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Research Article

HPMC MICROSPHERES OF ZIDOVUDINE FOR SUSTAINED RELEASE

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ABSTRACT

Zidovudine is a pyrimidine nucleoside analogue, active against Human Immunodeficiency Virus (HIV). The main objective of this research work was to prepare HPMC microspheres loaded with Zidovudine and *in-vitro* drug release study. In the present study, emulsification-heat stabilizing method is used for preparing microspheres. The polymer (HPMC) and drug (Zidovudine) was dissolved in deionsed water. Surfactant was added to this solution and stirred it for 30 min. The oil and 1% span-80 (as emulsifier) were mixed together and allowed to stir for 20 min at 800-1000 rpm. The aqueous phase was added to oil phase to form primary emulsion. This emulsion were added to preheated sunflower oil and stirred for 3 hrs at 1000-1200 rpm. microspheres were filtered and dried in dessicator over night. microspheres were spherical shape and smooth surface. Infra-red spectra showed identical peaks of drug and polymer drug entrapment efficiency was 69% determined by UV-Spectrophotometer at 267nm. *In-vitro* drug release studies were preformed using shaking flask method. The formulation ZM1 Showed 87.5% drug was released in 10 hrs. It is concluded that HPMC microspheres of Zidovudine can be prepared by emulsification heat stabilizing method and *in-vitro* release data is satisfactory.

Keywords: Zidovudine, Microspheres, HPMC, Drug release study

INTRODUCTION

Controlled release technology as rapidly emerged over the past three decades, as a new inter disciplinary science that offers novel approaches to the bioactive agents. Controlled drug delivery design involves the application of physical and polymer chemistry to dosage form design, to produces a well characterized and reproducible drug delivery profile. Environment bioactive agents to the target environment for an extended time controlled release delivery systems can achieve optimum therapeutic responses, prolong efficacy and decreased toxicity[1].

The Goal of any drug delivery system is to provide a therapeutic amount of drug to the proper sight in the body to achieve promptly and then maintain the desired drug concentration. The drug delivery system should deliver drug at a rate detected by the needs of the body over the entire period of treatment.

Zidovudine is a pyrimidine nucleoside analogue, active against Human Immunodeficiency Virus (HIV).The mean plasma Elimination half-life is 0.5-2.9hrs[2]. Microparticles are polymeric particles ranging in size from 1-1000 µm. The mechanism of drug release is either dissolution or diffusion of drug and the formulation are either as encapsulated or matrix. The number of methods is described for encapsulating medicaments with different coat materials[3]. The properties especially drug release characteristic of the microspheres depend on the coat material employed in preparation.

MATERIALS AND METHODS

Zidovudine was a gift sample obtained from Karnataka antibiotics, Bangalore, HPMC, Di-sodium hydrogen phosphate, potassium dihydrogen phosphate, acetone, diethyl ether, tween-80 and span-80 were obtained as a gift sample from A.R. Loba Chemical Pvt.Ltd, Mumbai. All other chemicals used were of L.R. grade.

Preparation of micro-spheres of zidovudine by emulsification-heat stabilizing method[4]

300 mg of zidovudine and polymer (HPMC) were dissolved in 20 ml of deionised water and added 5 ml of egg albumin solution, 0.1% of Tween-80, stirring it for 30 min. The prepared solution was used as aqueous phase. The oil phase was prepared by mixing 20 ml of sunflower oil and 5ml of diethyl ether with 1% span-80 (as emulsifier) and stirred it for 20 mins at 800-1000 rpm on a magnetic stirrer. The primary emulsion was prepared by adding the oil phase drop wise to the aqueous phase stirred it for 30 mins at 800-1000 rpm.

The prepared primary emulsion was added to pre-heated (65 to 70^{o}C) sunflower oil (80 ml) by using 21 No. needle and stirred it 1000-1200 rpm for 2 hrs till the solidification of microspheres formed. The suspension was then allowed to cool to room temperature with continuous stirring using a magnetic stirrer. On cooling, 100 ml of anhydrous ether was added. The suspension containing the micro-spheres was centrifuged for 15 min and the settled microspheres were washed three times with ether to remove traces of oil on microspheres surfaces[5]. The obtained microspheres were then vacuum dried in a desiccator overnight and stored at 4^{o} c in dark. Three batches of micro-spheres were prepared by the above-mentioned method and labeled as ZM-1, ZM-2, and ZM-3.

Determination of % yield of microspheres[6]

The dried microspheres were collected and weighed accurately. The percentage yield was then calculated using formula given below.

$$\% \text{ Yield} = \frac{\text{Mass of micro-spheres obtained}}{\text{Total weight of drug and polymer}} \times 100$$

Determination of drug content[7]

Zidovudine content in the micro-spheres was estimated by an UV spectrophotometer method based on the measurement of absorbance at 267 nm in phosphate buffer of p^{H} 7.4. The method was validated for linearity, accuracy and precision. The method obeyed Beer's law in the concentration range of 5-50 µg/ml.

$$\% \text{ Loading} = \frac{\text{Weight of drug in microspheres}}{\text{Weight of microspheres}} \times 100$$

Particle size determination[8]

For size distribution analysis, different sizes in a batch were separated by sieving using a range of standard sieves. The amounts retained on different sieves were weighed. Optical microscope was used to determine the size of the particle that lies within a range from 0.2 to 100 µm equal divisions and hence, each division is equal to 10 µm and the particles are measured along an arbitrarily chosen fixed line across the center of the particle. The particle size is the important factor to formulation of microspheres.

Scanning electron microscope (SEM) study

The microspheres were determined to particle size under a scanning electron microscope. The instrument used for this study was Hitachi S-450 scanning electron microscope. The micro-spheres were mounted directly on to the SEM sample stub, using double-sided sticking tape, and coated with gold film (thickness 200 nm) under reduced pressure (0.001 torr).

***In-vitro* release studies -Shaking flask method[9,10]**

Drug loaded microspheres equivalent to 100 mg of drug were weighed and transferred into a 100 ml conical flask. To this 100ml of pH 7.4 phosphate buffer saline was added, then the flasks were kept in a metabolic shaker and the shaker was adjusted to 50 horizontal shakes per minutes at 37 ± 0.5°C. One ml of the drug releasing media was withdrawn at various time interval of 30 min, 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 hours and replaced by the same volume of phosphate buffer saline. These samples were filtered through 0.45 µm membrane filter. The filtrate was diluted suitably. The drug was estimate in each batch by UV-Visible Spectrophotometer at 267 nm.

Size and shape of microspheres[11,12]

The microspheres were found to be discrete, spherical and free flowing. The nature of the microspheres indicates that the microspheres were multi-nucleated, mono-lithic type. The mean particle size of the obtained microspheres containing zidovudine was determined by the optical microscopy under 10X magnification. The arithmetic mean sizes of microspheres of formulations were shown in table 4. The particle size range increased as the combination ratio of HPMC was increased.

RESULTS AND DISCUSSION

In the present study an attempt was made to formulate zidovudine as microparticulate drug delivery system in order to localize drug at the absorption site, enhance its bioavailability, reduce dose, there by improving patient compliance. Microparticulate system of zidovudine was formulated using HPMC as carrier by emulsification heat stabilizing method.

Prior to formulation, Preformulation studies were carried out in order to establish compatibility between drug and polymer by IR spectroscopy. Three formulations (ZM1, ZM2, and ZM3) were prepared by varying the ratio of drug and polymer. Preformulation studies revealed that the drug zidovudine and HPMC were satisfactorily compatible, without any significant changes in the chemical nature of the drug. These formulations were subjected to various evaluation parameters like % practical yield, drug entrapment efficiency, particle size distribution, *in-vitro* release studies and stability studies. The results of all parameters are tabulated (*Table 1 and Table 2)* and depicted graphically (*Fig. 1*).

Percentage practical yield was found to be maximum in formulation ZM1. Particle size of the drug loaded microspheres revealed that the particles were in micron range. Drug entrapment efficiency was found to be maximum in ZM1. It was observed that drug entrapment efficiency increased with increase in concentration of drug added in consecutive formulations. *In-vitro* release study was analyzed using various mathematical models % drug releases with respect to time were found to be highest for formulation ZM1 and lowest for formulation ZM3.

Table 1: Particle yield, % practical yield, encapsulation efficiency % and actual drug content of zidovudine microspheres

Formulation code	Drug: Polymer	Particle size (µm)	% Practical yield	Encapsulation efficiency %
ZM1	1:1	290.9 ± 9.1	86.5	86.0
ZM2	1:2	340.6 ± 9.5	80.9	62.2
ZM3	1:3	438.1 ± 10.3	80.8	57.33

Table 2: In- vitro cumulative drug release data of zidovudine loaded microspheres

S. No	Time (Hrs)	Cumulative % drug release		
		ZM1	ZM2	ZM3
1	0.5	8.27	6.83	4.35
2	1	16.32	10.40	9.15
3	2	25.13	17.75	16.11
4	3	33.10	24.92	22.60
5	4	39.15	30.67	29.85
6	5	45.36	38.80	35.25
7	6	54.80	46.55	44.82
8	7	65.40	55.68	49.65
9	8	71.31	64.71	57.82
10	9	79.25	75.33	68.20
11	10	87.50	83.25	78.15

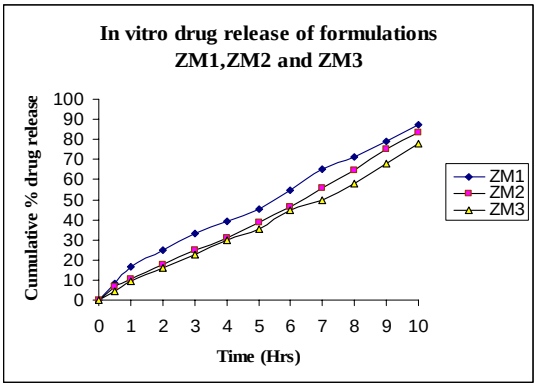

Fig. 1: *In- vitro* cumulative drug release data of zidovudine loaded microspheres

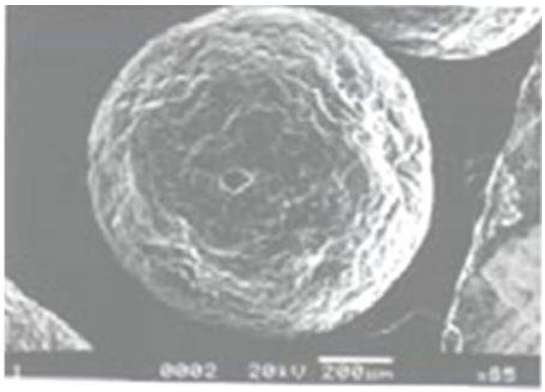

Fig. 2: Scanning electron micrograph of microsphere of ZM1

The scanning electron microscopy of the microspheres was shown in Fig. 2 The most of the microspheres were spherical in shape and size ranges from 265-425 µm. But some spheres were in large size.

The size analysis of different batches of microspheres showed that about 70% were in the size range of 350 µm. The size distribution of the microspheres was found to be normal in all the batches. The mean size of the microspheres was increased as the proportion of polymer in the microspheres was increased. The mean size of the microspheres were found to be 290.9 ± 9.1, 340.6 ± 9.5, 438.1 ± 10.3, respectively in the batches of microspheres prepared employing core: coat ratio of 1:1, 1:2, 1:3.

CONCLUSION

In the present study a satisfactory attempt was made to develop microparticulate drug delivery system of zidovudine with improved bioavailability, efficient targeting and dose reduction. From the experiment results it can be concluded that:

- HPMC polymer is a suitable macromolecule for the preparation of microspheres of Zidovudine.
- Increase in the amount of drug added to the formulations increasing of the experiment efficiency.
- Formulation of zidovuline microspheres ZM1 showed maximum drug content.
- Particle size analysis revealed that the microspheres were in the range (2 to 12µm) and all the formulations showed ideal surface methodology.
- Formulation ZM1 showed maximum percent drug release.
- Present study shows that the targeting efficiency of drug loaded microspheres over free drug was, higher, which may provide increased therapeutic efficacy.

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