Journal of Pharmaceutical and Scientific Innovation

www.jpsionline.com (ISSN : 2277 -4572)

Research Article

CONTROLLED DELIVERY OF HIV DRUG BY USING MUCOADHESIVE POLYMER

Nripendra Singh [1*], Ritu Singh [2], Surendra Kumar Singh [1], Sudhir K.Upadhyay [3]
[1]Department of Pharmacy, V.B.S. Purvanchal University, Jaunpur, India.
[2] Department of Pharmaceutics, R.R.S college of pharmacy, Amethi, Sultanpur, U.P., India.
[3] Department of Environmental Science, V.B.S. Purvanchal University, Jaunpur, India.
*Corresponding Author Email: nripendra2007@gmail.com

DOI: 10.7897/2277-4572.084144

Received on: 1/06/19 Revised on: 20/06/19 Accepted on: 24/06/19

ABSTRACT

One of the novel drug delivery systems are mucoadhesive drug delivery system. It utilizes the property of bioadhesion of polymers which becomes adhesive on hydration. This delivery system can be used to target a drug to a particular region of the body for extended period of time. Stavudine a nucleoside analogue of thymidine used in the treatment of HIV. Stavudine has short half-life of 2.3 hours and is taken twice daily in large number of patients which leads to no patient compliance. Thus, the development of mucoadhesive microspheres for controlled release would be advantageous. The objective of this study was to prepare, characterize and evaluate mucoadhesive microspheres of stavudine employing chitosan as coat that is used as natural mucoadhesive polymers. Mucoadhesive microspheres were found to be spherical, discrete, free flowing. Fourier transforms infrared spectroscopy (FTIR) revealed no interaction between drug and polymer(s). Scanning electron microscopy (SEM) shows microspheres were spherical. The microspheres appear with rough surface and encapsulation efficiency found to be in range of 72.18% to 80.65%. All the microspheres showed good mucoadhesive property and swelling index. The drug release was found to be in range of 94.57% to 87.66% over the period of 12 hours.

Keywords: Stavudine, Chitosan, Sodium alginate, Orifice ionic gelation technique, Microspheres.

INTRODUCTION

AIDS is a collection of symptoms and infections resulting from the specific damage to the immune system caused by the human immunodeficiency virus (HIV).[1] The late stage of the condition leaves individuals prone to opportunistic infections and tumors. Although treatments for AIDS and HIV exist to slow the virus's progression, there is no known cure. HIV is transmitted through direct contact of a mucous membrane or the blood stream with a bodily fluid containing HIV, such as blood, semen, vaginal fluid, preseminal fluid and breast milk [2]. Most researchers believe that HIV originated in sub–Saharan Africa during the twentieth century, [2] it is now pandemic, with an estimated 38.6 million people now living with the disease worldwide. As of January 2006, the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) estimate that AIDS has killed more than 25 million people since it was first recognized on June 5, 1981, making it one of the most destructive epidemics in recorded history. In 2005 alone, AIDS claimed an estimated 2.4–3.3 million lives, of which more than 570,000 were children. A third of these deaths are occurring in sub-Saharan Africa, retarding economic growth and destroying human capital. Antiretroviral treatment reduces both the mortality and the morbidity of HIV infection, but routine access to antiretroviral medication is not available in all countries[3]. HIV/AIDS stigma is more severe than that associated with other life-threatening conditions and extends beyond the disease itself to providers and even volunteers involved with the care of people living with HIV. Drug delivery systems (DDS) that can precisely control the release rates or target drugs to a specific body site have an enormous impact on the health care system. Carrier technology offers an intelligent approach for a drug delivery by coupling the drug to carrier particles such as microspheres, nanoparticles and liposome, which modulate the release and absorption characteristics of the drug. By virtue of their small size and efficient carrier characteristics microspheres constitute an important part of these particulate DDS. Due to their short residence time at the site of absorption the success of this novel drug delivery system is limited .It would be advantageous to have means for providing a close contact of the drug delivery system with absorbing membranes. It can be achieved by coupling mucoadhesion characteristics to microspheres and developing novel drug delivery system known as mucoadhesive microspheres.[4] Novel drug delivery systems [NDDS] can selectively control the release rate or target drugs to a specific body site have had a great impact on the healthcare system. Microspheres comprise of an important part of these particulate drug delivery systems because of their small size and efficient carrier characteristics. However, due to their short residence time at the site of absorption the success of these novel drug delivery systems is limited. It would be advantageous to have means for providing an intimate contact of the novel drug delivery systems with absorbing membranes. Mucoadhesion characteristics of microspheres and developing novel delivery systems as mucoadhesive microspheres can achieve it [4]. Mucoadhesive drug delivery systems utilize the property of bioadhesion of polymers that become adhesive on hydration[5]. These drug delivery systems can target a drug to a particular region of the body for extended period [6]. Bioadhesion is an interfacial phenomenon in which at least one of which is biological, are held together by means of interfacial forces[7]. The attachment could be between an artificial material and biological substrate. The term mucoadhesion is used in case of polymer attached to the mucin layer of mucosal tissue. Mucoadhesive materials have been investigated and identified[8]. These are generally hydrophilic macromolecules that contain many hydrogen bond forming groups (e.g. hydroxyl and carboxyl groups) and will swell when placed in contact with water. In many cases these materials require wetting to become adhesive. The

formation of slippery mucilage and a loss of adhesive properties may result due to over hydration. Mucoadhesive microspheres include microparticle and microcapsules ranging the diameter of 1-1000µm and including adhesive properties in the form of mucoadhesive[9]. In general microspheres have the potential to be used for targeted and controlled release drug delivery but coupling of mucoadhesive properties to microspheres have as an additional advantages e.g. efficient absorption and enhanced bioavailability of the drugs due to high surface to volume ratio, a much more intimate contact with the mucus layer. Mucoadhesive microspheres can be designed to adhere mucosal tissue including those found in eye, nasal cavity, urinary and gastrointestinal tract, thus offering the possibilities of localized as well as systemic controlled release of drugs. Many natural polymers have been used to prepare mucoadhesive microspheres. Stavudine (D4T, thymidine) is an FDA-approved drug for clinical use for the treatment of HIV infection, AIDS and AIDS-related conditions either alone or in combination with other antiviral agents. The stavudine has a very short half-life (1.30 h) with rapid absorption. The side effects of stavudine are dose dependent and a reduction of the total administered dose reduces the severity of the toxicity[10, 11]. Stavudine is typically administered orally as a capsule and oral solution. Dosage forms that are retained in the stomach would increase the absorption, improve drug efficiency and decrease dose requirements. In present investigation an attempt is made to prepare and evaluate mucoadhesive microspheres of stavudine by using polymer belonging to the natural polysaccharides for controlled release.

MATERIALS AND METHODS

Materials

Stavudine was gift sample from Matrix Laboratories Limited, Hyderabad, India. Chitosan was purchased from Marine Chemicals, Cochin, India. All other reagents were analytical grade and used as such.

Methods

Orifice ionic gelation method

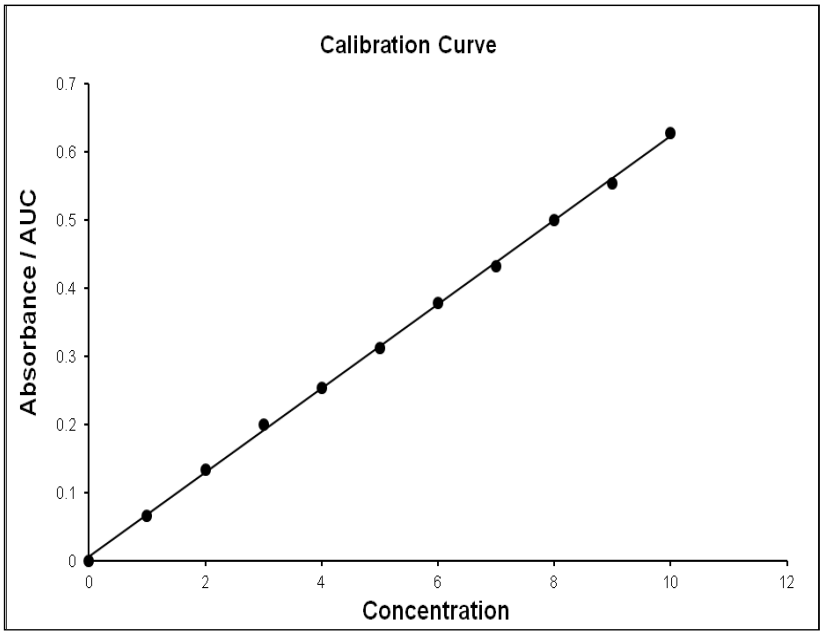
Sodium alginate and mucoadhesive polymer were dissolved in purified water (10ml) separately. Then both the solutions were mixed to form homogeneous polymer solution. The drug was added to the polymer solution and mixed thoroughly with help of pestle and mortar to form viscous dispersion. The resulting dispersion was added drop wise into 10% w/v calcium chloride solution (100ml) through a syringe with needle (size no 21) with continuous stirring at 500 rpm. The added droplets were retained in the calcium chloride solution for 15 minutes to produce spherical rigid microspheres. The microspheres were collected by decantation, and the product thus separated was washed repeatedly with water and dried at 45^0 C for 12 hours and stored in desiccators[12,13,14]. The details are summarized in table 1.

UV methodology of stavudine

Stavudine was dissolved in phosphate buffer pH 7.2 to prepare a stock solution of 100 µg/ml. Suitable dilutions were made to prepare solutions of 2-10 µg/ml and absorbance measured at 266 nm. Plot of absorbance vs concentration was plotted. The calibration curve was obtained at 266 nm[15].

Table1: Preparation of Mucoadhesive Microspheres

Batch	Core: Coat	Stavudine	Sodium Alginate	Chitosan
SF1	1:1	-	375	125
SF2	1:2	-	750	250
SF3	1:3	-	1125	375
SF4	1:1	500	375	125
SF5	1:2	500	750	250
SF6	1:3	500	1125	375



Slope= 28.97 R=0.9999 Intercept= + 0.027

Figure 1: Calibration curve for stavudine in pH 7.2 phosphate buffers

Evaluation

Production Yield: Of each batch the dried microspheres are weighed separately, and percentage yield is calculated by using following equation,[16 – 19]

$$\text{Production yeild} = \frac{\text{Practical weight}}{\text{Theoretical weight(polymer + drug)}} \times 100$$

Drug content: Mucoadhesive microspheres equivalent to 50 mg stavudine were weighed and powdered. This was extracted in methanol in 100 ml volumetric flask and made up to volume. The solution was shaken occasionally for 1h and filtered. From this 1ml of solution was taken and diluted up to 100 ml with phosphate buffer pH 7.2 in 100 ml volumetric flask. The drug content was analyzed by measuring absorbance at 266nm in a UV spectrophotometer using phosphate buffer pH 7.2 as blank. The studies were carried out in triplicate.[20]

Encapsulation efficiency: 100 mg of mucoadhesive microspheres were accurately weighed. They were powdered and extracted with 100 ml of methanol. Further it was serially diluted with phosphate buffer pH 7.2. The resulting solution was analysed for stavudine drug content by measuring absorbance in a UV- spectrophotometer at 266 nm using phosphate buffer pH 7.2 as blank. The studies were carried out in triplicate. Encapsulation efficiency (%) was calculated using the formula.[21]

$$\text{Encapsulation effeciency} = \frac{\text{Actual amount of drug encapsulated}}{\text{Theoretical drug content}} \times 100$$

FTIR spectral studies: The IR spectra obtained on Perkin Elmer 1600 series, (USA) detected the compatibility between pure drug and polymers. The pellets were prepared by using 2 mg of the mucoadhesive microspheres ground together in a mortar with about 100 times quantity of KBr. The finely ground powder was introduced into a stainless-steel die. The powder was then pressed in the die between polished stainless-steel anvils at a pressure of about 10t/in2. The spectra's were recorded over the wave number range of 4000 to 500 cm^{-1}.

Scanning electron microscopy: The particle size, shape and surface morphology of microspheres were examined by scanning electron microscopy (SEM). Microspheres were coated with gold by sputter coater SC 502 under vacuum [0.1 mm Hg] and fixed to it on aluminium studs. The microspheres were then analyzed by scanning electron microscopy [Model JSM-840 A, Joel. Japan][22].

Swelling index: 50 mg microspheres were inoculated in glass vial containing 10ml of phosphate buffer [pH 7.2 at 37°C±0.5°C] kept at incubator shaker. The microspheres were removed at different time intervals, weight was observed followed by its filtration. The swelling index was calculated [23,24].

$$\text{Swelling index} = \frac{We - Wo}{Wo} \times 100$$

Where, We - Weight of swollen microspheres; Wo – Weight of dried microspheres.

***In vitro* wash-off test:** The everted rat intestinal mucosa of $1cm^2$ area was tied to a glass slide (3X1 inch) with thread. Microspheres were spread (~50) onto wet and rinsed tissue specimen. The slide was then hung onto grooves of the USP tablet disintegrating test apparatus. The tissue specimen was given a slow, regular up-and-down movement in a beaker containing phosphate buffer pH 7.2 (500ml) at 37°C. The number of microspheres still adhering to tissue was calculated at the end of 30 min, 1h and at the hourly interval up to 8h[25 – 27].

***In vitro* dissolution study:** The amount of stavudine release from mucoadhesive microspheres was investigated by using USP type I basket apparatus and 900ml of phosphate buffer pH 7.2 used as dissolution medium[28]. Mucoadhesive microspheres equivalent to 50 mg of stavudine filled in hard gelatin capsules were used for the study. A speed of 50 rpm and temperature of 37 ± 0.5ºC was maintained throughout the experiment. At fixed intervals dissolution studies was carried out up to 12 h, aliquots (5 ml) was withdrawn and replaced with fresh dissolution media to maintain the sink condition. The concentration of drug released at different time intervals was then determined by measuring the absorbance at 266 nm against blank. The studies were carried out in triplicate. The absorbance was measured at 266 nm by using Shimadzu 1700 UV spectrophotometer, against a blank solution.

Stability

The stability studies were conducted according to International Conference on Harmonization guidelines by storing the transdermal films at 40±2°C with 75% RH in stability chamber for 3 months[29, 30]. The samples were withdrawn after 3 months and analyzed for drug content in UV spectrophotometer.

Table 2: Production yield of SF4, SF5 and SF6 formulations

Batches	Production Yield ±SD
SF4	97.18 ± 0.83
SF5	95.56 ± 0.31
SF6	96.69 ± 0.26

Table 3: Percent drug content of SF4, SF5 and SF6 formulations

Batches	Theoretical Drug Content (mg)	Practical Drug Content (mg)	% Drug Content ± SD
SF4	50	49.53	99.06± 0.83
SF5	50	49.61	99.22 ± 0.31
SF6	50	49.66	99.32 ± 0.26

Table 4: Percent Encapsulation efficiency of SF4, SF5 and SF6 formulations

Batches	Microencapsulation efficiency ±SD
SF4	72.12±0.54
SF5	76.43±0.46
SF6	80.65±0.31

Table 5: Swelling ratio of SF4, SF5 and SF6 formulations

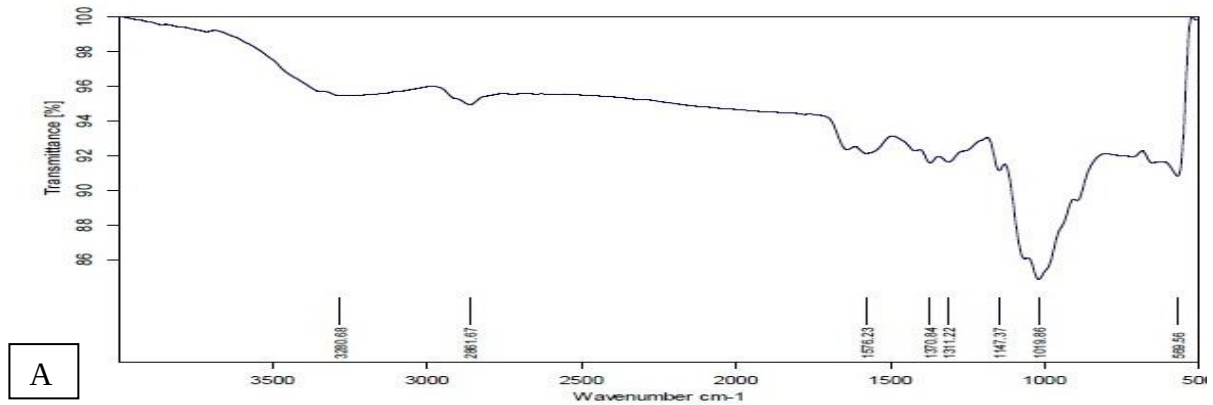
Time (h)	SF4		SF5		SF6	
	Wt. of MC after swelling	Relative swelling	Wt. of MC after swelling	Relative swelling	Wt. of MC after swelling	Relative swelling
0	50	0	50	0	50	0
30	73	0.46	75	0.5	74	0.48
1	79	0.58	81	0.62	80	0.6
2	99	0.98	98	0.96	101	1.02
3	103	1.06	106	1.12	108	1.16
4	104	1.08	108	1.16	112	1.24
5	108	1.16	110	1.2	116	1.32
6	116	1.32	118	1.36	121	1.42

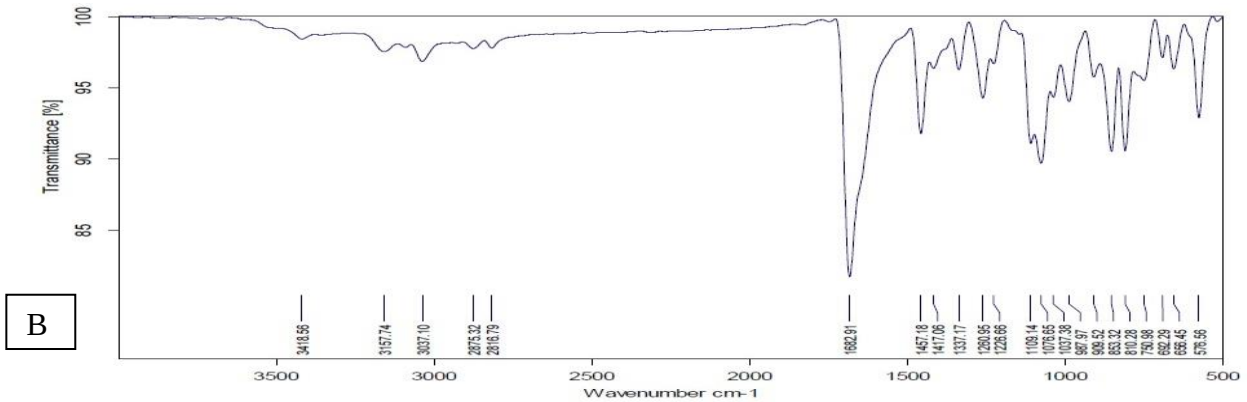
Table 6: Percent adhering of SF4, SF5 and SF6 formulations

Batches	% of microspheres adhering to tissue at different time intervals					
	0	1	2	3	4	6
SF4	50	94	83	74	71	71
SF5	50	96	88	79	68	68
SF6	50	93	82	75	67	67

Table 7: Stability Study Data of Stavudine microspheres

Formulation code	% Drug content ± SD before storage	% Drug content ± SD After 3 months
SF4	99.06± 0.77	98.86± 0.85
SF5	99.22 ± 0.23	98.89 ± 0.45





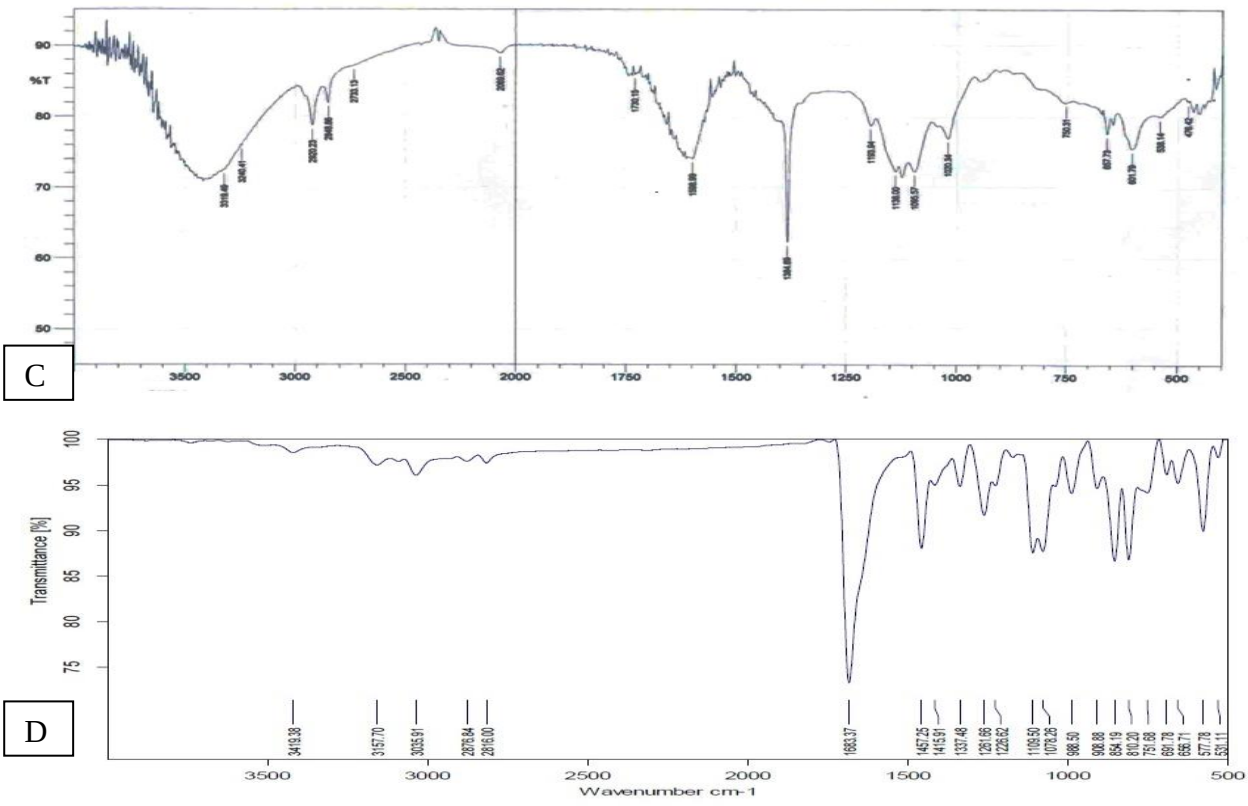
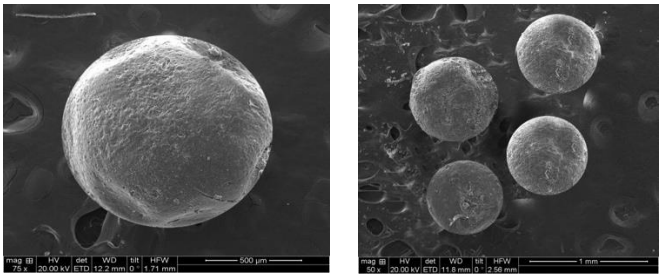


Figure 2: FTIR spectrum; figure [A] of Chitosan, figure [B] of Stavudine, figure [C] for Sodium Alginate and figure [D] of Stavudine microsphere.



SF1 SF4

Figure 3: Scanning electron micrographs of SF1 and SF4 formulations

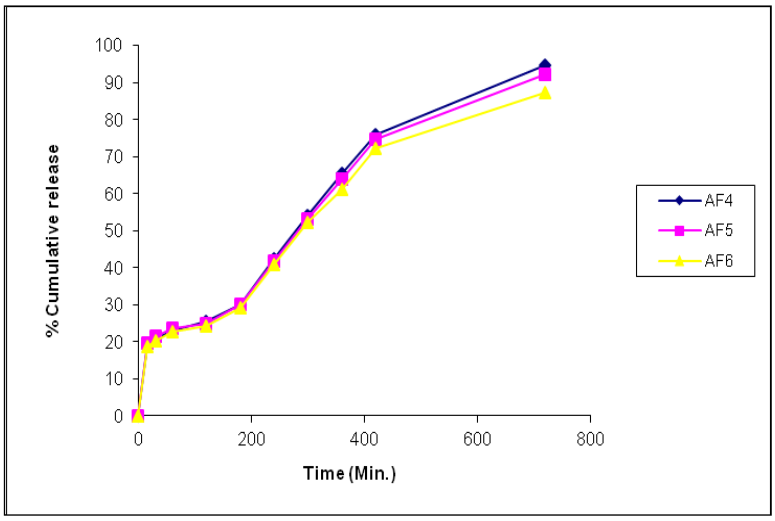


Figure 4: Cumulative % drug release of SF4, SF5 and SF6 formulations

RESULTS AND DISCUSSION

Production Yield

The results of production yields are shown in table 2. The percentage yield of chitosan formulations were in the range of 97.18 ± 0.83 to 96.69 ± 0.26.

Drug Content

The results of drug content are shown in tables 3. The percentage content of chitosan formulations was in the range of 99.06 ± 0.83 to 99.32 ± 0.26. The low SD and CV value indicates distribution of drug within the various batches of microspheres prepared. The drug content results suggest a negligible loss of drug during the formulation stage.

FTIR studies

The FTIR spectrum of pure stavudine, chitosan, and prepared mucoadhesive microspheres are shown in figure 2. The FTIR characteristic of stavudine bands are -OH stretching at 3426 cm^{-1}, ,-NH stretching at 3169 cm^{-1}, Ar-CH=C stretching at 3043 cm^{-1}, CH_2 and CH_3 stretching at 2882 cm^{-1}, and 2821 cm^{-1}, C=O stretching at 1682 cm^{-1} and NH bending at 1264 cm^{-1}. FTIR spectra of mucoadhesive microspheres showed all the characteristic absorption bands of stavudine with little shifting toward lower /higher wavelength especially Ar-CH=C stretching at 3043 cm^{-1} and C=O stretching at 1683 cm^{-1} indicating minor interaction or no interaction.

Encapsulation efficiency

Encapsulation efficiency was observed, and all the results of the formulations were shown in table 4. Chitosan formulation revealed that the range of 72.12±0.54 to 80.65±0.31 for their percent encapsulation efficiency and it depends on the concentration of sodium alginate which used in the formulation. In general encapsulation efficiency was proportional to the concentration of sodium alginate. This could be attributed due to formation of larger microspheres with increasing concentration of sodium alginate and entrapping more concentration of drug.

Scanning electron microscopy

Scanning electron microscopy was used to know surface morphology of microspheres. The SEM photographs of SF1 blank microsphere and SF4 drug loaded, batches revealed that microspheres were spherical, discrete given below in figure 3. The outer surface of microspheres was coarse rough texture, with few pores mild cracks and completely covered with coat materials.

Swelling studies by weight method

The swelling depends upon the polymer concentration, ionic strength as well presence of water and the data is shown in table 5. The relative swelling of mucoadhesive microspheres of chitosan formulations were found in the range of 1.32, 1.36, 1.42 at the end of 6h. The results clearly suggested swelling ratio depends upon concentration of polymer and type of mucoadhesive polymer used in the formulation. Swelling ratio shows direct relationship with sodium alginate concentration and increased with increasing concentration of sodium alginate.

In vitro wash-off test

The mucoadhesion is a phenomenon in which two materials, at least one of which is biological are held together by means of interfacial force. The tables 6 shows *in vitro* mucoadhesion data of mucoadhesive microspheres carried out with everted rat intestinal mucosa in presence of phosphate buffer pH 7.2. The percentage of microspheres retained on everted intestinal mucosa after 6 h in chitosan formulations were found in the range of 71, 68, 67 for SF4, SF5 and SF6 respectively. The overall results suggest that concentration and type of mucoadhesive polymer doesn't show much more difference in the mucoadhesive property.

Dissolution studies

The dissolution rate of mucoadhesive microspheres were studied by using USP type I apparatus. The percentage release of stavudine from SF4, SF5, and SF6 formulations prepared with Sodium alginate and Chitosan were 94.57±0.22, 92.11±0.28, 87.66.±0.45 respectively over the period of 12 hours given in figure 4.The release from formulations SF4 to SF6 follow higuchi and matrix with n value of 0.4472, 0.4291, 0.4470. In all formulations the release exponent n was found less than 0.5 indicating the release was fickian mechanism indicating the release rate was to be diffusion controlled and slow with increasing concentration of polymers[31].

Stability studies

Table **7** shows drug content of the formulations before and after stability study. These formulations were stored at 40±2°C/75%RH in stability chamber for 3 months. Drug content of the patches after stability studies did not show any significant variations. These results indicate that drug remain stable after stability studies[32].

CONCLUSION

Stavudine has short half-life of 2.3 hours and is taken twice daily in large number of patients which leads to no patient compliance. Thus, the development of mucoadhesive microspheres for controlled release would be advantageous. Mucoadhesive microspheres were found to be spherical, discrete, free flowing. The microspheres appear with rough surface and encapsulation efficiency found to be in range of 98.18% to 98.65%. All the microspheres showed good mucoadhesive property and swelling index. The drug release was found to be in range of 94.57% to 87.66% over the period of 12 hours.

ACKNOWLEDGEMENT

Authors are thankful to Matrix Laboratories Limited, Hyderabad, India for providing gift samples of Stavudine.

REFERENCES

1. Marx, J.L., 1982. New disease baffles medical community. Science. 217 (4560), 618-621.
2. Gao, F., Bailed, E., Robertson, D.L., Chen, Y., Rodenburg, C.M., Michael, S.F., Cummins, L.B., Arthur, L.O., Peeters, M., Shaw, G.M., Sharp, P.M., Hahn, B.H., 1999. Origin of HIV-1 in the Chimpanzee Pan troglodytes' troglodytes. Nature. 397 (6718), 436-441.
3. Palella, F.J.Jr, Delaney, K.M., Moorman, A.C., Loveless, M.O., Fuhrer, J., Satten, G.A., Aschman D.J., Holmberg, S.D., 1998. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. N. Engl. J. Med. 338 (13), 853-860.
4. Chowdary et al. mucoadhesive microspheres and micro particles. Indian J.Pharm.Sci, April 2005, 67(2): 141-150.
5. Dhavan S, Singla AK, Sinha VR. Evaluation of mucoadhesive properties of chitosan microspheres prepared by different method. AAPS Phar m Sci Tech2004; 5(4): 67.

6. Chowdary KPR, Srinivas RY. Design and *in vitro* and *in vivo* evaluation of mucoadhesive microcapsules of glipizide for oral controlled release. AAPS Pharm Sci Tech 2003; 4(3): 1-6.
7. Schaefer MJ, Singh J (2000) Effect of isopropyl myristic acid ester on the physical characteristics and in-vitro release of etoposide from PLGA microspheres. AAPS PharmSciTech. 1(4): article 32.
8. Hannah B. (2004). Novel bioadhesive formulation in drug delivery. The drug delivery companies report. 16-19.
9. Mathiowitz E, Chickering DE, Jacob JS (2001) US Pat. No. 6,197, 346
10. Reeves, J.D., Doms, R.W., 2002. Human Immunodeficiency Virus Type 2. J. Gen. Virol, 83 (Pt 6), 1253-1265.
11. Yazdanian M., 1999. Blood-Brain Barrier Properties of HIV Antiretrovirals. J. Pharma. Sci. 88, 950-954.
12. Shiva Kumar Y, Jeet Singh, Jawad Ali Syed, Rajkamal B, Sharada G, Naveen Kumar N. Design and Characterization of Amoxicillin trihydrate Mucoadhesive Microspheres for Prolonged Gastric retention. International Journal of\Pharma.Sci. and Drug Research 2010; 2(2): 112-114.
13. Benita S. Microencapsulation methods and industrial applications. New York: Marcel Dekker, 1996: 35-71.
14. S Ravi, KK Peh, Yusrida Darwis, B Krishna Murthy, T Raghu Raj Singh and C Mallikarjun. Development and Characterization of polymeric microspheres for controlled release protein loaded drug delivery system. Indian Journal of Pharmaceutical Science 2008; 70(3): 303-09.
15. Pandey JD, Singh R, Singh N (2014) Transdermal delivery of stavudine using penetration enhancers. World j pharmaceutical research 3: 3066-92.
16. T. M. Kalyankar, Nalanda T, Mubeena Khan, Avinash Hosmani and Arvind Sonwane. Formulation and Evaluation of Mucoadhesive Pioglitazone Hcl Microspheres. IJPWR 2010: 1(3).
17. Nagda Chirag, Chotai Narendra, Patel Sandip, Ahir Keyur, Nagda Dhruti. Design and characterization of bioadhesive microspheres prepared by double emulsion solvent evaporation method. Acta Pharmaceutica Sciencia 2009; 51: 261- 270.
18. Mehat KA. Formulation of enterosoluble microparticles for an acid labile Protein. J Pharm Pharmaceut Sci 2002; 5(3): 234-44.
19. Pandey Shivanand. Different Techniques of Formulation and Evaluation of Mucoadhesive Microspheres. International Journal of Pharma and Biosciences. 2010; 1(2): 1-7.
20. D Nagasamy Venkatesh, Reddy AK, Samanta MK. Development and *In vitro* Evaluation of Colonic Drug Systems for Tegaserod Maleate. Asian J Pharm 2009; Jan – Mar: 50-3.
21. Manavalan ramasamy. Physical pharmaceutics. 2nd ed. India: vignesh publisher;2004.
22. Prajapati R K, Mahajan H S, Surana S J. PLGA Based Mucoadhesive Microspheres for Nasal Delivery*: In Vitro / Ex Vivo* Studies. Indian Journal of Novel Drug delivery 2011; 3(1): 9-16.
23. Kothawade KB, Gattani SG, Surana SJ. Colonic Delivery of Aceclofenac Using combination of pH and Time Dependent Polymers. Indian Drugs Nov 2009; 46 (11): 67-70.
24. Cevher E, Orhan Z, Mulazimoglu L, Sensoy D, Alper M, Yildiz. Characterization of biodegradable chitosan microspheres containing vancomycin and treatment of experimental osteomyelitis caused by methicillin-resistant staphylococcus aureus with prepared microspheres. Int J Pharm 2006; 317: 127- 35.
25. Streubel A, Siepmann J and Bodmeier R. Multiple unit gastroretentive drug delivery systems: A new preparation method for low density microparticles. J. Microencapsulation 2003; 20: 329-347.
26. Jayvadan patel K, Rakesh Patel P, Avani Amin F and Madhabhai Patel M. Formulation and Evaluation of Mucoadhesive Glipizide Microspheres. AAPS Pharmscitech 2005; 6: E49-55.
27. Mathew ST, Gayathri Devi S, Sandhya KV. Formulation and evaluation of ketorolac tromethamine-loaded albumin microspheres for potential intramuscular administration. AAPS Pharm Sci Tech 2007; 8(1) Article 14: E1-9.
28. Hitendra Mahajan, Surendra Gattani, Sanjay Surana. Spray Dried Mucoadhesive Microspheres of Ondansetron for Nasal Administration. International Journal of Pharmaceutical Sciences and Nanotechnology 2008; 1(3): 267-274.
29. J Josephine LJ, Mehul RT, Wilson B, Shanaz B and Bincy R. Formulation and *In vitro* Evaluation of Floating Microspheres of Anti-Retro Viral Drug as a Gastro Retentive Dosage Form. IJRPC 2011; 1(3): 519-527.
30. Trivedi P, Verma A, Garud N. Preparation and characterization of aceclofenac microspheres. Asian J Pharm 2008; 2: 110-5.
31. Ping He, Stanley S, Davis, Lisbeth Illum. *In vitro* evaluation of the mucoadhesive properties of Chitosan microspheres. International Journal of Pharmaceutics 1998; 166: 75-68.
32. Shah P, Rajshree M, Rane Y. Stability testing of pharmaceuticals - A global perspective. J Pharm Res 2007; 6(1): 1-9.

How to cite this article:
Nripendra Singh *et al*. Controlled delivery of HIV drug by using mucoadhesive polymer. J Pharm Sci Innov. 2019;8(4):148-154. http://dx.doi.org/10.7897/2277-4572.084144

Source of support: Nil, Conflict of interest: None Declared