IJPSR (2011), Vol. 2, Issue 10 **(Research Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 13 June, 2011; received in revised form 11 July, 2011; accepted 18 September, 2011

PREPARATION AND EVALUATION OF HOLLOW MICROSPHERE DRUG DELIVERY SYSTEM OF ZIDOVUDINE

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Keywords:

Zidovudine,
Eudragit S100,
Hollow microspheres,
O/W emulsification solvent diffusion technique

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ABSTRACT

Zidovudine is the first approved compound for the treatment of HIV; however the main limitation to therapeutic effectiveness of Zidovudine is its dose dependent toxicity, short biological half-life and poor bioavailability. Thus, to overcome the problem the gastroretentive floating drug delivery system is developed. Floating drug delivery system is a low density system which have capacity to remain buoyant on gastric fluid in the stomach without affecting gastric emptying rate for prolonged period of time. The objective of present investigation was to developed hollow microsphere drug delivery system of Zidovudine using Eudragit S100 as polymer by novel O/W emulsification solvent diffusion technique. The hollow microspheres was evaluated for *in-vitro* buoyancy, micromeritic properties, particle size, percentage yield, entrapment efficiency, drug-polymer compatibility, scanning electron microscopy and in-vitro drug release. The prepared hollow microspheres were floated more than 12hrs on 0.1N HCl. The percentage yield and entrapment efficiency were found to be in range of 86.66% to 52.22% and 86.60% to 72.9%, respectively. The hollow microspheres were found to be regular in shape and highly porous. The release rate was determined on 0.1N HCl at 37^{o}C. The formulation demonstrated favorable in-vitro release characteristics. The data obtained for the designed system thus suggest that the dosing frequency of zidovudine thus can be reduce as well as increase the biological half-life which will subsequently improve the bioavailability.

INTRODUCTION: The main goal of drug delivery systems is to achieve desired concentration of the drug in blood or tissue, which is therapeutically effective and non toxic for a prolonged period. The pointing of the goal is towards the two main aspects regarding drug delivery, namely spatial placement and temporal delivery of a drug. Spatial placement means targeting a drug to a specific organ or a tissue while temporal delivery refers to controlling the rate of drug delivery to that specific organ or a tissue. An appropriately designed sustained or controlled release drug delivery system can be a solution towards solving these problems [1].

Control release implies the predictability and reproducibility to control the drug release, drug concentration in target tissue and optimization of the therapeutic effect of a drug by controlling its release in the body with lower and less frequent dose [2, 3].

Gastric retentive devices may be highly useful for the delivery of much different kind of drugs. Gastric retentive devices would provide the best results for drugs that act locally in the stomach or that are absorbed primarily in the stomach. Zidovudine absorption occurs mainly in stomach and undergoes extensive first pass metabolism.

Zidovudine, the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. Zidovudine is typically administered orally as a capsule. The bioavailability after oral administration is only 60% due to an extensive hepatic first-pass metabolism, which requires the administration of a high dose of the drug [4].

The mean plasma Elimination half-life is 0.5-2.9hrs [5], which requires the frequent administration of the drug. However, the main limitation to therapeutic effectiveness of Zidovudine is its dose-dependent hematological toxicity; patients receiving AZT frequently develop anemia and leucopenia [6]. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2µg/mL at 0.8 hours [7].

Zidovudine has all the requisite characteristics suitable for developing floating drug delivery system, which includes low bioavailability, dose dependent toxicity, and its short half life. Hence, Hollow microspheres were prepared to improve the Bioavailability and decrease dosing frequency.

MATERIALS AND METHODS:

Materials: Zidovudine was obtained as a gift sample from Smruthi Organics Ltd. Eudragit S100 was supplied by Degussa Pharmaceutical Ltd. All ingredients and solvents used were of analytical grade.

Preparation of Floating Microspheres (Table 1): Weighed amount of Zidovudine was mixed with Eudragit-S 100 (in ratios of 1:1, 1:2, 1:3, 1:4 & 1:5) in a solution of Dichloromethane and Ethanol (1:1) at room temperature. Glyceryl Monostearate was added as the emulsifying agent. The resulting drug-polymer solution was poured gradually into 200ml of water containing 0.75% Zidovudine and 0.75%w/v polyvinyl alcohol, maintained at constant temperature of 40^{o}C and the preparation was stirred at 300rpm for one hour. The finely developed microballoons were then filtered, washed with water and dried overnight at 40^{o}C .

Percentage Yield: The Percentage yield of microspheres of various formulations were calculated using the weight of final product after drying with respect to the initial total weight of the drug and polymer used for preparation of microspheres. The percentage yields were calculated as per the formula mentioned below [8].

$$\text{Percentage Yield} = \frac{\text{Practical Mass}}{\text{Theoretical Mass (Polymer + Drug)}} \times 100$$

***In-vitro* Buoyancy:** Floating behavior of hollow microspheres was studied using a USP dissolution test apparatus II. The microspheres (50 mg) was spread on 900 mL of 0.1M HCl containing 0.02% Tween 80 as surfactant. The medium was agitated with a paddle rotating at 100 rpm and maintained at 37°C. After 12 hours, both the floating and the settled portions of microspheres were collected separately. The microspheres were dried and weighed and the percentage of floating microspheres was calculated [9].

$$\% \text{ Buoyancy} = \frac{\text{Weight of Floating Microspheres}}{\text{Initial weight of Microspheres}} \times 100$$

Particle size: The particle size of the microspheres was measured using an optical microscope and the mean particle size was calculated by measuring 100 particles with the help of a calibrated ocular micrometer [10].

Micromeritic Properties:

Angle of Repose: It is the maximum angle possible between the surface of pile of powder and the horizontal plane. The angle of repose was determined by the fixed funnel method. The accurately weighed powders were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder. The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated using the following equation.

$\tan(\theta) = h/r$; $\therefore \theta = \tan^{-1}(h/r)$

Where, h- Height of the powder cone and r- Radius of powder cone.

Density: The Bulk Density (BD) and Tapped Density (TD) of microspheres were determined. Two grams of microspheres was introduced into a 10 ml calibrated measuring cylinder. After noting down the initial volume, the cylinder was allowed to fall under its own

weight onto a hard surface from the height of 2.5 inch at 2 seconds intervals. The tapping was continued until no further change in volume was noted. BD and TD were calculated using following equations.

$$\text{Bulk Density} = \frac{\text{Mass of Microspheres}}{\text{Volume of microspheres}}$$

$$\text{Tapped Density} = \frac{\text{Mass of Microspheres}}{\text{Volume of microspheres after Tapping}}$$

Hausner's Ratio: Hausner's ratio of the microspheres was calculated by using following formula,

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

Carr's Index: The Carr's index of microspheres was determined by following equations

$$\text{Carr's Index} = \frac{\text{Tapped Density - Bulk Density}}{\text{Tapped Density}} \times 100$$

Porosity: The porosity of the floating microspheres was determined by the following equation:

$$\% \text{ Porosity} = \frac{\text{Bulk Volume – Tapped Volume}}{\text{Bulk Volume}} \times 100$$

Drug Loading and Entrapment Efficiency: The drug loading was calculated from following equation. For the determination of drug entrapment efficiency, accurately weighed the quantity of 50 mg of microspheres. Crushed it by using mortar and pestle, add the crushed powder into 100ml volumetric flask. Then add some quantity of double distilled water to the volumetric flask and sonicate the resulting solution for 30 min. on Ultrasonicator. Further make up volume with double distilled water. Make up the suitable dilutions of resulting solution so that to obtained the solution of desired drug concentration. The drug entrapment efficiency was measured spectrophotometrically at 266 nm for Zidovudine.

$$\text{Drug Loading (\%)} = \frac{\text{Weight of Drug in Microspheres}}{\text{Weight of Obtained Microspheres}} \times 100$$

$$\text{Entrapment Efficiency (\%)} = \frac{\text{Actual amount of Drug in Microspheres}}{\text{Theoretical amount of Drug in Microspheres}} \times 100$$

***In-vitro* Drug Release:** The drug release was studied using a USP dissolution apparatus type II at 100 rpm in 0.1N HCl solution as dissolution medium (900 ml) maintained at 37±5°C. A sample (10 ml) of the solution was withdrawn up to 12 hour from the dissolution apparatus hourly and the samples were replaced with fresh dissolution medium. The samples were filtered and diluted to a suitable concentration with 0.1N HCl solution. Absorbance of these solutions was measured at 266 nm using UV spectrophotometer. Percentage drug release was calculated using an equation obtained from a standard calibration curve.

Evaluation of stability of Microballoon Capsules: The acceleration stability test was carried out according to the Technical Standard of Drug Stability Test (Ch. P appendix XIX C). When packaged in hard gelatin capsule shell, the microballoon capsules were stored at 40 ± 2^0C, RH 75% ±5% for 1 month in case of the accelerate stability examination, and sampled at days 1, 15 and 30. All the physical properties, % buoyancy ratio after 12 hour and % drug loading amount of all samples in both studies were determined according to the above method.

RESULT AND DISCUSSION:

TABLE 1; FORMULATION COMPOSITION OF MICROSPHERES

Ingredients	F1	F2	F3	F4	F5
Zidovudine (g)	0.4	0.4	0.4	0.4	0.4
Eudragit S100 (g)	0.4	0.8	1.2	1.6	2.0
Glyceryl Monostearate(g)	0.3	0.4	0.5	0.6	0.7
Dichloromethane (ml)	5	5	6	6	7
Ethanol (ml)	5	5	6	6	7

***In- vitro* Buoyancy:** The *in-vitro* buoyancy test was carried out to investigate buoyancy of prepared microspheres. The formulations (F_1 to F_5) floating ability is shown in **table 2**. Result also showed that longer the size of microsphere more the ability to float.

Percentage Yield: The percentage yield of floating microspheres was varied according to concentration of polymer. As the polymer concentration increases the percentage yield of floating microsphere decreases.

The percentage yield of different ratios is shown in **table 3**.

Particle Size: The mean particle size of the microspheres formulations (F_1 to F_5) was found to be in range of 43.48±1.06 to 59.67±2.45 (as shown in table 3). The result showed that as the polymer concentration increases the particle size also increases. The viscosity of the solution increases as the polymer concentration increases which result in enhanced interfacial tension. Shearing efficiency is also diminished at higher viscosities, hence the particle size increases.

Micromeritic Properties: The Bulk Density, Tapped Density and Hausner's ratio of formulation (F_1toF_5) was in range of 0.1000 to 0.1440, 0.1189 to 0.1690 and 1.080 to 1.189 respectively.

The Carr's index was in range of 7.4% to 15.8% and angle of repose was between 10.78° to 28.41° (as shown in table 2).

Drug Loading and Entrapment Efficiency: The Drug Loading and Drug Entrapment Efficiency of formulation (F_1toF_5) were found to be in range of 18.48 ± 0.62 to 57.71 ± 1.42 and 72.9% to 86.6% respectively (as shown in table 3).

TABLE 2: VARIOUS FLOW PROPERTIES OF FORMULATIONS

Formulation Code	Parameters				
	Angle of Repose (θ)	Bulk Density (gm/cm^3)	Tapped Density (gm/cm^3)	Hausner's Ratio (H_R)	Carr's Index (%)
F1	12.73°	0.1000	0.1189	1.189	15.8
F2	10.78°	0.1220	0.1360	1.114	10.2
F3	18.11°	0.1440	0.1690	1.173	14.1
F4	25.45°	0.1360	0.1470	1.080	7.4
F5	28.41°	0.1150	0.1280	1.113	10.1

TABLE 3: VARIOUS EVALUATION PARARMETERS OF FORMULATIONS F1 TO F5

Formulation Code	% Yield	Mean Particle Size (µm)	Drug Entrapment Efficiency (%)	Drug Loading (%)
F1	86.66 ± 2.13	43.48 ± 1.06	79.9%	57.71 ± 1.42
F2	85.10 ± 2.14	45.26 ± 1.25	84.4%	35.81 ± 0.82
F3	80.19 ± 1.71	46.93 ± 2.34	86.6%	26.66 ± 0.48
F4	68.58 ± 1.40	48.17 ± 1.58	80.0%	21.83 ± 0.33
F5	52.20 ± 3.08	59.67 ± 2.45	72.9%	18.48 ± 0.62

***In-vitro* Drug Release:** The Drug release of formulations (F_1 to F_5) is shown in figure no. The formulation F_1 showed percentage drug release 96.77% at the end of 9th hour and F_2, F_3, F_4 & F_5 showed percentage drug release 95.92%, 81.93%, 66.41% and 43.30% at the end of 12 hour respectively. Among all the formulations the F_2 formulation was found to be best formulation, as it released Zidovudine in sustained manner. As the Eudragit S100 concentration increased the release of Zidovudine decreased. The increased concentration of polymer increased the density of polymer matrix, which results in increase diffusional path length, this decrease the overall release of drug from polymer matrix (**figure 1**).

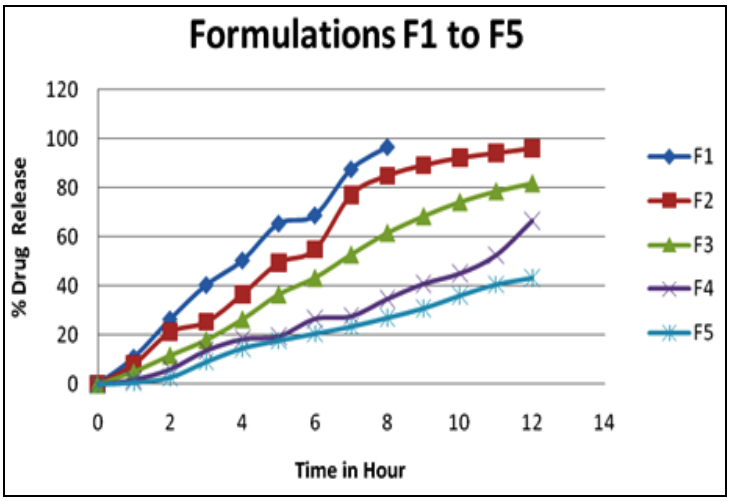


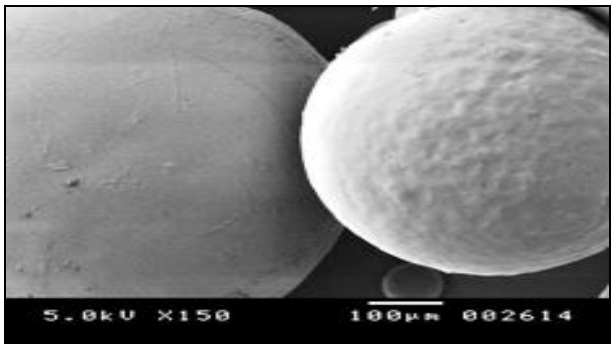
FIG. 1: COMPARATIVE DRUG RELEASE PROFILE OF FORMULATIONS F1 TO F5

Accelerated Stability Studies: Stability of preparation is an important factor to estimate the quality of the dosage forms. Thus accelerating testing was carried out to study on stability of Zidovudine loaded microballoons (as shown in **Table 4**). The results showed no marked change in physical properties (color, surface morphology and particle flow) and no significant difference in floating ratio and drug loading was observed in comparison with the Zidovudine loaded microballoons capsules before storage in stability chamber.

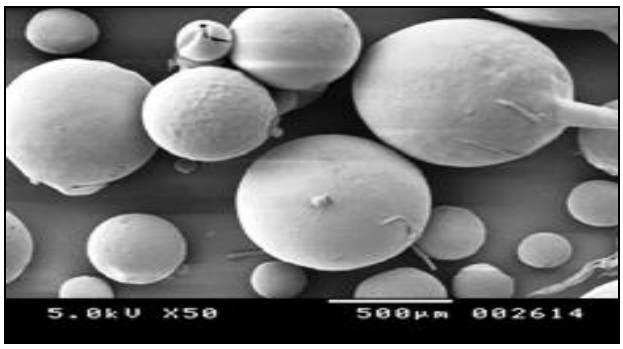
TABLE 4: ACCELERATED STABILITY STUDY FOR OPTIMIZED FORMULATION

Items	Time (Days)		
	0	15	30
% Buoyancy	92 %	91.45%	91.21%
% Drug loading	28.04%	27.92%	27.59%

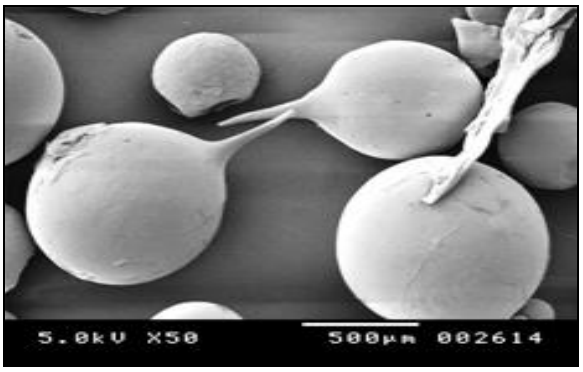
Scanning Electron Microscopy: Morphology of floating microspheres was examined by scanning electron microscopy. The view of the microspheres showed hollow structure with a smooth surface morphology (**Figure 2. A, B, C and D**) exhibited range of sizes within each batch. The outer surface of microspheres was smooth and dense, while the internal surface was porous. The shell of microspheres also showed some porous structure it may be caused by evaporation of solvent entrapped within the shell of microsphere after forming smooth and dense layer.



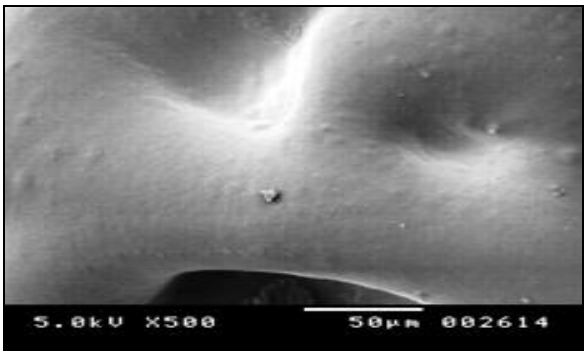
A



B



C



D

FIG. 2: SCANNING ELECTRON PHOTOMICROGRAPHS OF FORMULATIONS

Fourier Transform Infrared Spectroscopy: The FT-IR spectra study showed no change in the finger print of pure drug spectra, thus confirming absence of drug and polymer interaction (**fig. 3, 4 & 5**).

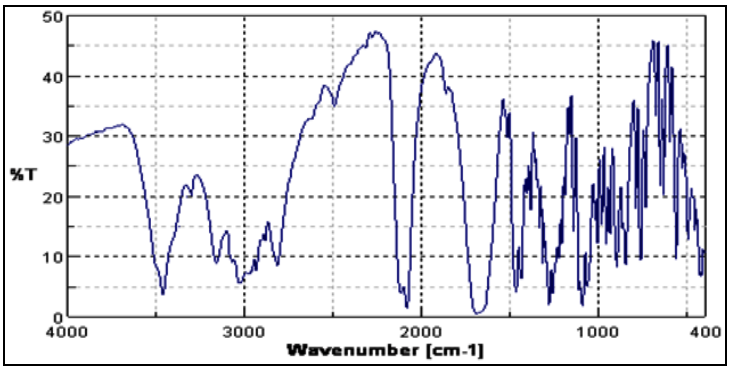


FIG. 3: FTIR SPECTRA OF ZIDOVUDINE

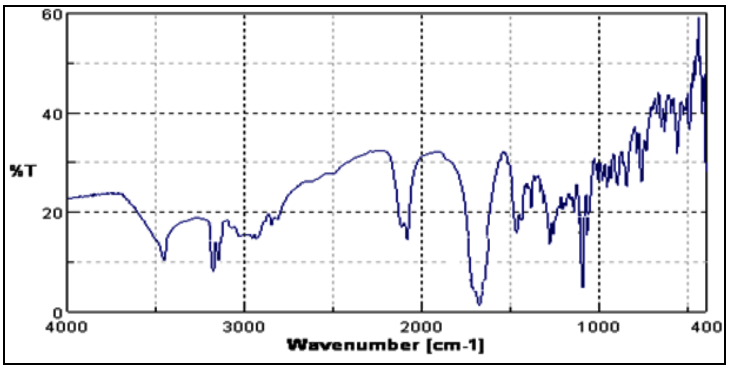


FIG. 4: FTIR SPECTRA OF EUDRAGIT S100

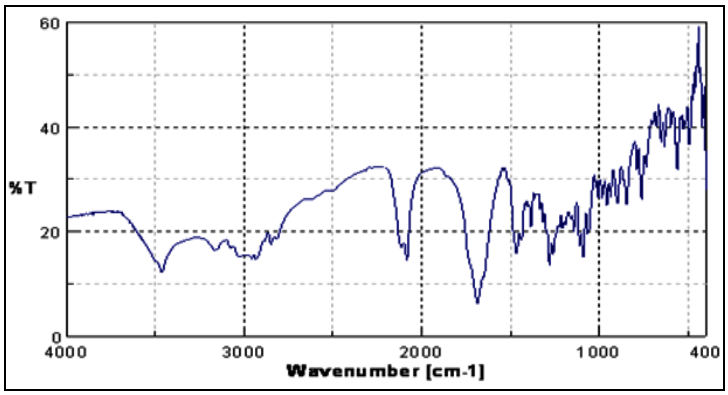


FIG. 5: FTIR SPECTRA OF OPTIMIZED FORMULATION F2

CONCLUSION: The hollow floating microspheres of Zidovudine with Acrylic polymer Eudragit S100 was successfully prepared by Emulsion solvent diffusion technique. The entrapment efficiency of microspheres was enhanced by modifying aqueous phase. F_2 formulation showed good result among all other formulations. The polymer concentration played important role in Particle size, Buoyancy time and Drug Release. Microballoons could be administered in hard gelatin capsule shell for better and prolonged therapeutic effect.

ACKNOWLEDGEMENT: I would like to thank Matrix Lab., Nashik and Evonik Degussa Ltd. Mumbai for providing gift sample of Zidovudine and polymer respectively. I am especially thankful to Department of Microbiology, P.S.G.V.P.M's Arts, Science and Commerce, Shahada for utilizing the facilities.

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