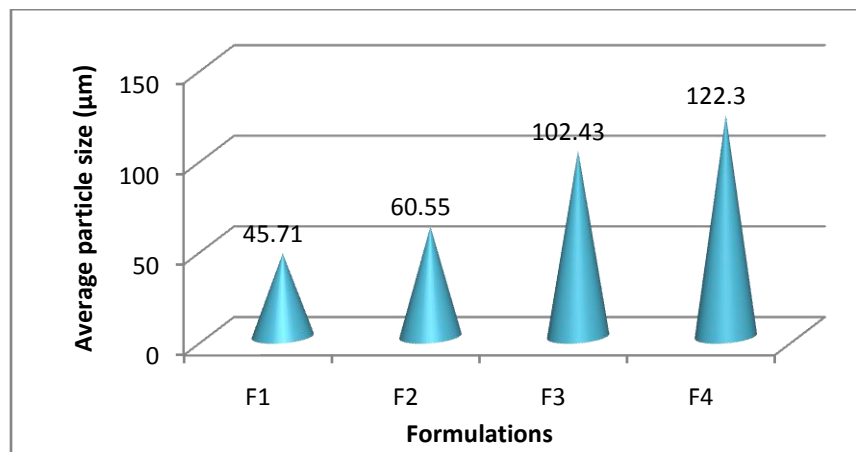**Fig 1: SEM photograph of RZM floating microbaloons.**

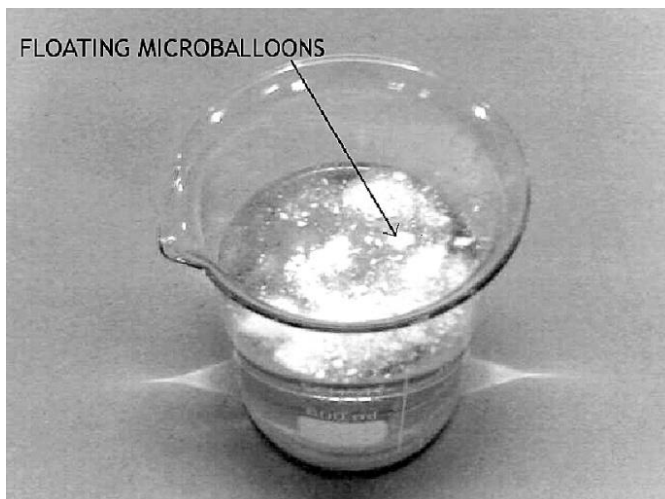**Fig 2: Average Particle size of floating microbaloons.**

Fig3: Floating microbaloons of RZM microbaloons.

Table 1: Formulation design of floating microbaloons of RZM.

Sl.so	Formulation code	Polymer ratio HPMC:EC	Solvent ratio Ethanol: DCM	Stirring rate	Time for stirring
1	F1	1:1	1:1	300	30 min
2	F2	1:2	1:2	400	30min
3	F3	1:3	1:3	500	40min
4	F4	1:4	1:4	600	50min

Table 2: Formulation code, percentage yield, buoyancy time, Incorporation efficiency, particle size distribution.

Batch code	% yield	Average Particle size	Buoyancy time	% drug entrapment efficiency
F1	70.22	45.71$\pm$1.80	65.87$\pm$2.65	72.28$\pm$3.75
F2	78.41	60.55$\pm$1.45	74.73$\pm$1.80	75.35$\pm$3.85
F3	83.35	102.43$\pm$6.83	79.81$\pm$2.80	82.00$\pm$4.39
F4	91.02	122.30$\pm$0.60	81.80$\pm$3.07	86.67$\pm$4.39

SD =Standard deviation (n=3)

Table 3: Drug content and In vitro drug release study of RZM microbaloons.

Formulation Code	% Drug content	% cumulative drug release at 10 hrs
F1	41.5	95.4
F2	35.6	89.2
F3	28.0	78.6
F4	16.9	71.7

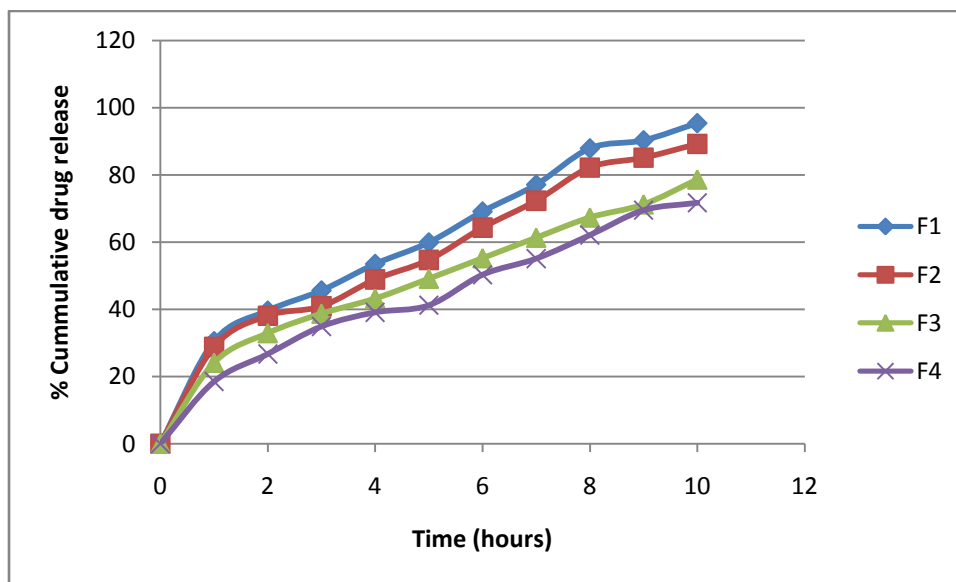SD =Standard deviation (n=3)

Fig 4: In vitro release profile of RZM microbaloons.

RELEASE KINETICS

Table 4 Regression co-efficient (r2) values of different kinetic models and diffusion exponent (n) of Peppas model for RZM microbaloons.

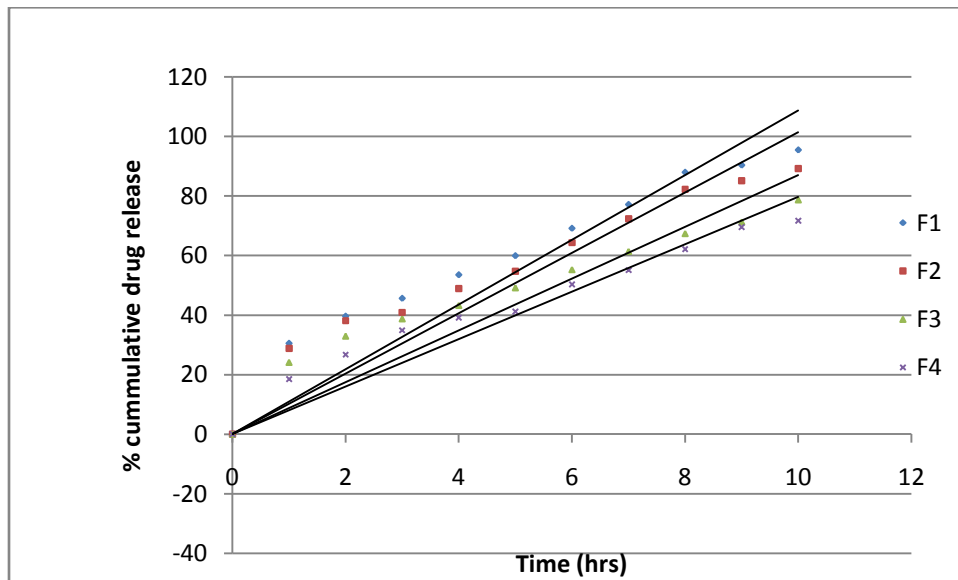| Formulation	Zero order	First order	Higuchi Matrix	Peppas plot	
				r^2 value	'n' value
F1	0.9860	0.8572	0.9464	0.9717	0.6692
F2	0.9827	0.9479	0.9536	0.9752	0.6522
F3	0.9774	0.9759	0.9472	0.9769	0.6402
F4	0.9770	0.9750	0.9469	0.9757	0.6398

Fig 5. Zero order release kinetics of RZM microbaloons

CONCLUSION

Novel floating microbaloons were successfully prepared by solvent evaporation method for prolonged as well as controlled action of Rosiglitazone maleate. Due to their low densities, microbaloons drug delivery system showed good floating ability (more than 10 h). From *in vitro* drug release studies, it is concluded that by changing the ratio of polymers (HPMC k14 and EC) and solvent (DCM and ethanol) Rosiglitazone maleate release can be controlled. It was noticed that increase in the polymer concentration decreased the drug release from the microbaloons due to increased thickness of the outer shells. These microbaloons could be dispensed by filling them in the empty capsule.

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