Tuijin Jishu/Journal of Propulsion Technology
ISSN: 1001-4055
Vol. 44 No. 3 (2023)

Formulation and evaluation of dabigatran loaded microballoons for prolonged drug release

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Abstract: The objective of the present investigation was to formulate microballoons loaded with dabigatran in the polymeric core for achieving sustained release and hence improved bioavailability. Microballoons loaded with dabigatran in the polymer shell were prepared by simple solvent evaporation method using either ethyl cellulose alone or a blend of ethyl cellulose with HPMC/PVP-K30/Eudragit S100/Methyl cellulose in a fixed ratio. The percent yield of the microballoons ranged from 38.7 to 62.4% with highest yield obtained in F3. The particle size was measured using optical microscopy and the particles were observed to be spherical in shape. The particle size ranged from 28.50 ± 16.378 µm (F3) to 48.14 ± 16.748 µm (F1). The angle of repose ranged from 26.37° to 28.09° and the Carr's index and Hausner's ratio were in between 6.38 to 19.95 and 1.07 to 1.25 respectively. It was found that all the formulations exhibited buoyancy in the range of 61.42 to 71.71% over a period of 8h. This suggests that the formulations were able to float for sufficient time and would be able to control the release of dabigatran for longer duration. The *in vitro* drug release study depicted that the highest amount of drug was released from F3 (66.79%) while the lowest was released from F1 (50.27%) at the end of 8 hours of study.
Keywords: Dabigatran, microballoons, prolonged release, Eudragit, HPMC

1. Introduction

Traditional oral dosage forms such as tablets and capsules provide a specific drug concentration in systemic circulation but they are not able to release the drug at a constant rate for a longer duration of time.[1] Gastro retentive drug delivery is based on design and development of systems that might be able to retain the dosage form in the stomach for longer time periods. These systems are particularly beneficial in improving the bioavailability of drugs that possess low solubility in the high pH environment (like intestine).[2,3] Microballoons are the gastro retentive drug delivery system and it is based on the non-effervescent approach usually possessing spherical shape and lack a core with a particle size of less than 200 micrometer.[4]

Dabigatran etexilate is an anticoagulant used for the prevention of venous thromboembolic events or stroke in patients with recent elective hip or knee replacement surgery and atrial fibrillation.[5,6] Dabigatran is a univalent reversible direct thrombin inhibitor (DTI) that competitively inhibits thrombin. Additionally dabigatran has also been shown to inhibit platelet aggregation, another step in the coagulation pathway. It has an oral bioavailability of 3 to 7% and a half-life of 12-15 h.[6] The objective of this work was the development and investigation of floating microspheres (microballoons) of dabigatran to modulate its pharmacokinetic profile and increase its half-life. Treatment of disease requires maintenance of uniform concentration of drug in blood for a long period of time. Floating microspheres were envisaged as the most promising drug delivery system owing to their slow dissolution in gastric fluid thereby rendering the capability to prolong the release of drug at the site of absorption.

2. Material and Methods

Dabigatran was purchased from Yarrow Pharmaceuticals, Mumbai and all other ingredients were procured from various suppliers.

Formulation of Microballoons[7]

Emulsion solvent diffusion method has been used for formulating the microballoons using ethyl cellulose, HPMC, Eudragit S100, methyl cellulose and PVP-K30 as the polymer for forming the shell of the particles (Table 1). A blend of dichloromethane and ethanol in the ratio 1:1 (solvent blend) was used as the solvent to impart floating characteristic to the particles.

The drug and the polymers were accurately weighed using a calibrated electronic weighing balance and dissolved in 20 mL of the solvent blend. In a separate beaker, 100 mL aqueous solution comprising of 0.75% w/v polyvinyl alcohol and 0.2 % w/v Tween 80 was prepared at and stirred continuously at 40°C using mechanical stirrer. The stirring speed was maintained at 200 rpm. To this solution was added dropwise under stirring the solvent blend containing the drug and polymers. The microballoons formed were collected, washed with distilled water, dried in hot air oven and stored in desiccator for evaluation studies.

Table 1: Composition of microballoons

Ingredients	F1	F2	F3	F4	F5
Dabigatran (mg)	100	100	100	100	100
EC (mg)	2000	1500	1500	1500	1500
HPMC (mg)	0	500	0	0	0
PVP-K30 (mg)	0	0	500	0	0
Eudragit S100 (mg)	0	0	0	500	0
Methyl cellulose (mg)	0	0	0	0	500

Evaluation of Microballoons

Percentage Yield

The yield of each batch of microballoon was calculated by measuring the dry weight of the microballoons and calculating the yield percent considering the weight of polymers and drug used for preparing the formulation.

$$\%\ yield = \frac{weight\ of\ dry\ microballoons\ X\ 100}{(Weight\ of\ drug + polymers)}$$

Determination of particle size

The size of the microballoons was determined using optical microscope using a calibrated stage and ocular micrometer. The microballoons were dispersed in small amount of water a drop was placed on a glass slide. The drop was covered with a cover slip and observed under the microscope. The number of graduations covered by each particle was counted and the particle size was calculated using the calibration data of the ocular micrometer.

Entrapment Efficiency

An accurately weighed 10 mg of microballoons were crushed and to it was added 10 mL of ethanol. The contents were vortexed for 2 min to extract out the drug and dissolve it. The solution was filtered and the filtrate was diluted using phosphate buffer. The absorbance of the diluted filtrate was recorded using UV spectrophotometer against phosphate buffer as the solvent blank. The concentration of dabigatran was calculated from the absorbance using the calibration curve equation. The entrapment efficiency was calculated by the formula:

$$\%\ Entrapment\ efficiency = \frac{Drug\ content\ calculated\ X\ 100}{Theoretical\ Drug\ Content}$$

Determination of floating capacity (buoyancy)

Microballoons (20 mg) were transferred to a 100 mL Simulated Gastric Fluid (SGF), pH 1.2 consisting of 0.02% Tween 20 (for preventing aggregation of microballoons) maintained at 37°C. The mixture was stirred on a magnetic stirrer. After 8 h, the settled microballoons and the floating microballoons were separately collected and dried at 40°C and weighed. The buoyancy was calculated by the following equation:

$$\%\ Buoyancy = \frac{Weight\ of\ floating\ microballoons\ \ X\ 100}{(Weight\ of\ floating + settled\ microballoons)}$$

Micromeritic features

The flow properties of all the prepared batches of microballoons was studied as under.

Angle of Repose[7]

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (h). The angle of repose (θ) was then calculated by measuring the height and radius (r) of the heap of powder formed using the following formula

$$\tan\theta = \frac{h}{r}$$

Bulk and Tapped Density[8]

A weighed quantity of blend (1 g) was taken into a graduated cylinder (50 mL) and measuring the volume of this weight. The bulk density (ρ bulk) was calculated by the formula

ρ bulk = weight of the powder/initial volume

The above cylinder containing the powder blend was tapped until no further volume change occurs. The tapped density (ρ tap) was calculated by the formula

ρ tap = weight of the powder/finial volume

Hausner's ratio and Carr's Index[8,9]

Hausner's ratio is the ratio of tapped density to bulk density and is calculated by the following formula

HR = ρ tap/ ρ bulk

The Compressibility index is also known as Carr's Index and is calculated using the values of bulk and tapped density using the formula

$$\text{Carrs Index} = \frac{\rho\ \text{tap} - \rho\ \text{bulk}}{\rho\ \text{tap}}\ \text{X}\ 100$$

***In vitro* drug release**

The amount of drug released at various time intervals for various batches of microballoons was determined using paddle type dissolution apparatus. The dissolution medium comprised of 900 mL of simulated gastric fluid, pH 1.2 supplemented with 0.02% Tween 20 maintained at 37 ± 0.5°C and stirred at 100 rpm. A weighed amount of microballoons equivalent to 50 mg of dabigatran was transferred to the dissolution flask and at predetermined time intervals, 1 mL of sample were withdrawn from the dissolution medium, replenishing with fresh medium after each withdrawal up to 8th hour. Samples were appropriately diluted and analyzed by UV spectrophotometer at 325 nm. The concentration of dabigatran after each withdrawal was determined using the equation of the calibration curve.

3. Results and Discussion

Gastro-retentive floating microspheres are low density systems that possess adequate buoyancy to let them float over the contents of the gastric medium and linger in stomach for enhanced period. As the system floats over gastric contents, the loaded drug releases slowly resulting in reduced fluctuations in plasma drug concentration. Microballoons loaded with dabigatran loaded in their polymer shell were prepared by simple solvent evaporation method using either ethyl cellulose alone or a blend of ethyl cellulose with other polymers in a fixed ratio.

Percentage yield

The percentage yield of the microballoons was calculated in relation to weight of drug and polymers used for formulation. It was witnessed from the results that the yield was dependent on the binding properties of the polymer which could be inferred as the highest yield was obtained when PVP-K30 was used as the copolymer in the formulation (Table 2).[10]

Table 2: Percent yield of the microballoon formulations

Formulation	Yield	
	mg	%
F1	967.5	38.7
F2	1230	49.2
F3	1560	62.4
F4	1427.5	57.1
F5	1207.5	48.3

The highest yield was obtained in F3 using a blend of PVP-K30 and ethyl cellulose for preparing the shell of the particles whereas the lowest yield was obtained when only ethyl cellulose was used. The hydrophobicity of ethyl cellulose decreases the binding capability and hence the formulation of particles is reduced.

The particle size was measured using optical microscopy and the particles were observed to be spherical in shape (Figure 1). It was found that F3 had the lowest particle size suggesting a potential effect of the binding capability of the blend in comparison to the other blends or ethyl cellulose alone (Table 3).

The entrapment of dabigatran was also found to be maximum in F3 though all the formulations exhibited almost similar entrapment of dabigatran. The higher amount in F3 suggests that the blend of PVP K30 and ethyl cellulose was able to form a strong polymeric shell of the microballoons.

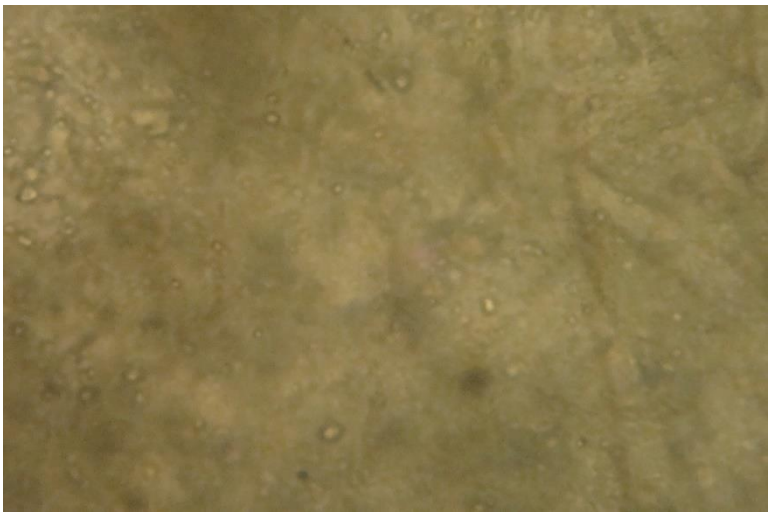

Fig 1: Microscopic image of F3

Table 3: Particle size and entrapment efficiency of microballoons

Formulation	Particle Size (µm)	Entrapment Efficiency (%)
F1	48.14 ± 16.748	60.81
F2	32.30 ± 17.183	64.25
F3	28.50 ± 16.378	71.69
F4	31.04 ± 11.966	67.54
F5	31.67 ± 15.103	68.72

The flow properties of all the microballoon formulations were studied and it was found that all the formulations were able to exhibit optimum flow properties. The angle of repose ranged from 26.37° to 28.09° (a value less than 35° suggest good flow of powder). The Carr's index and Hausner's ratio were in between 6.38 to 19.95 and 1.07 to 1.25 respectively (Table 4).

Table 4: Micromeritic features of microballoons

Formulation code	Angle of Repose (°)	Bulk density (g/cm3)	Tapped density (g/cm3)	Carr's Index	Hausner's Ratio
F1	26.37	0.396	0.423	6.38	1.07
F2	27.18	0.406	0.503	19.28	1.24
F3	27.13	0.333	0.416	19.95	1.25
F4	27.22	0.313	0.38	17.63	1.21
F5	28.09	0.38	0.416	8.65	1.09

It could be concluded from the results that increasing the hydrophilicity of the blend (F2-F4) decreased the flow property with the lowest flow exhibited by F2 containing HPMC and F3 containing PVP. The particle size of the formulations suggests that the formulations are suitable for oral delivery.
The buoyancy was calculated using the reported formula from the weight of floating as well as settled microballoons over 8 h of study (Table 5)

Table 5: Buoyancy of microballoons

Formulation	Wt of float (mg)	Wt of settled (mg)	Buoyancy (%)
F1	12.1	7.6	61.42
F2	13.4	6	69.07
F3	14.2	5.6	71.71
F4	13	6.7	65.98
F5	12.6	6.3	66.66

It was found that all the formulations exhibited buoyancy in the range of 61.42 to 71.71% over a period of 8h. This suggests that the formulations were able to float for sufficient time and would be able to control the release of dabigatran for longer duration. Formulation F3 exhibited the highest buoyancy percentage of all the formulations.

Result of *in-vitro* release of dabigatran from microballoons

The amount of drug that released from the microballoons was determined using paddle type dissolution apparatus. The *in vitro* drug release study depicted that the highest amount of drug was released from F3 (66.79%) while the lowest was released from F1 (50.27%) at the end of 8 hours of study. An initial burst release was witnessed in each formulation suggesting loosely trapped drug on the surface of the polymeric particles. Higher drug release was observed in all the formulations having hydrophilic polymer (F2-HPMC, F3-PVP and F4-Eudragit) (Table 6, Figure 2).

Table 6: *In vitro* release of dabigatran from microballoons

Time	Cumulative drug release (%)				
	F1	F2	F3	F4	F5
0	0	0	0	0	0
1	17.89	19.87	22.34	20.13	19.01
2	23.46	30.61	34.48	28.58	30.16
4	32.13	38.27	42.23	36.75	38.94
6	40.18	47.84	53.46	50.19	46.72
8	50.27	61.23	66.79	63.48	57.82

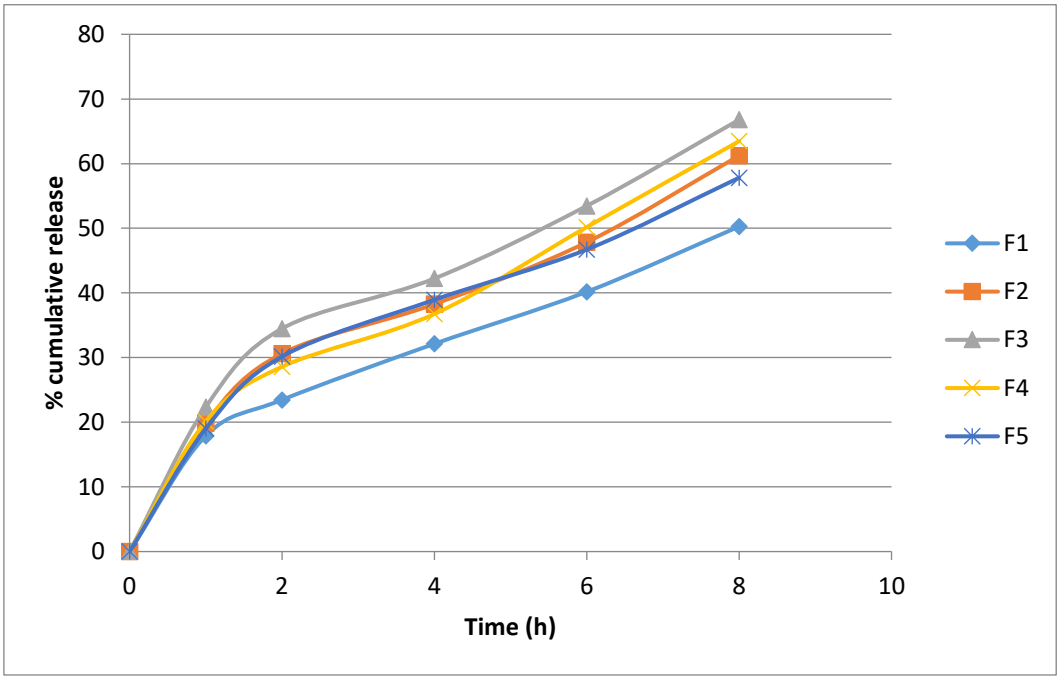

Fig 2: *In vitro* release of dabigatran from microballoons

4. Conclusion

The primary objective of the present investigation was formulating microballoons loaded with dabigatran, for sustained release and improved bioavailabilty. The formulation was achieved using ethyl cellulose either alone or in blend with HPMC/PVP/Eudragit/methyl cellulose as the polymeric shell. The formulation F3 released the highest amount of drug and presented highest entrapment efficiency as well as the lowest particle size. Thus is could be concluded that F3 was the best formulation with optimum properties required for improving the oral bioavailability of dabigatran.

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