

Gastroretentive microballoons of metformin: Formulation development and characterization

Akash Yadav, Dinesh Kumar Jain

Department of Pharmaceutics,
College of Pharmacy, IPS Academy,
Knowledge Village, A. B. Road,
Rajendra Nagar, Indore,
Madhya Pradesh, India

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ABSTRACT

The present study involves preparation and evaluation of floating microballoons with metformin as model drug for prolongation of gastric residence time. The microballoons were prepared by the solvent evaporation method using polymers hydroxypropylmethyl cellulose and ethyl cellulose. The shape and surface morphology of prepared microballoons were characterized by optical and scanning electron microscopy, respectively. *In vitro* drug release studies were performed and drug release kinetics was evaluated using the linear regression method. Effects of stirring rate during preparation, polymer concentration, solvent composition and dissolution medium on the size of microballoons, and drug release were also observed. The prepared microballoons exhibited prolonged drug release (8 hours) and remained buoyant for >10 hours. The mean particle size increased and the drug release rate decreased at higher polymer concentration. No significant effect of the stirring rate during preparation on drug release was observed. *In vitro* studies demonstrated diffusion-controlled drug release from the microballoons.

Key words: Ethyl cellulose, floating microballoons, hydroxypropylmethyl cellulose, *in vitro* release, metformin

INTRODUCTION

Floating drug delivery systems or hydrodynamically balanced systems are among the several approaches that have been developed in order to increase the gastric residence time of dosage forms.^[1-3] Both single and multiple unit systems have been developed. The single-unit floating systems are more popular but have a disadvantage owing to their “all-or-nothing” emptying process leading to high variability of the gastrointestinal transit time.^[4,5] Still, the multiple-unit dosage forms may be better suited because they are claimed to reduce the inter subject variability in

absorption and lower the probability of dose dumping.^[6] Such a dosage form can be distributed widely throughout the gastrointestinal tract (GIT), affording the possibility of a longer lasting and more reliable release of the drug from the dosage form.^[7]

Both natural and synthetic polymers have been used to prepare floating microballoons. Kawashima *et al.* prepared hollow microballoons or microballoons of ibuprofen by the emulsion-solvent diffusion method using acrylic polymers.^[8] The microballoons exhibited good *in vitro* floatability and drug release decreased drastically with increasing polymer concentration. Floating microballoons of cellulose acetate loaded with four different drugs were prepared using the solvent diffusion-evaporation method.^[9] The microballoons remained buoyant for more than 12 hours. Methylcellulose and chitosan micropellets loaded with lansoprazole had a lower density than gastric contents and exhibited better encapsulation efficiencies.^[10] Other polymer solution systems that have been used to prepare floating microballoons are polycarbonate/dichloromethane,^[11,12] cellulose acetate butyrate/Eudragit RL100 mixture in acetone,^[13] and Eudragit S100/*i*- propanol.^[14]

Metformin was used as a model drug. It is an antihyper-

Address for correspondence

Mr. Akash Yadav,
Department of Pharmaceutics, College of Pharmacy,
IPS Academy, Rajendra Nagar, Indore – 452 012,
Madhya Pradesh, India. E-mail: akash.ipsa@gmail.com

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glycemic agent which improves glucose tolerance in type II diabetes.^[15] It is poorly absorbed from the lower GIT and has a short elimination half life (5-6 hours). The objective of the present study was to develop floating microballoons of metformin in order to achieve an extended retention in the upper GIT, which may result in enhanced absorption and there by improved bioavailability. The prepared microballoons were evaluated for size, *in vitro* metformin release, buoyancy, and incorporation efficiency (IE). The effect of various formulation variables on the size and drug release was investigated.

MATERIALS AND METHODS

Metformin was obtained as a gift sample from Sohan Healthcare, India. Sodium chloride was obtained from S.D. Fine Chemicals Ltd., India. Dichloromethane, hydroxypropylmethyl cellulose (HPMC K4M), ethyl cellulose (EC), and Tween 80 were obtained from Central Drug House (P) Ltd., India. All other chemicals/reagents used were of analytical grade.

Preparation of Microballoons

Microballoons were prepared by the solvent evaporation technique as employed by Struebel *et al.*^[16] Metformin, HPMC K4M, and EC were dissolved in a mixture of ethanol and dichloromethane at room temperature [Table 1]. These were poured into 250 ml water containing 0.01% Tween 80 maintained at a temperature of 30 to 40°C and subsequently stirred at ranging agitation speed to allow the volatile solvent to evaporate. The microballoons formed were filtered, washed with water, and dried at 40°C.

Characterization of Microballoons

Buoyancy percentage

Microballoons (0.3 g) were spread over the surface of a USP XXIV dissolution apparatus (type II) filled with 900 ml 0.1 mol l⁻¹ HCl containing 0.02% Tween 80. The medium was agitated with a paddle rotating at 100 rpm for 12 hours. The floating and the settled portions of microballoons were recovered separately. The microballoons were dried and weighed. Buoyancy percentage was calculated as the ratio of the mass of the microballoons that remained floating and the total mass of the microballoons.

Incorporation efficiency

To determine the incorporation efficiency (IE), microballoons were taken, thoroughly triturated, and suspended in a minimal amount of alcohol. The suspension was suitably diluted with water and filtered to separate shell fragments. Drug content was analyzed spectrophotometrically at 237 nm.

In vitro release

A USP (United State Pharmacopoeia) basket apparatus has been used to study *in vitro* drug release from

microballoons.^[18-20] In the present study, drug release was studied using a modified USP XXIV^[17] dissolution apparatus type I (basket mesh #120, equals 125 m) at 100 rpm in distilled water and 0.1 mol l⁻¹ HCl (pH 1.2) as dissolution fluids (900 ml) maintained at 37±0.5°C. Withdrawn samples (10 ml) were analyzed spectrophotometrically as stated above. The volume was replenished with the same amount of fresh dissolution fluid each time to maintain the sink condition. All experiments were performed in triplicate. Linear regression was used to analyze the *in vitro* release mechanism.

Statistical Analysis

Experimental results were expressed as mean SD. Student's *t*-test and one-way analysis of variance (ANOVA) were applied to check significant differences in drug release from different formulations. Differences were considered to be statistically significant at *P*<0.05.

RESULTS AND DISCUSSION

Floating microballoons were prepared by the solvent evaporation method using HPMC K4M and EC [Table 1]. The scanning electron microscope (SEM) photographs showed that the fabricated microballoons were spherical with a smooth surface and exhibited a range of sizes within each batch [Figure 1]. The microballoons floated for prolonged time over the surface of the dissolution medium without any apparent gelation. Buoyancy percentage of the microballoons was in the range 63.1±3.1 (batch B3) to 87.3±5.3% (batch A6) [Table 2].

Microballoons were prepared using a gradually increasing EC concentration in combination with a fixed concentration

Table 1: Batch specifications of the prepared microballoons

Batch	Polymer ratio (HPMC K4M/EC)	Temperature (°C)	Solvent ratio (alcohol/dichloromethane)
A ^a	1:1	30	1:1
A2 ^a	1:2	30	1:1
A3 ^a	1:3	30	1:1
A4 ^a	1:4	30	1:1
A5 ^a	1:5	30	1:1
A6 ^a	1:6	30	1:1
B1 ^b	1:2	30	1:1
B2 ^b	1:3	30	1:1
B3 ^c	1:2	30	1:1
B4 ^c	1:3	30	1:1
C1 ^a	1:3	30	2:1
C2 ^a	1:3	30	3:1
C3 ^a	1:3	30	1:2
C4 ^a	1:3	30	1:3

Stirring rate; a = 300 rpm, b = 500 rpm, c = 1 000 rpm; HPMC: Hydroxypropylmethyl cellulose; EC: Ethyl cellulose

of HPMC K4M to assess the effect of polymer concentration on the size of microballoons. The mean particle size of the microballoons significantly increased with increasing EC concentration ($P < 0.05$) and was in the range 203.2 ± 8.2 to $385.2 \pm 9.7 \mu\text{m}$ [Table 2]. The viscosity of the medium increases at a higher polymer concentration resulting in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities.^[21,22] This results in the formation of larger particles.

To observe the effect of agitation speed on the size of the resulting microballoons, formulations were prepared at varying agitation speeds (batches B1–B4) and the effect of agitation speed on the size of microballoons were observed. *In vitro* metformin release studies were performed in 0.1 mol l^{-1} HCl for 8 hours. The cumulative release of metformin significantly decreased with increasing EC concentration ($P < 0.05$, [Figure 2]). The increased density of the polymer matrix at higher concentrations results in an increased diffusional pathlength. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller

Table 2: Various formulation parameters for microballoons

Batch code	Mean particle size ^a (μm)	Incorporation efficiency ^b (%)	Buoyancy (%)
A1	237.4 ± 3.2	51.9 ± 2.2	71.2 ± 2.7
A2	256.1 ± 6.6	55.4 ± 4.9	74.8 ± 4.4
A3	272.4 ± 9.8	57.5 ± 2.9	76.2 ± 3.6
A4	310.5 ± 2.3	57.4 ± 5.4	80.6 ± 4.3
A5	338.7 ± 5.7	58.4 ± 1.7	83.8 ± 2.1
A6	385.2 ± 9.7	60.5 ± 3.9	87.3 ± 5.3
B1	220.1 ± 2.6	57.2 ± 4.7	78.4 ± 2.1
B2	241.2 ± 3.4	58.5 ± 3.8	72.2 ± 2.4
B3	203.2 ± 8.2	56.5 ± 3.9	63.1 ± 3.1
B4	212.2 ± 7.3	58.7 ± 5.1	69.5 ± 3.6
C1	253.4 ± 4.7	53.5 ± 2.1	73.8 ± 3.5
C2	238.9 ± 3.7	52.6 ± 3.7	71.2 ± 1.5
C3	275.2 ± 5.2	62.1 ± 2.3	79.5 ± 3.2
C4	288.1 ± 2.9	63.4 ± 5.4	76.5 ± 1.9

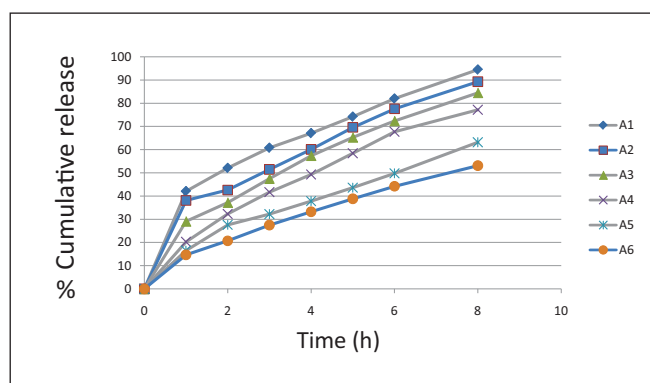


Figure 2: Effect of polymer concentration on *in vitro* release of metformin from floating microballoons

microballoons are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release. Metformin release was higher in the case of microballoons prepared at a higher agitation speed, but the difference in drug release was not statistically significant [Figure 3]. No significant effect of solvent composition was observed on the *in vitro* release of metformin [Figure 4].

The data obtained for *in vitro* release were fitted into equations for the zero-order, first-order, and Higuchi release models.^[23-26] The interpretation of data was based on the value of the resulting regression coefficients. The *in vitro* drug release showed the highest regression coefficient values for Higuchi's model, indicating diffusion to be the predominant mechanism of drug release.

The drug dissolution rate of diffusion-controlled systems in biological fluids is affected by the variability of pH and hydrodynamic conditions of the GI tract. Hence, a comparison was made in order to see the effect of different dissolution media on drug release. The solubility of metformin in distilled water and 0.1 mol l^{-1} HCl at 37°C was reported to be 11.4 and 250 mg ml^{-1} , respectively.^[27] This lower aqueous solubility might have resulted in a marked decrease in drug release. Significantly lower cumulative

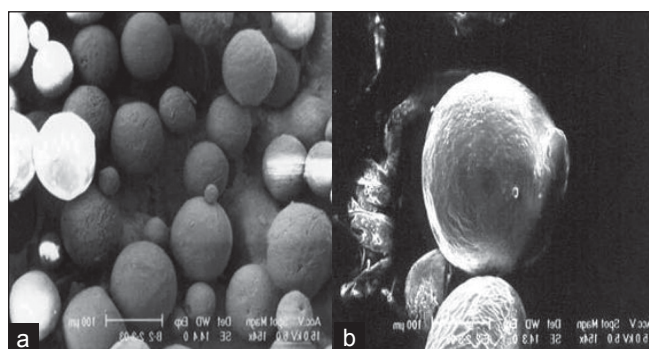


Figure 1: Scanning electron microphotographs of floating microballoons (batch A3): (a) the size range of microballoons; (b) smoothness of the surface of spherically shaped microballoons

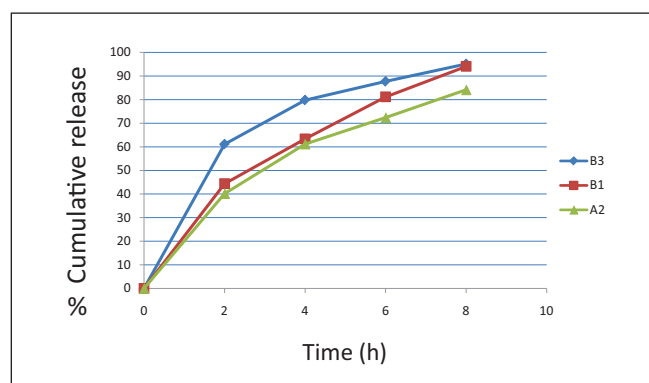


Figure 3: Effect of stirring rate during microballoons preparation on *in vitro* release of metformin from microballoons

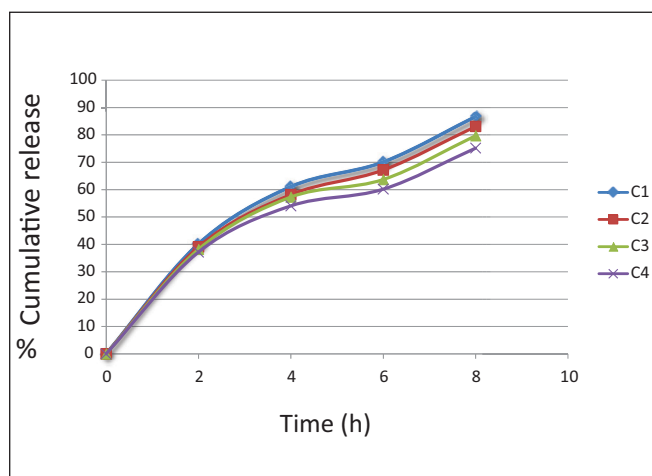


Figure 4: Effect of solvent composition on *in vitro* release of metformin from floating microballoons

drug release ($P < 0.05$) was observed in distilled water compared with that in 0.1 mol l⁻¹HCl [Figure 5].

CONCLUSION

In vitro data obtained for floating microballoons of metformin showed excellent floatability, good buoyancy, and prolonged drug release. Microballoons of different size and drug content could be obtained by varying the formulation variables. Diffusion was found to be the main release mechanism. Thus, the prepared floating microballoons may prove to be potential candidates for multiple-unit delivery devices adaptable to any intragastric condition.

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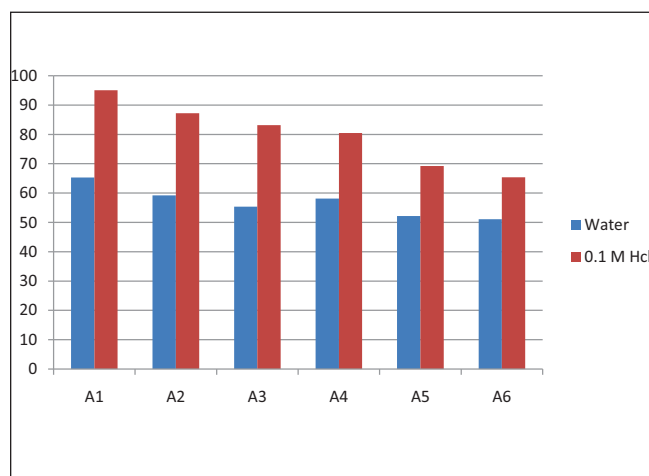


Figure 5: *In vitro* release of metformin from floating microballoons in distilled water and 0.1 mol l⁻¹HCl (pH 1.2) after 8 hours

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