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FORMULATION DEVELOPMENT AND EVALUATION OF STAVUDINE MUCOADHESIVE MICROSPHERES

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ABSTRACT

The goal of the current work is to create and assess Stavudine mucoadhesive microspheres using carbapol, sodium alginate, and calcium chloride as cross-linking agents, as well as fenugreek mucilage and mucilage as polymers. Orifice ionic gelation was used to create microspheres of stavudine with controlled release. The flow features of the produced microspheres, such as angle of repose, compressibility index, particle size, encapsulation effectiveness, and drug release profiles, were used to identify them. The prepared microspheres were all spherical and had excellent flow characteristics. FDA-approved medication stavudine (D4T, thymidine) is used in clinical settings to treat HIV infection, AIDS, and diseases associated to AIDS, either alone or in combination with other antiviral medications. Stavudine rapidly absorbs and has a very brief half-life (0.8 to 1.5 hours). It was heavily encapsulated in carbapol and fenugreek mucilage. There were no incompatibilities between the medicine and the polymers utilised in the current investigation, according to FTIR analyses that were done on pure drugs, polymers, and optimised formulations. A SEM study of the microspheres revealed that they were homogeneous, spherical, and had good surface properties. among the varieties of Stavudine controlled release microcapsules. The extended drug release of up to 12 hours was discovered in the improved formulation (AF6) made with carbapol in a 1:3 ratio.

Keywords: Stavudine, fenugreek mucilage, carbapol, orifice ionic gelation method.

INTRODUCTION

Microparticles and microcapsules with a drug-filled core that are composed totally of or partially of a mucoadhesive polymer fall under the category of mucoadhesive microspheres and range in size from 1 to 1000 nm, respectively[1]. In general, microspheres have the potential to be used for targeted and controlled release drug delivery, but coupling mucoadhesive properties to microspheres has additional benefits, such as efficient absorption and enhanced bioavailability of the drugs due to high surface to volume ratio, a much more intimate contact with the mucus layer, and specific targeting of the drug to the absorption site achieved by anchoring plant lectins, bacterial adhesives, and antibodies on the t microsphere surface [2-4].

Any mucosal tissue, such as that in the eye, nasal cavity, urinary tract, and gastrointestinal tract, can be made to attach to mucoadhesive microspheres, opening the door to the possibility of localised as well as systemic controlled release of medication. The M cells of peyer patches in the gastrointestinal (GI) mucosa selectively take up microspheres made with mucoadhesive and biodegradable polymers. Antigens for immunisation, protein and peptide medicines, and plasmid DNA for gene therapy have all been delivered using this absorption method [5-7].

MATERIALS AND METHODS

MATERIALS

Stavudine is a complimentary sample from the Hyderabad-based Aurobindo Pharma Limited (India). The commercial suppliers of carbapol were Yarrow Chemical Products in Mumbai. Commercial supplies of sodium alginate and calcium chloride were purchased from Mumbai's Colorcon Chemicals Asia Pvt, Ltd.

Preparation of mucoadhesive microspheres by Orifice ionic gelation method

Separately, 10 ml of filtered water were used to dissolve sodium alginate and mucoadhesive polymer. To create a homogenous polymer solution, the two solutions were then combined. With the aid of a pestle and mortar, the medication was added to the polymer solution and vigorously mixed to create a viscous dispersion. Through a syringe with a needle (size no. 21) and continuous stirring at 500 rpm, the resultant dispersion was introduced dropwise into a 10% w/v calcium chloride solution (100 ml). For 15 minutes, the additional droplets were kept in the calcium chloride solution to form spherical hard microspheres. The microspheres were obtained using decantation, and the resulting product was repeatedly washed with water before being dried at 450°C for 12 hours and kept in desiccators. Similar sodium alginate-fenugreek, sodium alginate-black gramme, and sodium alginate-okra microspheres were created by combining the necessary amount of sodium alginate with mucoadhesive polymer in water. The medicine is then mixed thoroughly with the polymeric solution using a pestle and mortar to create a viscous dispersion. [8-10]. Then follow the procedure as mentioned above. The composition of Stavudine controlled release microspheres were given in table 1.

Evaluation of Stavudine Controlled Release microspheres

The produced microspheres' flow characteristics, such as their angle of repose and compressibility index, as well as their drug content, degree of encapsulation, and particle size, were assessed. The results were given in table 2.

Angle of Repose

To determine whether the material flow was good or bad, the powder flow parameters were examined. The powder was poured through a funnel after being placed inside of one. This was covered with a graph sheet, creating a heap-like structure whose radius and height were measured. The formula based on these was used to calculate the angle of repose; $\theta = \tan^{-1}(h/r)$

Compressibility Index

A simple test was used to assess a powder's ability to flow by contrasting the density of a powder when it is poured and when it is tapped, as well as the rate at which it is packed down.

$$\text{Carr's Index} = \frac{\text{Tapped density} - \text{Poured density}}{\text{Tapped density}} \text{ x } 100$$

Drug Content

Mucoadhesive microspheres weighing 50 mg were measured and ground. In a 100 ml volumetric flask, this was dissolved or extracted with methanol before being made to volume. After one hour of intermittent shaking, the solution was filtered. In a 100 ml volumetric flask, 1 ml of this solution was diluted up to 100 ml with pH 7.2 buffer solution. By measuring absorbance in a UV spectrophotometer at 266 nm with pH 7.2 phosphate buffer as the blank, the drug content was examined. The research was done in triplicate.[11-12].

Encapsulation Efficiency

Mucoadhesive microspheres were precisely weighed at 100 mg. They were pulverized, and 100 ml of methanol was used to extract them. It was also serially diluted with phosphate buffer solution at pH 7.2. By measuring absorbance in a UV spectrophotometer at 266 nm and using phosphate buffer pH 7.2 as a blank, the resulting solution was examined for the presence of the medication stavudine. The research was done in three copies. Using the formula, encapsulation efficiency (%) was determined.

$$\text{Encapsulation efficiency} = \frac{\text{Actual drug content}}{\text{Theoretical drug content}} \times 100$$

Particle Size Determination

The release characteristics of microspheres are greatly influenced by their size dispersion. The microscopic method was used to determine the average particle size of microspheres. For these experiments, the particle size of 100 microspheres was measured using a calibrated optical microscope.

Invitro Dissolution Studies

Using a USP type I equipment and 900 ml of pH 7.2 phosphate buffer solution as a dissolution medium, the release of stavudine from microspheres was studied. In the basket,

a sample of microspheres containing 50 mg of stavudine was taken. Throughout the experiment, a speed of 50 rpm and a temperature of 37.50C were held constant. Fresh dissolution medium was added in place of removed aliquots (5 ml) at predetermined intervals. Then, using a Hitachi U-2000 spectrophotometer at 266 nm and a blank, the absorbance was measured to quantify the concentration of medication released at various time intervals. The research was done in three copies. Using the dissolution programme PCP DISSO V3.0, the in vitro dissolution data of oral mucoadhesive microspheres were tabulated and computed.

Characterization Studies

The optimized formulations were chosen based on the findings of the dissolving trials, and Fourier Transform Infrared (FTIR) was used to look at the interactions between the medicine and the polymer. To learn more about the surface properties, scanning electron microscopy (SEM) investigation was done on the pure drug stavudine, as well as on polymers like carbapol and fenugreek mucilage.

RESULTS AND DISCUSSION

Preparation of Stavudine Controlled Release microspheres by orifice Ionic Gelation Method

Ionic gelation was used in the experiment to develop Stavudine controlled release microspheres. For the creation of microspheres, controlled release coated polymeric materials including fenugreek mucilage and carbapol were used. Agents for encapsulating and cross-linking were calcium chloride and sodium alginate. The compositions of various Stavudine controlled release microspheres were given in table 1

Evaluation of Physical Parameters of Stavudine Controlled Release microspheres

The prepared microspheres were evaluated for angle of repose, compressibility index, % drug content, encapsulation efficiency and particle size. Angles of repose values for various microspheres ranged from 21.36^0 to 34.36^0, indicating that microspheres have good flow characteristics. The compressibility indexes for all microspheres were ranged from 11.33 to 14.56 %, indicating good flow of microcapsule characteristics. The average particle size was assessed using a simple microscopic method, and all of the formulations were between 158 and 171 um. The drug content of microspheres manufactured using the ionic gelation process ranged from 36 to 39 mg, depending on the polymeric concentration. The encapsulation efficiency of Stavudine controlled release microspheres were found to be in the range of 51 % to 62%.The physical parameters evaluated for various microspheres were given in table 2 and Fig 1.

All microcapsule formulations were found to be linear with first order release rate, with R2 values ranging from 0.933 to 0.988. As a result, the drug release rates from all of the microcapsule formulations were dependent on concentration and linear with a first order release rate constant (K1). All microcapsule formulations of the higuchi constant were found to be linear, with R2 values ranging from 0.936 to 0.977. Diffusion was used to calculate the drug release rates for each microcapsule composition. The release exponent (n values) calculated from Peppa's plot ranged from 0.741 to 0.875 for all of the microcapsule formulations, demonstrating that drug release was through erosion. The dissolution parameters were given in Table 3.

Characterization of microspheres

The optimum formulations were chosen and subsequent characterization tests were carried out on the basis of the dissolving studies carried out on all of the formulations.

Fourier-Transform Infra Red (FT-IR) Spectroscopic Analysis

All of the primary peaks found in the pure medication Stavudine were present in the spectra of the optimized microspheres AF6. As a result, no characteristic peak appeared or vanished, proving that there is no chemical interaction between the medication and the employed polymer. The FTIR spectra of drug and optimized formulation AF6 were shown in figures 2 to 5.

Scanning Electron Microscopy

Some of the microspheres created using the orifice ionic gelation process underwent SEM analysis. The created microspheres were found to be uniformly round and spherical. The SEM images were shown in figures 4 to 5.

Table 1: Composition of Stavudine Controlled Release microspheres

Batches	Stavudine	Fenugreek mucilage	Carbopol	Sodium alginate	Calcium Chloride (%)
AF1	40	40	--------	100	10
AF2	40	80	--------	100	10
AF3	40	160	--------	100	10
AF4	40	--------	40	100	10
AF5	40	--------	80	100	10
AF6	40	--------	160	100	10

Table 2: Evaluation of Stavudine Controlled Release microspheres

S. No	Formulation	Angle of Repose (θ)	Compressibility Index (%)	Drug Content (mg)	Encapsulation Efficiency (%)	Particle Size (µm)
1	AF1	21.36	11.33	38	55	158
2	AF2	24.56	12.55	37	62	167
3	AF3	24.10	14.56	36	57	166
4	AF4	24.96	13.74	38	54	169
5	AF5	23.87	12.98	39	52	170
6	AF6	24.36	11.77	39	51	171

Table 3: *Invitro* Dissolution Parameters of Stavudine Controlled Release microspheres

Formulation	First Order		Higuchi		Peppas	
	K_1 (h^{-1})	R^2	K_H ($mg/h^{1/2}$)	R^2	n	R^2
AF1	0.124	0.931	31.22	0.966	0.875	0.950
AF2	0.241	0.941	33.52	0.951	0.741	0.936
AF3	0.369	0.959	35.10	0.974	0.863	0.978
AF4	0.114	0.966	34.11	0.958	0.796	0.969
AF5	0.201	0.955	35.78	0.936	0.856	0.988
AF6	0.333	0.988	36.99	0.977	0.789	0.999

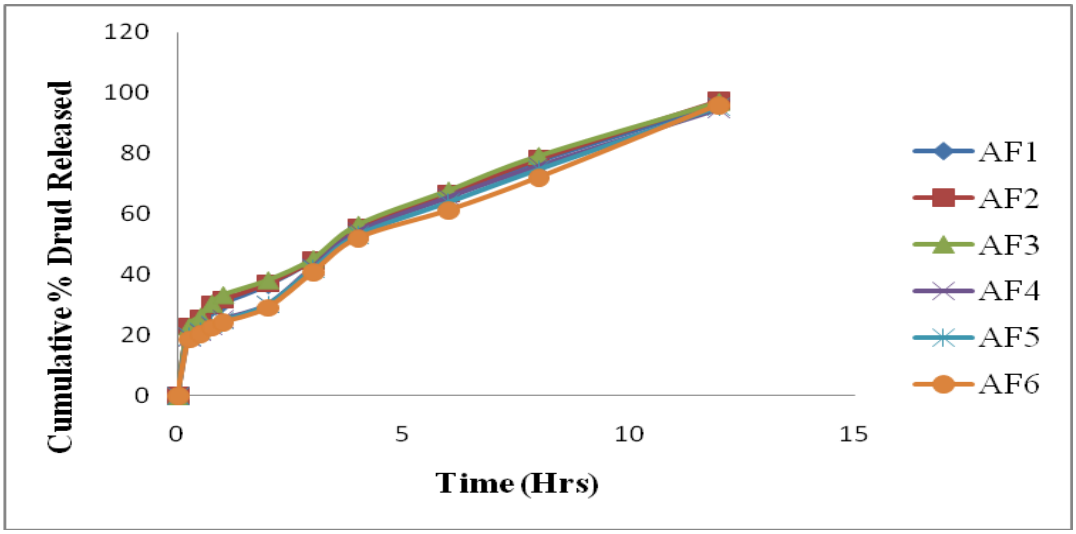

Fig. 1: *Invitro* Drug Release Profiles of Stavudine Controlled Release Microspheres (AF1 to AF6)

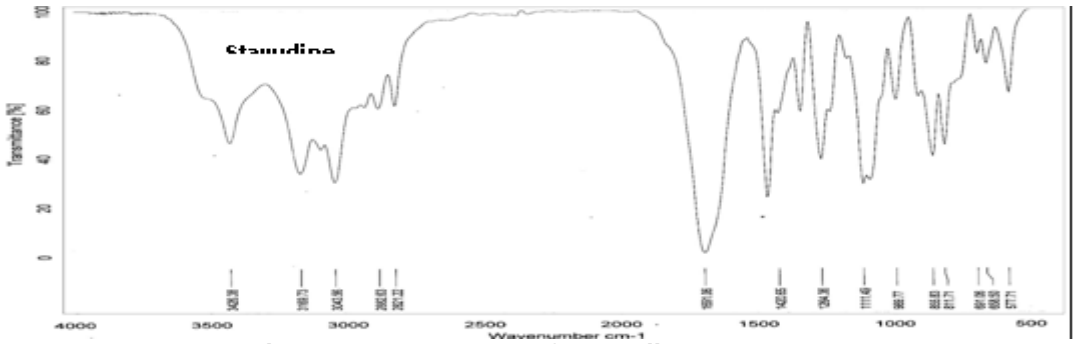

Fig. 2: FTIR Spectrum of Stavudine Pure Drug

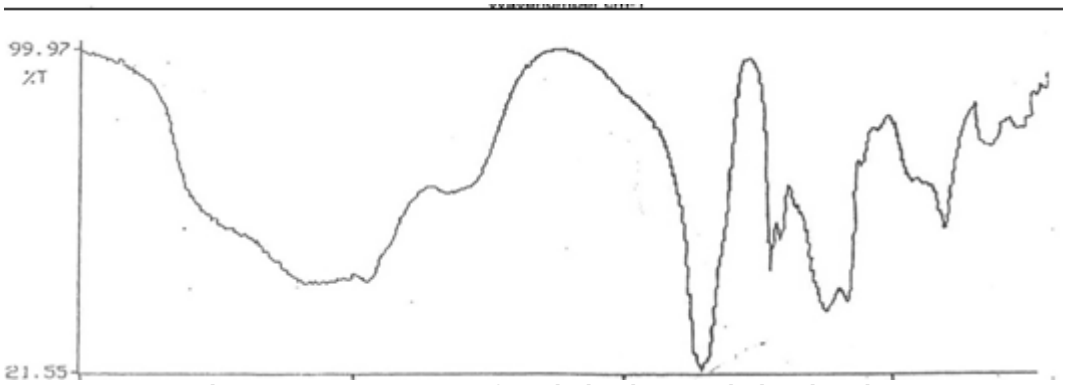

Fig. 3: FTIR Spectrum of Optimized Formulation (AF6)

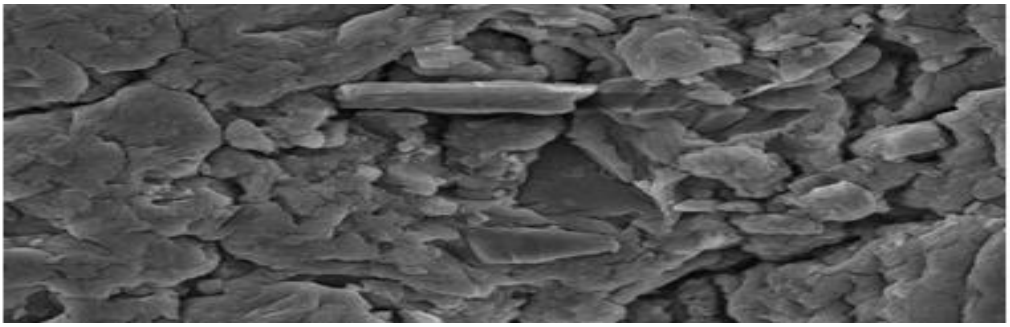

Fig. 4: SEM Image of Stavudine Pure Drug

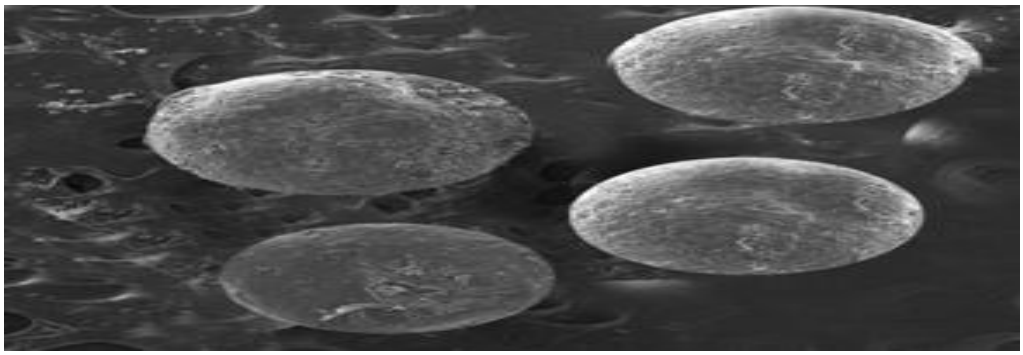

Fig. 5: SEM Image of Optimized Formulation (AF6)

CONCLUSION

The concept of formulating microspheres containing Stavudine offers a suitable, practical approach to achieve a prolonged therapeutic effect by continuously releasing the medication over an extended period of time. Thus, the microspheres of Stavudine were successfully prepared by orifice ionic gelatin method using the different concentration of polymers fenugreek mucilage and Carbapol.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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