ISSN: 0976-4607
Research Article

International Journal of Innovative Pharmaceutical Research

Journal homepage: www.ijipr.com

Formulation and Evaluation of Controlled Release Microspheres of Acyclovir Sodium

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ABSTRACT

The purpose of this study was to prepare controlled release microspheres of acyclovir sodium using different polymers like sodium alginate, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose using calcium chloride as cross linking agent. The microspheres were prepared using ionotropic gelation technique. The prepared microspheres were evaluated for particle size analysis, drug entrapment efficiency; *In vitro* drug release and Fourier transform infra red spectroscopy (FTIR). The results of study revealed that retention time of acyclovir at its absorption site could be increased by formulating it into microspheres using sodium alginate, hydroxyl propyl methyl cellulose and sodium carboxy methyl cellulose in different ratios. The acyclovir sodium microspheres prepared from sodium alginate and hydroxyl propyl methyl cellulose at the concentrations of 1:2:1.5 weight ratios with 2% calcium chloride as cross linking agent showed the highest drug release of 98.8 % over a period of 12 hours. The microspheres prepared were found to be spherical without aggregation and free flowing. The percentage yield and drug entrapment in all the formulations were good. The average particle size was found to be within the range of 100-200 micrometers. All the formulations show excellent flowability as expressed in terms of angle of repose (< 25°).FTIR Spectroscopy reveals that there is no chemical interaction between the drug and excipients.

Keywords: Ionotropic gelation technique, Bioavailability, Sodium alginate, FTIR.

INTRODUCTION

The basic concept in the design of oral controlled-release drug delivery systems is that the kinetics of drug release, rather than the kinetics of drug absorption, controls the availability of the drug. Acyclovir is currently marketed as tablets (200, 400 and 800 mg) and suspension for oral administration, intravenous injection and topical ointment. Oral acyclovir is mostly used as 200 mg tablets, five times a day (Wagstaff *et al*., 1994). In addition, long term administration of acyclovir (6 month or longer) is required in immune competent patient with relapsing herpes simplex infection (Ruhnese *et al*., 1985). The main problem with the therapeutic effectiveness of acyclovir is its absorption that is highly variable and dose dependent thus reducing the bioavailability to 10–20%. In commercially available dosages forms, the amount of drug absorbed is very low (10–20%) due to short residence time of the dosage forms at the absorption site.

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The presently available conventional therapy is associated with a number of drawbacks such as highly variable absorption and low bioavailability (10–20%) after oral administration (O'Brien *et al*., 1989). Furthermore, with increase in dose, there was decrease in bioavailability. Moreover, because the mean plasma half life of the drug is 2.5 h, five times a day administration is required. In order to make oral therapy of acyclovir more patient compliance there is need to develop controlled drug delivery dosage form. The present investigation, therefore aimed at formulating controlled release microspheres of acyclovir using sodium alginate, Sodium carboxy methylcellulose and hydroxyl propyl methylcellulose as polymers (Chowdary *et al*., 2000).

MATERIALS

Acyclovir sodium was a gift sample from Arochem industries, Thane, Mumbai India. Sodium alginate, calcium chloride, Sodium carboxy methylcellulose and hydroxyl propyl methylcellulose were obtained as gift sample from Colorcon Ltd., Mumbai, India.

METHODS

Preparation of Acyclovir sodium microspheres

Acyclovir sodium micro spheres were prepared by Ionic gelation method using polymers such as sodium alginate, HPMC and SCMC by using calcium chloride as cross linking agent in the drug and polymer ratio 1:1.5:0(F1), 1:3:0(F2), 1:1.5:0(F3) 1:3:0(F4), 1:5:0(F5), 1:2:0.5(F6), 1:2:1(F7), 1:2:1.5(F8), 1:2:2(F9). Sodium alginate and sodium carboxy methyl cellulose in drug polymer ratio 1:2:0.5(F10), 1:2:1(F11), 1:2:1.5(F12), 1:2:2(F13). Sodium alginate and HPMC were dissolved in 100ml of distilled water to form homogeneous polymer solution using magnetic stirrer with the temperature maintainance of 40^{o} c for 45 minutes (Jalonde and Santoyo. S, 2003). Acyclovir sodium was added to polymer solution and mixed thouroughly to form a viscous dispersion. Resulting dispersion was added drop wise into 1%Calcium chloride solution for F1 and F2 formulations and 2% Calcium chloride solution for remaining formulations through syringe fitted with a needle of 24gauge (Park and Mitra. A. K., 1992). Spherical rigid micro spheres were formed in $Cacl_2$ solution. Micro spheres were collected by decantation and product thus produced was washed repeatedly with water and dried at room temperature overnight and stored in dessicator.

Percentage Practical Yield

The yield of microspheres was determined by comparing the whole weight of microspheres formed against the combined weight of the copolymer and drug.

$$\% \text{ Practical yield} = \frac{\text{Mass of microspheres obtained}}{\text{Total weight of drug and polymer used}} \times 100$$

EVALUATIONS OF MICROSPHERES

Micromeritic properties

The microspheres were characterized for true density, tapped density, Carr's index , Hausner's ratio (H_R) and angle of repose using the following equations(Devarajan Jain, 2002). The tapping method was used to determine the tapped density and Carr's index as follows.

D_O = True density = W/V_O

D_t = tapped density = W/V_t

Hausner's ratio (H_R) = Tapped density / true density

Carris index = (Tapped density – True density / (Tapped density *100

V_O and V_t are the true volume and tapped volume respectively

Particle size analysis

It is possible to use ordinary microscope for particle size determination in the range of 0.2 to above 100 µm to measure particle size of individual microsphere. Optical micrometer was calibrated using stage micrometer. According to microscopic method of analysis, slides of dilute suspensions of microspheres were prepared in liquid paraffin and slides were placed on mechanical stage of microscope (Grabovac and Schnurch, A.B., 2005). Size of microspheres from each batch was measured for calculating average particle size.

Entrapment Efficiency of Acyclovir sodium microspheres

Known quantity of alginate beads were added 50ml of pH 7.4 buffer and kept aside about 12 hours. Then the volume was made up to 100ml and filtered through whatmann filter paper No. 40 (Asane *et al.*, 2011). The absorbance of the filtrate was measured at 254 nm.

In vitro dissolution studies (pH 7.4 buffer)

In vitro drug release study was carried out in USP type-II dissolution test apparatus. The dissolution medium 900 ml of 7.4 phosphate buffer was maintained at (37±1°C and stirred at 50rpm. Aliquots of samples (5 ml) at an interval of 1 hour were withdrawn and filtered through a whatmann filter paper(Lehr CM and Junginer HE.1990). The samples were analyzed for Acyclovir sodium content by UV-Visible spectrophotometer at 254 nm.

Fourier Transform infrared spectroscopy

FTIR spectral measurement was performed using thermo electron FTIR spectrometer to confirm the presence of any interaction between the polymer and drug (Meadows K. C and Dressman J. B., 1990). The microspheres were finely ground with KBr to prepare the pellets under a hydraulic pressure of 600psi and spectra were scanned between 400 and 4000.

RESULTS AND DISCUSSION

In the present research work acyclovir sodium drug was prepared into microspheres with sodium alginate, HPMC and SCMC to made as a controlled release formulations using calcium chloride as a cross linking agent.

The percentage practical yield of all the formulations (F1-F13) was found to be within the range of 75 to 99 % which denotes the suitability of the method of formulation. The percentage practical yields of all the formulations are shown in Table.2. The compressibility index ranged from 13.70% to 16.75%. All formulations showed excellent flow ability as expressed in terms of angle of repose in the range of 17°-26°.

Prepared microspheres were evaluated for average article size. The average particle size was found to be with the range of 100 to 200 µm. So, the average particle sizes for all the formulations were within the range. The average particle size of all the formulations is shown in Table.2.

Entrapment efficiency

Prepared microspheres were evaluated for entrapment efficiency. The entrapment efficiency was found to be with the range of 10 to 50 %. Amongst formulations (F1-F13) F3, F4 and F8 show good entrapment efficiency. Based on good entrapment efficiency F3, F4 and F8 formulations are subjected to invitro dissolution studies. Entrapment efficiency of F3, F4 and F8 formulations are shown in Table.2.

Table.1 Formulation of acyclovir sodium microspheres

S.No.	FORMULATION	ACYCLOVIR SODIUM (gm)	SODIUM ALGINATE (gm)	HPMC (gm)	SCMC (gm)	CALCIUM CHLORIDE (%)
1	F1	1	1.5	0	0	1
2	F2	1	3	0	0	1
3	F3	1	1.5	0	0	2
4	F4	1	3	0	0	2
5	F5	1	5	0	0	2
6	F6	1	2	0.5	0	2
7	F7	1	2	1	0	2
8	F8	1	2	1.5	0	2
9	F9	1	2	2	0	2
10	F10	1	2	0	0.5	2
11	F11	1	2	0	1	2
12	F12	1	2	0	1.5	2
13	F13	1	2	0	2	2

Table.2 Average particle size of all the formulations

S.No	Formulation	% Practical yield	Average Particle size	Entrapment efficiency
1	F1	78.8 %	105.13 µm	34.0%
2	F2	82.5 %	136.12 µm	24.0%
3	F3	85.0 %	139.44 µm	39.8%
4	F4	87.5 %	124.50 µm	41.7%
5	F5	88.0 %	196.20 µm	25.5%
6	F6	98.8 %	149.40 µm	12.7%
7	F7	97.2 %	104.80 µm	20.0%
8	F8	75.5 %	105.30 µm	42.3%
9	F9	76.0 %	126.36 µm	18.4%
10	F10	92.1%	107.29 µm	10.3%
11	F11	81.7%	116.32 µm	25.11%
12	F12	82.0 %	138.38 µm	30.8%
13	F13	82.2 %	132.24 µm	33.17%

Table.3 *In vitro* dissolution profiles in pH 7.4 phosphate buffer (% drug release)

S.No.	Formulation	1hr	2hr	3hr	4hr	5hr	6hr	7hr	8hr	9hr	10hr	11hr	12hr
1	F3	18.8	28.8	38.4	50.5	55.3	59.9	64.5	69.5	75.5	80.2	89.2	96.0
2	F4	10.5	39.7	52.1	54.5	59.5	62.5	68.9	71.5	76.4	81.2	88.5	94.5
3	F8	19.2	24.5	35.6	45.6	58.5	62.5	71.6	79.8	81.5	86.5	91.5	98.8

The *in vitro* drug release studies were performed for F3, F4, F8 formulations. From the study it is revealed that F8 formulation shows better release of the drug 98.8%at the end of 12hrs in comparison with F3 and F4 formulations (Table.3 and Fig.1).

Fourier Transform infrared spectroscopy

Pure acyclovir showed prominent peaks at 1413 cm^{-1}, 1352 cm^{-1} and 1111 cm^{-1} because of hydroxyl, carboxy and aromatic amine respectively. These peaks were retained in acyclovir loaded microspheres indicating the stability of acyclovir during processing of microspheres (Fig.2 to Fig.4).

Fig.1 *In vitro* dissolution profiles of acyclovir sodium

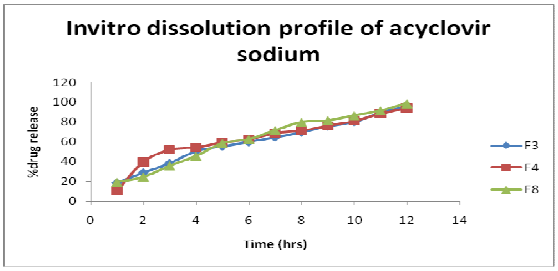


Fig.2. F3 formulation

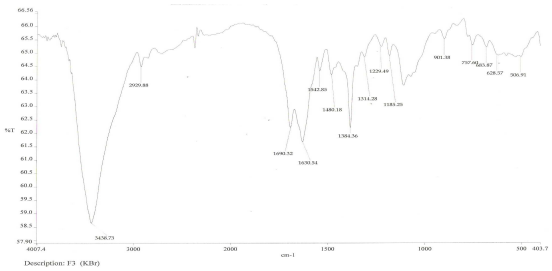


Fig.3 F7 formulation

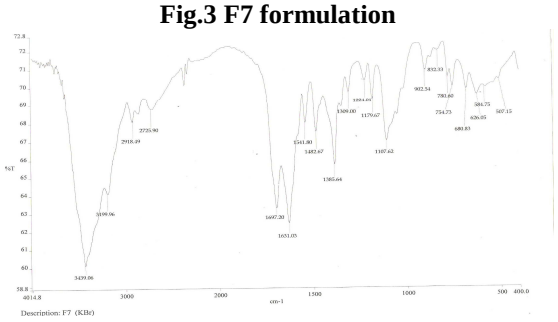
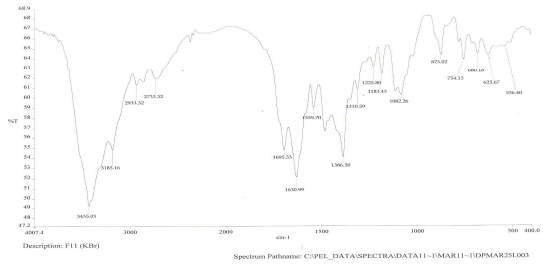


Fig.4 F11 formulation



CONCLUSION

The present study demonstrates the feasibility of efficiently encapsulating acyclovir sodium microspheres using ionotropic gelation technique. The acyclovir sodium microspheres prepared from sodium alginate and hydroxyl propyl methyl cellulose at the concentrations of 1:2:1.5 weight ratios with 2% calcium chloride as cross linking agent showed the highest drug release of 98.8 % over a period of 12 hours. FTIR Spectroscopy reveals that there is no chemical interaction between the drug and excipients. So the controlled release microspheres developed in this investigation is ideal drug delivery for acyclovir sodium.

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