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RESEARCH ARTICLE

DEVELOPMENT AND EVALUATION OF RITONAVIR HOLLOW MICROBALLOONS FOR FLOATING DRUG DELIVERY

Uroko Robert Ikechukwu[1], Dingwoke Emeka John Francis[2], Ambi AA[2]
[1]*Department of Biochemistry, College of Natural Science, Micheal Okpara University of Agriculture Umudike, Abia State, Nigeria.*
[2]*Department of Biochemistry, Ahmadu Bello University Zaria, Kaduna State, Nigeria.*

ABSTRACT
Objective: Ritonavir is human immunodeficiency virus (HIV) protease inhibitor used as the antiretroviral agent. The objective of the present investigation was to formulate and evaluate Ritonavir gastro-retentive floating microballoons for controlled release.
Methods: Five batches of microballoons were prepared by the emulsion solvent diffusion method. The resultant microballoons were evaluated for percentage yield, entrapment efficiency, particle size, and *in vitro* drug release, stability study.
Results: The densities of floating microspheres were found to be less than the density of gastric fluid (1.004 g/cm^3). The entrapment efficiency of prepared floating microspheres was satisfactory (68.37 to 88.52%). Among all formulations, FM1 prepared with polymer HPMC was found to be the best as it exhibited highest drug release (89.07%) in 12 hrs and was stable for three months at ambient conditions.
Conclusion: Study concludes that Ritonavir can be delivered in the form of floating hollow microballoons in an efficient way. Based on different evaluation parameters, formulations of batch FM1 were found to an optimum formulation.
Keywords: Floating drug delivery, gastro-retentive, hollow microballoons, *in vitro* drug release, Ritonavir.

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Address for Correspondence:
Uroko Robert Ikechukwu, Department of Biochemistry, College of Natural Science, Micheal Okpara University of Agriculture Umudike, Abia State, Nigeria, E-mail: *greaturoko@gmail.com*

INTRODUCTION

The oral route is being used for the delivery of therapeutic agents because of different advantages including the low cost of the therapy and ease of administration lead to high levels of patient compliance. More than 50% of the drug delivery systems available in the market are oral drug delivery systems[1]. The purpose of any drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to attain promptly and then maintain desired drug concentration[2]. Drugs that are easily absorbed from the gastrointestinal tract and have a short half-life are eliminated quickly from the blood circulation, so there is a need of frequent dosing to maintain therapeutic concentration of drug. To eliminate this limitation, the oral sustained controlled release formulations have been developed in an attempt to release the drug slowly into the gastro-intestinal tract and maintain an effective drug concentration in the blood over long period of time[3]. Floating systems or dynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system floats over the gastric contents, the drug is released slowly at the desired rate. Conventional oral dosage forms do not offer any control over drug delivery and cause great fluctuations in plasma drug concentrations[4]. Ritonavir is human immunodeficiency virus (HIV) protease inhibitor primarily absorbed from stomach used as the antiretroviral agent[5]. Its biological half-life is 3-5 hrs. In order to maintain adequate plasma concentrations Ritonavir requires multiple daily doses[6]. So, Ritonavir is selected as the model drug to prepare floating micro balloons.

MATERIALS AND METHODS

Ritonavir was obtained from Silva Hill Pharma Limited, Nigeria city, Eudragit L 100 and hydroxypropyl methylcellulose (HPMC) were purchased from the Jagal Pharmaceutical, Lagos, Nigeria. All other chemicals used were of analytical reagent grade.

Preparation of floating microballoons

Floating microballoons were prepared by the emulsion solvent diffusion method. Ritonavir, Eudragit L100 and HPMC were dissolved in a mixture in different ratio in ethanol and dichloromethane (Table 1). The resulting solution was added slowly to stirred 250 ml of aqueous solution of 0.50% (w/v) PVA at room temperature. The stirring was done for 2 hrs at 1000-1200 rpm by mechanical stirrer equipped with four bladed propellers, to evaporate the volatile solvent. The floating microballoons formed were screened (#12), washed with water and dried at room temperature in a desiccator for 24 hrs[7].

Table 1: Composition of floating microballoons formulations of Ritonavir.

Batch code	Eudragit L100 (mg)	HPMC (mg)	Dichloromethane: Ethanol::1:1
FM1	-	300	10
FM2	300	-	10
FM3	150	150	10
FM4	100	200	10
FM5	200	100	10

Evaluation of microballoons

The percentage yield

It was determined by weighing the Ritonavir hollow microballoons after drying. The percentage yield was calculated as follows[8]:

$$\% \text{ Yield } = \frac{\text{Total weight of hollow microballoons}}{\text{Total weight of drug and polymer}} \text{ X } 100$$

Tapped density

Tapped density of Ritonavir hollow microballoons was determined by the tapping method. Accurately weighed quantity of hollow microballoons was transferred in to a 10 ml measuring cylinder. After observing the initial volume of floating microballoons, the tapping was continued on a hard surface until no further change in volume was noted and the tapped density was calculated[9].

Angle of repose

The angle of repose of Ritonavir hollow microballoons was determined by fixed funnel method. The hollow microballoons were allowed to fall freely through a funnel until apex of conical pile just touched the tip of the funnel[10].

Carr's Index

It indicates the ease with which a material can be induced to flow and powder compressibility[11]. It is expressed in percentage and is given by

$$\text{Carr, s Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \text{x} 100$$

Hausners ratio

Hausner ratio (Hr) is an indirect index of ease of powder flow[12]. It is calculated by the following formula:

$$\text{Hausner}'\text{s ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Buoyancy study

Ritonavir microballoons (100 mg) were placed in 0.1 N HCI (300 ml) containing 0.02% Tween 20 and stirred at 100 rpm. The layer of buoyant microballoons was pipetted and separated by filtration at 1, 2, 4 and 6 h. The collected microballoons were dried in a desiccator over night[13]. The percentage of microballoons was calculated by the following equation:

$$\% \text{ Buoyancy} = \frac{\text{Weight at time t}}{\text{Initial weight}} \text{x} 100$$

Drug entrapment efficiency

Ten mg of hollow Ritonavir microballoons from all batches were accurately weighed and crushed. The powdered microballoons were dissolved with 10 ml ethanol in 100 ml volumetric flask and volume was made up with 0.1 N HCl. The resulting solution is then filtered (Whatman filter paper No. 44), suitably diluted and the absorbance was measured at 246 nm against 0.1 N HCI as blank[14].

***In vitro* release studies**

A 12 hrs study of drug release rates from floating Ritonavir microballoons was carried out using USP type II dissolution paddle assembly. Floating microballoons equivalent to 100 mg drug were dispersed in 900 ml of 0.1 N HCI pH 1.2 maintained at 37±0.5°C and stirred at 100 rpm. Five ml sample was withdrawn at predetermined intervals while replacing equal amount of fresh dissolution medium. The samples were filtered, suitably diluted and analyzed spectrophotometrically at 246 nm to determine the concentration of drug present in the dissolution medium[15].

Drug release kinetic data analysis

The dissolution data of all the formulations was fitted to zero order, Higuchi matrix and Korsemeyer-Peppas to ascertain the kinetic modeling of drug release. The value of 'n' gives an indication of the release mechanism. When n=1, the release rate is independent of time (typical zero order release/case II transport); n=0.5 for Fickian release (diffusion/case I transport); and when 0.5<n<1, anomalous (non-Fickian or coupled diffusion/ relaxation) are implicated. Lastly, when n>1.0 super case II transport is apparent[16].

Stability study

From the prepared Ritonavir microballoons, best formulation was selected on basis of buoyancy and the percentage drug released. The selected formulation was placed in borosilicate screw capped glass containers and stored at different temperatures (27±2°C), oven temperature (40±2°C) and in the refrigerator (5-8°C) for a period of 3 months. The samples were assayed for drug content at regular intervals[17].

RESULTS AND DISCUSSION

The hollow microballoons of Ritonavir were successfully prepared using eudragit L100 and HPMC as a polymer by emulsion solvent diffusion method.

Mean particle size range was varied from 543 to 928 mm and was found to be affected by change in drug and polymer ratio. In general if sizes of microballoons are less than 500 mm, release rate of drug will be high and floating ability will reduce, while if size lies in the range of 500-1000 mm, the floating ability will be more and release rate will be in sustained manner[18].

Table 2: Micromeritic properties of Ritonavir microballoons formulations.

Code	Mean particle size (mm)	Bulk density (gm/cm^3)	Tapped density (gm/cm^3)	Hausners ratio	Carr's Index	Angle of repose
FM1	928±0.56	0.741±0.24	0.801±0.42	1.08	7.49	19.32°±0.13
FM2	734±0.31	0.763±0.09	0.825±0.08	1.08	7.51	20.12°±0.24
FM3	627±0.25	0.863±0.36	0.920±0.13	1.06	6.19	15.21°±0.09
FM4	543±0.38	0.792±0.47	0.840±0.51	1.06	5.71	18.35°±0.08

(Mean± S.D., n=3)

Table 3: Different evaluation parameters of Ritonavir microballoons formulations.

Code	Particle Size (µm)	% Yield	Entrapment Efficiency (%)	% Buoyancy
FM1	255.03±0.57	87.34±0.36	88.52±0.08	85.23±0.08
FM2	268.56±0.48	82.32±0.48	74.64±0.22	68.46±0.36
FM3	270.52±0.52	75.46±0.08	68.37±0.43	80.84±0.46
FM4	300.37±0.35	79.22±0.33	71.37±0.63	78.53±0.33

(Mean± S.D., n=3)

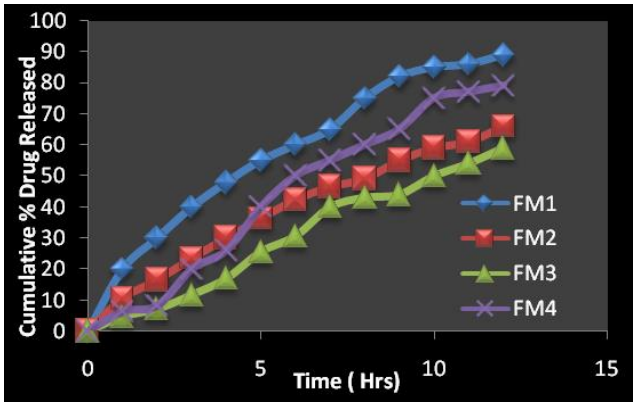

Figure 1: *In-vitro* release profile of different Ritonavir microballoons formulations.

Density values for all formulations were less than that of gastric fluid (1.004 g/cm^3), suggesting that they exhibit good buoyancy. The floating ability pattern differed according to the formulation tested and medium used. Microballoons formulation of batch FM1 showed the best, 85.23% floating ability in 0.1 N HCl. This can be mainly due to its low bulk density value obtained before and after tapping respectively. The microballoons remain buoyant for prolonged time over the surface of the dissolution medium without any apparent gelation, which might be responsible for good floating property. All formulations showed excellent flowability as represented in the terms of angle of repose (<40°). All the formulations showed satisfactory entrapment efficiency ranging in 68.37 to 88.52%.

Percentage drug release for the formulations FM1, FM2, FM3 and FM4 was found to be 89.07%, 66.14%, 58.43% and 77.43% respectively in 12 hrs. It was observed that drug release rate increased by increasing the ratio of HPMC respectively. FM1 formulation showed appropriate balance between buoyancy and drug release rate of which is considered as a best formulation. The *in vitro* release data was applied to various kinetic models to predict the drug release kinetic mechanism. Kinetics and mechanism of drug release from all formulation was evaluated on the basis of zero order, Higuchi equation and Peppas model. Zero order plots for all formulations were found to be linear. Higuchi plot was found to be linear, which indicates diffusion may be the mechanism of drug release for each formulation.

Table 4: Kinetic models applied on Ritonavir microballoons formulations.

Code	Zero order	Higuchi	Korsemeyer-Peppas
FM1	0.9214	0.9763	0.9867, n=0.4073
FM2	0.8860	0.9565	0.9835, n= 0.5138
FM3	0.8761	0.9825	0.9836, n=0.5836
FM4	0.9213	0.9235	0.9937, n=0.5367

Correlation coefficient (r^2) and slope value for each equation in the range of (0.9835-0.9937 and n in the range of 0.4073- n=0.5836 for Peppas model.

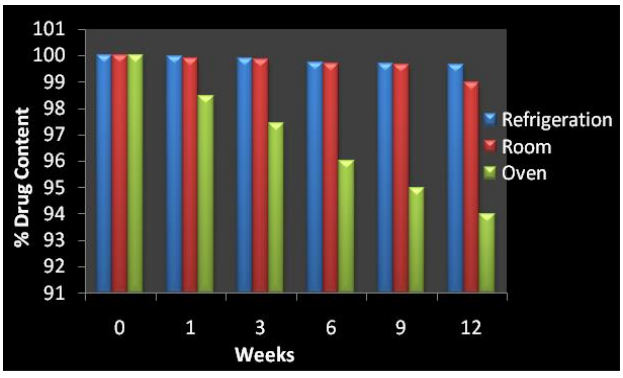

Figure 2: Stability study of Ritonavir microballoons formulations of batch FM1.

Peppas plot was found with good linearity, its n>0.5 for all formulations, indicating that drug release may follow anomalous diffusion. Stability study was carried out for the FM1 formulation by exposing it to 5-8°C, 27°C. There was no remarkable change in content of FM1 formulation during 3 months/12 weeks.

CONCLUSIONS

Floating hollow microballoons of different size and drug content could be obtained by varying the formulation variables. Prepared hollow microballoons of Ritonavir showed excellent micromeretic properties, good buoyancy and prolonged drug release for 12 hrs. Thus the prepared floating microballoons may prove to be potential candidates for multiple-unit delivery devices adaptable to any intra gastric condition. Based on different parameters i.e. micromeritic properties, entrapment efficiency, drug content, *in-vitro* release study and stability study floating hollow microballoons of batch FM1 were found to an optimum formulation.

AUTHOR'S CONTRIBUTION

Ikechukwu UR: writing original draft, methodology, investigation, formal analysis, conceptualization. **John Francis DE:** writing, review and editing, methodology, formal analysis, conceptualization. **Ambi AA:** writing, review, and editing, methodology.

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DATA AVAILABILITY

Data will be made available on request.

CONFLICT OF INTEREST

None to declare.

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