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DEVELOPMENT AND CHARACTERIZATION OF BUOYANT MICROSPHERES OF ZIDOVUDINE FOR TREATMENT OF VIRAL DISEASE

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Abstract:

Hollow buoyant microspheres of Zidovudine with Eudragit RS100 were successfully prepared by the oil in water emulsion solvent diffusion technique with better percentage yield. The problem associated with less Entrapment efficiency of drug in microspheres was overcome by modification of aqueous phase. The concentration of polymer also affected Buoyancy of microspheres in same proportionality. All the formulation exhibited excellent to good flow properties when evaluated for micromeritic properties. The drug release pattern was greatly affected by the concentration of polymer. The release was slower in the high polymerconcentration formulation as compare to low polymer concentration formulations. The drug release of various formulations of microsphere was through Zero order model and drug release mechanism was through Non-Fickian case-II transport mechanism.

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INTRODUCTION:

A viral disease is any illness or health condition caused by a virus. Viruses are probably the most common cause of infectious disease acquired within indoor environments and have considerable impact on human health, ranging from severe life–threatening illnesses to relatively mild and self limiting or asymptomatic diseases [1]. The drug delivery system should deliver drug at a rate dictated by the needs of the body over a specified period of time. Oral intake has been the most sought-after route of drug delivery by both patients and drug manufacturers for the treatment of most pathological states. Despite tremendous strides made in novel non oral drug delivery systems to date, the majority of the drugs available commercially are oral formulations. The goal of any drug delivery system is to provide a therapeutic amount of drug to a proper site in the body, so that the desired drug concentration can be achieved promptly and then maintained. The idealized objective points to the two aspects most important to drug delivery, namely, spatial placement and temporal delivery [2]. An appropriately designed sustained or controlled release drug delivery system can be a solution towards solving these problems. 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. Sustain-release formulation simply prolongs the release and hence plasma drug level maintained for an extended period of time, not necessarily at a predetermined rate. These makes oral controlled release much important, which provides a complete and controlled release of drug throughout the GI tract [3]. The term oral controlled release implies a system that provides continuous delivery of drug for a predetermined period in a predictable and reproducible manner which increases the bioavailability. It includes the system and provides control over movement of dosage form through the GI tract for either a local or a systemic action. Increased bioavailability of CDDS excluded by several physiological difficulties and highly variable nature of gastric emptying process turns to unpredictable and reduced bioavailability. Most limiting biological factor in development of once daily oral controlled release is the transit time of dosage form through the GI tract [4].

Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration [5]. Hydrodynamically balanced systems (HBS) are designed to prolong the stay of the dosage form in the gastro intestinal tract and aid in enhancing the absorption. Such systems are best suited for drugs having a better solubility in acidic environment and also for the drugs having specific site of absorption in the upper part of the small intestine. Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method. The advantages of hollow microspheres are to improve patient compliance by decreasing dosing frequency and gastric retention time is increased because of buoyancy for better therapeutic effect of short half-life drugs can be achieved [6]. The bioavailability enhances despite first pass effect because fluctuations in plasma drug concentration is avoided, a desirable plasma drug concentration is maintained by continuous drug release. The floating microspheres can be used as carriers for drugs with so called absorption windows. These substances, for example antiviral, antifungal and antibiotic agents are taken up only from very specific sites of the gastrointestinal mucosa. The oral bioavailability of various drugs is very low and many of them undergoes extensive first-pass metabolism, with only one third of the dose reaching to systemic circulation unchanged. The low bioavailability is mainly attributable due to incomplete absorption and first- pass metabolism. According to literature, gastric retained dosage form is particularly beneficial for delivery of such type of drug which have prolonged transit in the upper gastrointestinal tract, which allows the drug to be absorbed adequately, thus enhancing the bioavailability [7]. In addition, a gastric retained dosage form increases the t max and allows for a smoother, more prolonged effect. Furthermore, a gastric retained dosage form also reduces the Cmax, which may reduce the incidence of side effect. It has been reported that, the gastric retained dosage form improves bioavailability of drug relative to an equal dose of an immediate release dosage form. Hence in the present work, an attempt will be made to design gastro retentive dosage form for particular drug in the form of floating drug delivery system so that to achieve the prolonged drug therapy. The objective of proposed study is to develop Hollow microspheres of compatible drug using compatible polymer. Also used to evaluate the prepared hollow microspheres and to prepare and evaluate single unit floating drug delivery system of optimized microspheres formulation [8].

MATERIAL AND METHODS:

Preparation of Floating Microspheres: Weighed amount of Zidovudine was mixed with Eudragit-RS 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 0.85% Zidovudine and 0.75%w/v polyvinyl alcohol, maintained at constant temperature of 40oC and the preparation was stirred at 300rpm for one hour [7]. The finely developed microballoons were then filtered, washed with water and dried overnight at 40°C. These proposed formulations were prepared by varying the concentration of polymer used, while the concentration of drug was kept constant (Table 1).

Evaluation of buoyant Microspheres:

Buoyancy Test: 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.

% Buoyancy = Weight of Floating Microspheres / Initial Weight of Microspheres ×100

Micromeritic Properties: The micromeritics properties of prepared buoyant microspheres was done in terms of angle of repose, bulk density (BD) and tapped density (TD), hausner's Ratio and compressibility Index etc.

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.

Percentage Yield = Practical Mass (Microspheres) / Theoretical Mass (Polymer+Drug) ×100

Measurement of Microsphere Size: The microspheres were evaluated for the particle size. The microsphere size was determined by the optical microscopy method using a calibrated stage micrometer (µm) by measuring 100 particles. All the experimental units were analyzed in triplicate (n=3).

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 mechanically such as by the use of mortar and pestle, add minimal quantity of 0.1N HCL solution. Now sonicate the resulting solution for 30 min. on ultrasonicator. Further dilute it with 0.1N HCL solution. 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 266nm for Zidovudine.

Drug Loading (%) = Weight of Drug in Microspheres/ Weight Obtained of Microspheres Sample

Entrapment Efficiency (%) = Actual Amount of Drug in Microspheres / Theoretical Amount of Drug in Microspheres ×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 12hour 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 [8].

Drug Release Kinetics:

To study the release kinetics of optimized formulations, data obtained from in-vitro drug release studies were plotted in various kinetic models: zero order as cumulative amount of drug released Vs time, first order as log cumulative percentage of drug remaining Vs time, and Higuchi's model as cumulative percentage of drug released Vs square root of time. A graph of concentration Vs time would yield a straight line with a slope equal to K0 and intercept the origin of the axes.

RESULT AND DISCUSSION:

Initially, the microspheres were evaluated for Buoyancy test. The in-vitro floating efficiency results of formulations ZFM1 to ZFM5 are shown in **Table**

2. The microspheres were respectively dispersed on the surface of 0.1N HCL solution containing 0.02% Tween 80 as surfactant. The use of Tween 80 was to account the wetting effect of the natural surface active agent in gastrointestinal tract. The resulting microspheres tended to float over the 0.1N HCL solution for than 12 hour. The maximum percentage Buoyancy was observed with formulation ZFM2 which is 92%, while the minimum percentage Buoyancy was observed with formulation F5 i.e. 48%. Even after the study of 12 hours, microspheres had shown excellent floating properties. This was because the channels of hollow microspheres on the surface were too small to be penetrated inside the hollow cavities by the 0.1N HCL solution. On the contrary, most of the microspheres with less number of channels sank within the early h. of the study and never rose to the surface again. The % Buoyancy of formulations ZFM1 to ZFM5 goes on decreasing with increase in the concentration of polymer. As the concentration of polymer increases, the bulk density of formulation also goes on increase, Hence the capacity of microspheres to float on dissolution medium containing 0.1N HCL solution gets decreased. All the formulations showed an angle of repose within the range of 10.78º - 28.41º, which were found to be in excellent to good range. Bulk density and Tapped density were found to be in the range of 0.1000- 0.1440 g/cm^3 and 0.1189- 0.1690 g/cm^3 respectively. Hausner's ratio were found to be in the range of 1.080- 1.189, whereas Carr's index was inthe range of 7.4- 15.8 %. All these parameters are in excellent to good range as shown in **Table 3**.

All the parameter showed good flow property of microspheres. The percentage yield of hollow microsphere varies from 86.66% to 52.20 % as shown in **Table 4**. The effect of polymer concentration on the percentage yield of the resulting microspheres formulation was observed. The Percentage yield decreased as the concentration of Eudragit RS100 increased in formulation. Maximum yield was found to be 86.66% in ZFM1 formulation, while formulation ZFM5 resulted in minimum percentage yield up to 52.20 %. The polymer fiber formation took place due to increased concentration of polymer in the formulation, which led to decreased in Percentage Yield. The formulation ZFM5 showed high yield of polymer fibers. The proposed microspheres prepared using emulsification solvent diffusion technique found to be spherical, discrete and of well-defined shape when observed through optical microscopy. It was clear from the results as shown in Figure 1, the increase in concentration of polymer led to increase in particle size of Hollow microspheres. The Mean particle size was also affected by stirring speed of the external aqueous phase. The rotating speed of the stirrer usually controls the size of microspheres; however, it does not change the shape of microspheres significantly. At low stirring speed, polymer solution was aggregated around the propeller shaft, and the resultant yield of microspheres was relatively low. Again the increase in stirring speed decreased the particle size due to droplet break-up by impaction on the baffles. The optimum stirring speed was in range of 200-300 rpm and the size of microspheres was relatively uniform in this stirring range. The percentage of Drug loading and Entrapment efficiency of the drug depended on solubility of drug in the solvent and continuous phase and physicochemical properties of drug and polymer. Sparingly water soluble drug Zidovudine is used as a model drug. The percentage of Drug loading and Entrapment efficiency of the drug was very low, due to solubility of drug in aqueous phase. To overcome this problem the aqueous phase was partially saturated with Zidovudine (0.75%). The percentage of Drug loading varies from 57.71% to 18.48% with the maximum drug loading was observed with formulation ZFM1, while minimum is with ZFM5 **(Table 4)**.

During all the formulations the drug loading decreases with increase in drug: Eudragit RS100 ratio. The drug entrapment efficiency of all the formulations was found to be in the range of 86.6% to 72.9%. This variation may result due to variation in the concentration of Eudragit RS100 used in the formulation. The maximum drug entrapment is observed with formulation ZFM3, while ZFM5 shows lowest drug entrapment efficiency. This observation shows that partial saturation of the aqueous phase with Zidovudine significantly increased the Percentage Drug loading as well as Percentage Entrapment efficiency. The in-vitro dissolution studies of Zidovudine Loaded Hollow microspheres were performed in 0.1 N HCL for 12 hours using USP dissolution test apparatus II. The results of drug release of all five batches starting from ZFM1 to ZFM5 for 12 h are shown in **Table 5**.

The amount of drug released over the period of 12 h was found to vary with each formulation. The plot of % drug release v/s Time (h.) was plotted for each formulation as shown in **Figure 1**.

The formulations ZFM1 with lower level of polymer concentration exhibited fast release which can be due to the insufficient amount of polymer to control the drug release rate. All other formulations showed slower and controlled release rate. As dissolution

progresses, the gradual erosion of the outer layers of microspheres creates proportionately new areas for drug diffusion which shows subsequent drug release. Hence the steady and continuous drug release was observed. In general, there are two factors affecting the drug release rate. First, the effect of the concentration of Eudragit RS100 on the vitro drug release. It is clear that release rate of Zidovudine decreased with increasing of polymer concentration. The higher the concentration of Eudragit RS100 was, the denser the polymer shell was formed, the slower the drug was released. Second, the effect of the different particle size of hollow microspheres on the vitro drug release. The smaller hollow microspheres have more rapid release, probably due to the shorter diffusion path and higher surface area for a given amount of drug. On the other hand, drug release rate from hollow microspheres at the later stage was slower because of the depletion of drug reservoir. The presence of hollow pockets inside the microspheres allowed easy penetration of dissolution medium within the matrix and resulted in higher drug release. The drug release of the batch ZFM2 was found to be more satisfactory than other formulations. Also the drug entrapment efficiency of ZFM2 was 84.4% which is comparatively more than ZFM1, ZFM4 and ZFM5 except ZFM3. Also floating capacity of ZFM2 is more than ZFM1, ZFM3, ZFM4, and ZFM5. Thus here among all ZFM1 to ZFM5, ZFM2 was selected as the best formulation on the basis of drug entrapment efficiency, floating capacity and dissolution data.

SUMMARY AND CONCLUSION:

In the present investigation, an attempt was made to deliver Zidovudine via floating drug delivery system to the vicinity of its absorption site by prolonging the gastric residence time of the dosage form, with an aim of improving the bioavailability as well as avoiding the loss of drug by First pass metabolism. Hollow Floating microspheres were prepared by using Eudragit RS100 as a polymer. The oil in water emulsification solvent diffusion method was used for the preparation of Hollow microspheres of Zidovudine. The result showed high Entrapment efficiency of the drug in prepared microspheres which are modified by saturating aqueous phase by Zidovudine. The prepared microspheres were evaluated for various evaluation parameters. The size of microspheres was dependent on concentration of polymer, as the polymer concentration increased the particle size was also increased. Among all the formulations, the ZFM2 formulation with (1:2) ratio of drug: polymer, satisfactorily gave excellent results in terms of excellent all properties with highest *in-vitro* drug release in sustained manner with constant fashion over extended period of time for 12 h.

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Table 1: Formulation Composition of Microspheres

S. No.	Ingredients	ZFM1	ZFM2	ZFM3	ZFM4	ZFM5
1	Zidovudine (g)	0.5	0.5	0.5	0.5	0.5
2	Eudragit RS100 (g)	0.5	1	1.5	2	2.5
3	Glyceryl Monostearate (g)	0.3	0.4	0.5	0.6	0.7
4	Dichloromethane (ml)	5	5	6	6	7
5	Ethanol (ml)	5	5	6	6	7

Table 2: Percent Buoyancy of Formulations

Formulation code	Weight of Microspheres (mg)		Percent Buoyancy
	Initial	Final (After 12h)	
ZFM1	50	42	84%
ZFM2	50	46	92%
ZFM3	50	45	90%
ZFM4	50	37	74%
ZFM5	50	24	48%

Table 3: Various Flow Properties of Formulations

Formulation Code	Angle of Repose (θ)	Bulk Density (g/cm3)	Tapped Density (g/cm3)	Hausner's Ratio (HR)	Carr's Index (%)
ZFM1	12.73º	0.1	0.119	1.189	15.8
ZFM2	10.78º	0.122	0.136	1.114	10.2
ZFM3	18.11º	0.144	0.169	1.173	14.1
ZFM4	25.45º	0.136	0.147	1.08	7.4
ZFM5	28.41º	0.115	0.128	1.113	10.1

Table 4: Various Evaluation Parameters of Formulations ZFM1 to ZFM5

Formulation Code	Percent Yield	Mean Particle Size (µm)	Drug Entrapment Efficiency (%)	Drug Loading (%)
ZFM1	86.66 ± 2.13	43.48 ± 1.06	79.90%	57.71 ± 1.42
ZFM2	85.10 ± 2.14	45.26 ± 1.25	84.40%	35.81 ± 0.82
ZFM3	80.19 ± 1.71	46.93 ± 2.34	86.60%	26.66 ± 0.48
ZFM4	68.58 ± 1.40	48.17 ± 1.58	80.00%	21.83 ± 0.33
ZFM5	52.20 ± 3.08	59.67 ± 2.45	72.90%	18.48 ± 0.62

Table 5: in-vitro drug release study of various formulations ZFM1 to ZFM5

Time (h)	Cumulative percentage of drug release				
	ZFM1	ZFM2	ZFM3	ZFM4	ZFM5
0	0.00	0.00	0.00	0.00	0.00
1	10.90	8.10	5.17	1.80	0.68
2	26.40	21.10	11.77	6.12	2.74
3	40.30	25.32	18.07	13.67	9.13
4	50.35	36.63	26.50	18.31	14.66
5	65.30	49.38	36.70	19.45	17.81
6	68.63	54.78	43.46	26.58	20.63
7	87.33	77.06	52.91	27.62	23.47
8	96.38	84.82	61.71	34.65	27.09
9	96.77	89.09	68.55	40.81	30.93
10		92.10	74.33	44.99	36.12
11		94.00	78.67	52.39	40.62
12		95.92	81.93	66.41	43.30

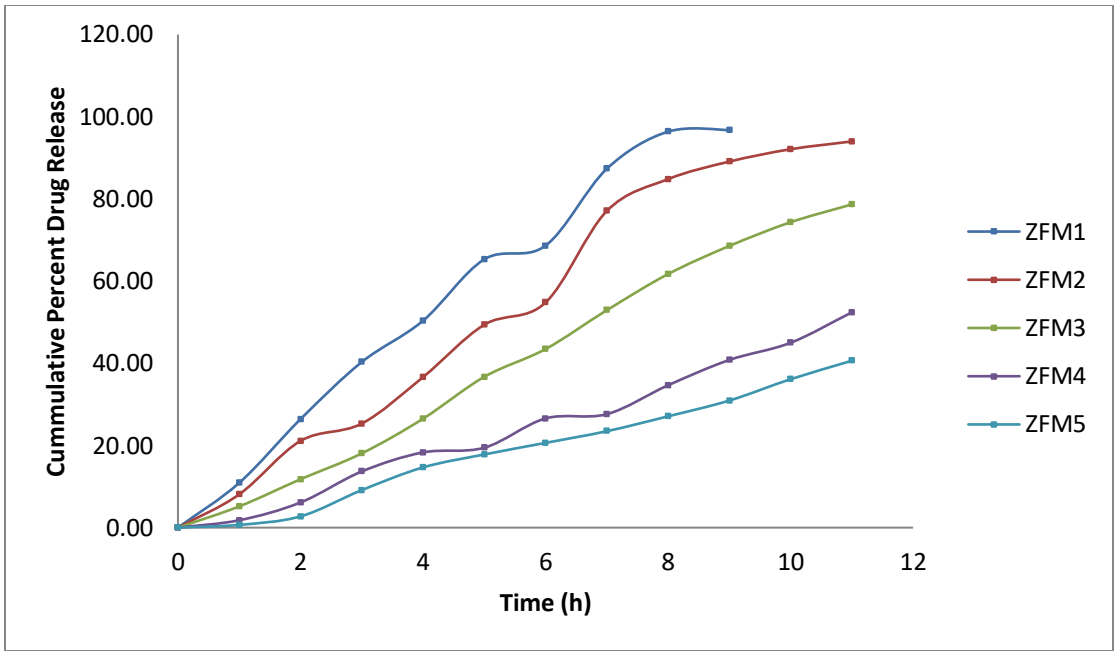

Figure 1: Zero – order kinetic plot of in-vitro drug release study of various formulations ZFM1 to ZFM5