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RESEARCH ARTICLE

FORMULATION AND *IN-VITRO* EVALUATION OF FLOATING MICROBALLOONS OF STAVUDINE

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ABSTRACT

Objectives: Objective of present study involves preparation and evaluation of floating microballoons of Stavudine. It is a potent antiviral agent, used for treatment of human immunodeficiency virus (HIV) infection. In present study Stavudine is used as a model drug, to increase its residence time in the stomach without contact with the mucosa.

Methods: Eight floating microballoons formulations of Stavudine were prepared by using different polymers i.e. Eudragit S100, EC and PVP K30, in different ratio by emulsion solvent diffusion method. The microballoons were prepared by the emulsion solvent diffusion technique using different ratio of polymers (Eudragit S100, Ethyl cellulose and PVP K 30) as carriers.

Results: The mean particle diameter of the microballoons was between 230.23-238.33µm.The yield of microballoons was up to 68.32-80.22%. The cumulative percent drug release after 24 hrs of the Stavudine microballoons was in the range of 53.62 to 87.45%. The mean percentage buoyancy of the microballoons was between 69.23-82.53%. The cumulative percent drug release after 24 hrs of the Stavudine microballoons was 53.62 to 87.45%.

Conclusion: Stavudine floating microballoons formulations of batch MB4 was concluded as the optimum formulations among the all 8 formulations based on different parameters.Study concludes that stavudine can be delivered through floating microballoons dosage form in an effective way.

Keywords: Emulsion solvent diffusion method, floating drug delivery system, floating microballoons, Stavudine.

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INTRODUCTION

The main purpose of any drug delivery system is effective control of disease, minimum side effects and better patient compliance in the cost effective way[1]. Dosage forms retained in the stomach are called gastro retentive drug delivery systems. Gastroretentive drug delivery is an approach to prolong gastric residence time, thus targeting site-specific drug release in the upper gastrointestinal tract for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence prolong the gastric retention time of drugs[2]. Floating drug delivery systems have a bulk density lower than gastric fluids and thus remain buoyant in stomach for a prolonged period of time, without affecting the gastric emptying rate[3]. Microballons, refer to hollow microsphere in gastro-retentive drug delivery based non-effervescent approach. They are spherical empty particles without core made up of synthetic polymers or natural proteins, ideally having a size less than 200µm. They float immediately upon contact with gastric fluid and gives promising approaches for increasing the bioavailability of drugs with absorption windows in upper small intestine and stomach[4].

Stavudine is a potent antiviral agent belongs to the class of nucleoside reverse transcriptase inhibitors. It is used along with other drugs for treatment of human immunodeficiency virus (HIV) infection. It decreases the amount of HIV in blood[5]. While Stavudine administered orally as a capsule and an oral solution, it has a very short half-life (1.30 hrs). Thus there is need of frequent administration of large doses of it to maintain therapeutic concentration[6,7]. Moreover use of Stavudine is associated with many limitations such as adverse effects due to accumulation of drug during multi dose therapy, poor patient compliance, and high cost[8,9].

The objective of the present study was to prepare floating microballoons of Stavudine to overcome these problems and to increase its gastric residence time in the stomach, consequently enhance its bioavailability and increase patient compliance.

MATERIALS AND METHODS

Stavudine was received as gift sample from ASPEN Pharmacare NIG. LTD, Eudragit S 100 from BOLAR Pharmaceuticals Ltd, and EC from Drugfield Pharmaceuticals Ltd, Nigeria. All other chemicals were of analytical grade.

Development of floating microballoons

Stavudine floating microballoons were prepared by emulsion solvent diffusion method[10]. 200 mg Stavudine and polymers in different ratio were mixed in ethanol by using blending solvent dichloromethane and heavy liquid paraffin. The slurry was introduced into 250 ml beaker containing 0.2% Tween 80. The stirring was done for 2 hrs at 1000-1200 rpm by mechanical stirrer equipped with four bladed propellers, to evaporate the volatile solvent. After evaporation of solvent, microballoons were collected by filtration, washed with water and dried at room temperature in a desiccator for 24 hrs. The composition of different formulations are shown in Table 1.

Table 1: Composition of floating microballoons formulations of Stavudine.

Batch code	Eudragit S100 (mg)	EC (mg)	PVP (mg)	Tween 80 (mg)	Di-chloromethane: Ethanol ::1:1	Liquid Paraffin (ml)
MB1	200	-	-	5	-	50
MB2	-	200	-	5	-	50
MB3	100	200	-	-	10	-
MB4	200	100	-	-	10	-
MB5	-	200	100	5	-	50
MB6	-	100	200	5	-	50
MB7	100	-	200	-	10	-
MB8	200	-	100	-	10	-

Estimation of % Yield of microballoons: Percentage yield of microballoons was calculated using the following formula[11].

$$\% \text{ Yield} = \frac{\text{Actual weight of product}}{\text{Total weight of Product}} \times 100$$

Microballoons size: The size was measured using an optical microscope and the mean microballoons diameter was calculated by measuring 100 particles with the help of a calibrated ocular micrometer[11].

Sphericity of the microballoons

Sphericity, of prepared microballoons were taken on a black paper using camera lucida[13].

Circulatory factor (S) was calculated using,

$$S = \frac{P^2}{12.56 \times A}$$

Where A is area (cm^2) and, P is the perimeter of the circular tracing

Drug entrapment efficiency

Accurately weighed 10 mg of crushed microballoons were dissolved in 0.1N HCl, and then transferred to 100 ml volumetric flask. The volume was made up to 100 mL with 0.1N HCl. The solution was filtered using Whatman filter paper no. 41. The samples were assayed for drug content using UV spectrophotometry at 265 nm[14].

The amount of drug entrapped in the microballoons was calculated by the following formulae:

$$\text{DEE} = \frac{\text{Amount of drug actually present}}{\text{Theoretical drug load expected}} X100$$

Assessment of *in-vitro* buoyancy

The floating microballoons about 100 mg were spread over the surface of the dissolution medium of 900 ml simulated gastric fluid (SGF, pH 2.0), which is placed in USP dissolution apparatus II. The medium temperature was maintained at 37°C and was agitated by paddle at 100 rpm[15]. After agitation the microballoons that floated over the surface of the medium and those that settled down at bottom of the flask were recovered separately and dried. The percentage of floating microballoons was determined by the following equation:

$$\text{Buoyancy (\%)} = \frac{WF}{WF + WS} X100$$

Where WF and WS are the weight of floating and settled microballoons respectively.

***In-vitro* drug release studies**

The *in-vitro* dissolution studies were carried out by using USP II paddle type dissolution apparatus. Accurately 100 mg of microballoons was introduced into 900 ml of 0.1 N HCl (pH 2), used as a dissolution medium, maintained at a temperature of 37°C, and a rotational speed of 100 rpm. Samples were withdrawn at predetermined time intervals of every one hour for twelve hours. The samples were analyzed UV spectrophotometrically at 265 nm to determine the percentage of drug release[16].

RESULTS AND DISCUSSION

Eight floating microballoons formulations of Stavudine were prepared by using different polymers i.e. Eudragit S100, EC and PVP K30, in different ratio by emulsion solvent diffusion method. The mean particle diameter of the microballoons was between 230.23-238.33 µm. In general as the polymer concentration increases, the particle size also increases. This is because the viscosity of the polymer solution increases with increasing polymer concentration, which in turn decreases the stirring efficiency. The sphericity factor obtained for the microballoons lies in the range of 1.04-1.14. The sphericity value nearer to 1 indicates that the prepared formulations were spherical in nature. High incorporation efficiencies are seen with lower concentrations of polymer with the drug.

Table 2: Characterization of floating microballoons formulations of Stavudine.

Batch Code	Particle Size (µm)	Sphericity	Yield (%)	Entrapment Efficiency (%)	% Buoyancy
MB1	230.23±0.35	1.08±0.04	70.34±0.05	80.52±0.23	69.23±0.21
MB2	235.53±0.24	1.11±0.13	68.32±0.08	79.64±0.41	74.46±0.12
MB3	228.12±0.31	1.09±0.09	66.46±0.41	83.37±0.52	75.84±0.21
MB4	230.21±0.18	1.07±0.06	80.22±0.63	85.37±0.13	82.53±0.12
MB5	234.12±0.27	1.04±0.21	79.44±0.53	79.64±0.29	73.46±0.21
MB6	235.16±0.22	1.08±0.11	75.46±0.22	75.64±0.31	76.46±0.17
MB7	236.21±0.13	1.14±0.41	78.46±0.51	74.64±0.42	77.46±0.32
MB8	239.33±0.33	1.11±0.32	75.46±0.32	78.64±0.53	78.46±0.33

The percentage entrapment efficiency of the micro-balloons was between 74.64-85.37%. The % yield of the microballoons was between 68.32-80.22%.The floating ability test was carried out to investigate the floatability of the prepared microballoons. The mean percentage buoyancy of the microballoons was between 69.23-82.53%. *In-vitro* buoyancy studies reveal that in spite of stirring the dissolution medium for more than 12 hrs formulations were still continued to float without any apparent gelation, thus indicating that microballoons exhibit excellent buoyancies which can be attributed to the pores and cavities present in them.

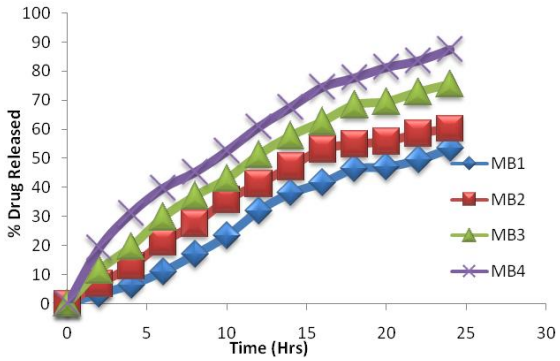

Figure 1: Percentage drug released from microballoons of batch MB1 to MB4.

In general with increase in the amount of polymers there is an increase in the buoyancy percentage. The increase in the buoyancy percentage may be attributed to air which caused swelling because of increased amount of the polymers present.

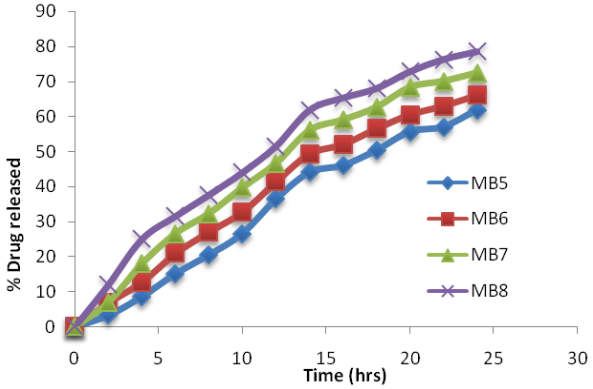

Figure 2: Percentage drug released from microballoons of batch MB5 to MB8.

The good buoyancy behavior of the microballoons may be attributed to the hollow nature of the microballoons. The cumulative percent drug release after 24 hrs of the Stavudine microballoons was 53.62 to 87.45%. Maximum percent release was shown by formulation containing Eudragit S 100 and Ethylcellulose of batch MB4. It was also observed that the drug release generally decreased as the polymer ratio increased. The release of the drug was retarded due to the hydrophobic and insoluble nature of the polymers used. The increased density of the polymer matrix at higher concentrations results in an increased diffusion path length. This may decrease the overall drug release from the polymer matrix. Furthermore, smaller microballo-ons are formed at a lower polymer concentration and have a larger surface area exposed to dissolution medium, giving rise to faster drug release.

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 $p<0.05$.

CONCLUSIONS

In present study 8 different Stavudine floating microballoons formulations were prepared with a view of improving its oral bioavailability and giving a prolonged release of drug. The microballoons show satisfactory yield and impressive drug entrapment efficiency. Release properties were satisfactory and the formulations hold promise for further development into drug delivery systems for oral administration of Stavudine. *In vitro* drug release studies showed that the drug release was more in case of formulations MB4. Stavudine floating microballoons formulations of batch MB4 was concluded as the optimum formulations among the all 8 formulations based on different parameters. However there is need of *in-vivo* study to justify the development of Stavudine floating microballoons.

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DATA AVAILABILITY

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest was associated with this work.

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