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Formulation and *In Vitro* evaluation of sustained release microspheres of aceclofenac

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Abstract

The objective of the present study was preparation and invitro evaluation of sustained release microspheres of aceclofenac. Generally administration of microspheres will provide the localization of active substance at the site of action for prolonged period of the time. The microspheres of aceclofenac was prepared by emulsion cross linking method and solvent evaporation technique by using different grades of gelatin with varying concentrations and Eudragit (S-100,L-100) polymers respectively. The formulations were evaluated for particle size distribution analysis, flow properties like Angle of repose, bulk density, tapped density, true density, Hausner's Ratio, Carr's index, microencapsulation efficiency, Scanning electron microscopy(SEM) and invitro release studies. The optimized formulation showed good invitro sustained release activity of the drug Aceclofenac.

Key-Words: Sustained release microspheres, Eudragit S-100, L-100, Gelatin, Cross linking agent

Introduction

Aceclofenac is a new generation NSAID showing effective anti-inflammatory and analgesic properties and a good tolerability profile in a variety of painful conditions like ankylosing spondylitis[1-2], rheumatoid arthritis[3]and osteoarthritis[4]. It has short biological half life of 2.3-4 hrs[6]. This necessitates multiple daily dosing for maintenance of its plasma concentration within the therapeutic index, hence there is impetus for developing sustained release dosage form that maintains therapeutic plasma drug concentration for long period compared to conventional dosage forms 4-5hrs[7-8]. Among these systems microspheres have emerged as an attractive dosage forms due to the advantages it offers like effective taste masking, improvement of flow, safe handling and good sustaining drug release properties. Much interest is also being shown these days to the formulations based on the natural polymers owing to its biocompatibility, biodegradability, non toxicity[9], and ease in availability. As the current study also deals with the same natural available polymer gelatin.

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Material and Methods

Aceclofenac was obtained as gift sample from orchid pharma private limited,Chennai, Gelatin from aurobindo Pharma Pvt. Ltd., Hyderabad. Eudragit – S100 & Eudragit –L100 from aurobindo Pharma Pvt. Ltd., Hyderabad, Isopropanol, Ethanol, dichloromethane, polyvinyl alcohol, D-Glucose and span-80 from Qualigens fine chemicals, Mumbai.

Preparation of microspheres

Microspheres were prepared by emulsion cross linking method& solvent evaporation technique

Emulsion Crosslinking method

Aqueous solution of gelatin was allowed to react with required amount of sugar and then drug was dispersed in gelatin solution[10-11]. The resultant mixture was added to liquid paraffin containing span-80, the mixture was stirred rapidly, to get microspheres washed with isopropanol, filtered and allowed to dry.

Solvent evaporation technique

In this technique, Eudragit was dissolved in solvent containing (dichloromethane: ethanol) of equal ratio, then drug was dissolved in the polymer solution[12], to that 1% PVA solution was added and mechanically stirred to get microspheres, filtered washed with demineralised water and dessicated at room temperature.

***Invitro* evaluation of microspheres**

The evalution of microspheres can be done by determining its particle size distribution, bulk density, true density, Carr's index, Hausner's ratio, Angle of repose, entrapment efficiency, drug content and percentage yield are tabulated in (Table 1&2).

Scanning Electron Microscopy (SEM)

The samples for the SEM analysis were prepared by sprinkling the microspheres on one side of the double adhesive stub. The stub was then coated with fine gold dust[15]. The microspheres were then observed with the scanning electron microscope (Leica Electron Optics, Cambridge, USA) at 15 kv. (fig.1&2)

***In Vitro* Release Studies**

The in vitro release studies of drug-loaded microspheres were carried out at 37±0.5 ^{O}C and 100 rpm using 0.1N Hcl (900 ml) for 2 hrs and followed by phosphate buffer pH6.8 (900 ml) in a USP dissolution apparatus (Electro lab, India) under sink conditions[13]. Accurately weighed samples of microspheres (containing approximately 200 mg of drug) were filled in gelatin capsule and placed in a dissolution medium and at present time intervals aliquots were withdrawn and replaced by an equal volume of fresh dissolution medium. After suitable dilution, the samples were analyzed spectrophotometrically at 275 nm. The concentration of
aceclofenac in test samples was corrected and calculated using a regression equation of the calibration curve.(Table3 and Fig.3)

Analysis of release data

The dissolution data were fitted to the well-known exponential equation (Korsmeyer–Peppas equation), which is often used to describe the drug release behavior from polymeric systems[14].

$$\frac{M_t}{M_f} = k \cdot t^n$$

Where k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism and Mt/Mf represents the drug dissolved fraction at time t.

In case of Fickian release (diffusionally controlled release), the n have the limiting values of 0.45 for release from cylinders. (table-4)

$$\log\left[\frac{M_t}{M_f}\right] = \log k + n \log t$$

Results and Conclusion

The microspheres of aceclofenac are prepared by Emulsion Cross linking method. The microspheres prepared by this method found to be discrete, spherical, free flowing. The results of micromeritic properties of the microspheres are shown in table.1

The results revealed that gelatin microspheres containing aceclofenac would be successfully prepared by using native glucose as crosslinking agent. Sugar crosslinked gelatin microspheres were able to sustain the release of aceclofenac. It may be noted that at higher level of glucose and lower level of gelatin better sustain release was achieved. Sugar crossslinking can be considered as safer methods, which obviate the toxicity problems associated with the use of chemical crosslinkers. The formulation which showed better and sustains release with (GELATIN 15%, D-GLUCOSE-2%) is 98.35% at 11hours.

Eudragit loaded aceclofennac microspheres were prepared successfully using solvent evaporation technique. Both Eudragit S-100 and L-100 microspheres showed better sustain release properties. From the six formulations of Eudragit loaded microspheres, Eudragit L-100 micropsheres show better sustain release property. The assessment of the release kinetics revealed that drug release from microspheres follows Peppa's model. It was suggested that mechanism of drug release from microspheres was diffusion coupled with erosion non fickian anamolus transport mechanism. The formula which showed better release among the six formulations is F-XII is of 98.51% at 11hours of dissolution study. Sustain release without initial peak level achieved with these formulations may reduce frequency and side effects as well as improve patient compliance.

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Table 1: Characterization of Aceclofenac Microspheres Formulated Using emulsion cross linking method

Formula code	Angle of Repose^{o}	Bulk Density (g/cm^3)	True Density (g/cm^3)	Hausner's ratio	Carr's Index	Average Particle Size (µm)
F-I	25.16±0.444	0.29±0.55	3.3±0.52	1.34±0.52	25.64±0.55	855.1±0.44
F-II	19.74±0.47	0.43±0.57	6.5±0.54	1.20±0.55	17.30±0.5	977.8±0.42
F-III	15.13±0.50	0.53±0.51	7.3±0.58	1.09±0.49	8.62±0.547	1035.4±0.47
F-IV	22.49±0.58	0.34±0.45	2.3±0.55	1.23±0.52	19.04±0.57	890.75±0.49
F-V	17.78±0.56	0.38±0.59	4.1±0.49	1.17±0.57	15.55±0.44	1034.6±0.53
F-VI	13.44±0.51	0.54±0.51	5.3±0.55	0.93±0.49	5.55±0.47	1101.5±0.54
F-VII	16.79±0.52	0.534±0.8	0.64±0.52	1.205±0.54	17.2±0.23	14.9±0.52
F-VIII	16.18±0.6	0.44±0.39	0.52±0.45	1.170±0.65	14.91±0.2	19.5±0.45
F-IX	16.95±0.32	0.52±0.52	0.67±0.65	1.181±0.52	15.3±0.9	25.7±0.25
F-X	17.99±0.3	0.49±0.65	0.72±0.35	1.43±0.35	30.1±0.8	15.6±0.65
F-XI	17.68±0.8	0.45±0.25	0.73±0.85	1,551±0.2	35.7±0.82	19.2±0.32
F-XII	18.91±0.96	0.55±0.42	0.65±0.95	1.21±0.5	17.9±0.62	26.3±0.98

Table 2: Drug Content

S/No	Formula code	Encapsulation efficiency	%yield	Drug content(mg)
1	F-I	61.12	72.00±0.32	30.56
2	F-II	55.30	77.50	27.65
3	F-III	77.26	81.50	38.63
4	F-IV	55.08	74.00	27.54
5	F-V	51.52	76.40	25.76
6	F-VI	59.96	79.50	29.98
7	F-VII	67.00	76.50	33.50
8	F-VIII	72.10	78.00	36.05
9	F-IX	79.00	81.50	39.50
10	F-X	71.00	79.00	35.50
11	F-XI	77.00	82.00	38.50
12	F-XII	82.10	84.50	39.00

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The aceclofenac loaded microspheres prepared by solvent evaporation technique are found to be discrete, spherical, free flowing and particle size in the range of 14-26µm.

SEM photographs of aceclofenac microspheres formulated by employing emulsion cross linking method and solvent evaporation technique[15]

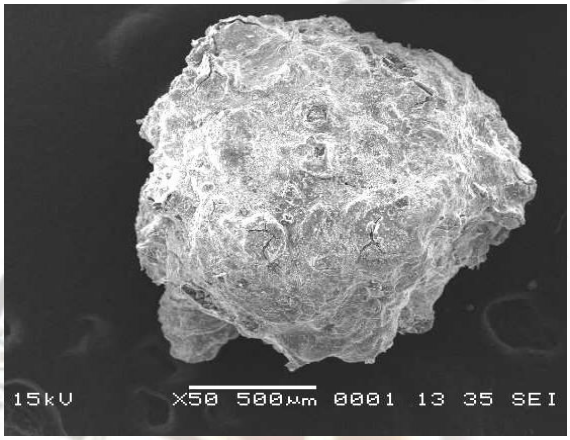

Fig. 1: Gelatin Microspheres

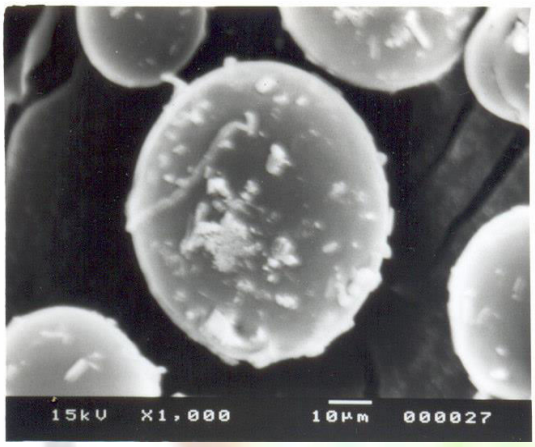

Fig. 2: Eudragit Microspheres

Table 3: Release data of aceclofenac microcapsules formulated by emulsion crosslinking method&solvent evaporation method

Cummulative percentage of aceclofenac released

T (Hrs)	F-I	F-II	F-III	F-IV	F-V	F-VI	F-VII	F-VIII	F-IX	F-X	F-IX	F-XII
0	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**
1	21.489 ±0.71	18.160 ±0.45	11.883 ±0.65	15.379 ±0.76	19.383 ±0.89	13.490 ±0.45	0.785 ±0.25	1.012 ±0.12	1.032 ±0.35	0.785 ±0.35	1.012 ±0.3	1.032 ±0.85
2	33.31 5±0.56	29.621 ±0.76	25.741 ±0.87	29.256 ±0.87	28.278 ±0.52	27.323 ±0.85	1.750 ±0.36	1.752 ±0.24	1.747 ±0.82	1.734 ±0.36	1.752 ±0.32	1.712 ±0.45
3	43.106 ±0.76	41.149 ±0.98	35.417 ±0.87	37.633 ±0.74	41.150 ±0.56	37.664 ±0.96	29.185 ±0.92	26.914 ±0.22	25.69 ±0.62	28.195 ±0.22	26.697 ±0.32	25.696 ±0.62
4	52.956 ±0.77	50.985 ±0.56	43.206 ±0.98	45.880 ±0.23	49.417 ±0.76	45.509 ±0.24	41.057 ±0.82	37.550 ±0.62	35.09 ±0.92	41.057 ±0.39	37.550 ±0.92	35.066 ±0.22
5	63.035 ±0.21	59.131 ±0.78	51.134 ±0.67	55.570 ±0.23	57.554 ±0.36	53.109 ±0.65	55.266 ±0.32	52.788 ±0.92	47.752 ±0.92	55.366 ±0.75	52.784 ±0.32	47.418 ±0.12
6	75.091 ±0.12	69.147 ±0.98	55.784 ±0.45	67.061 ±0.46	67.482 ±0.96	61.105 ±0.35	70.601 ±0.92	66.71 ±0.382	57.047 ±0.98	70.061 ±0.89	65.712 ±0.82	57.047 ±0.32

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7	87.096 ±0.65	77.312 ±0.12	63.779 ±0.53	75.292 ±0.76	77.389 ±0.79	71.208 ±0.45	83.049 ±0.23	74.944 ±0.35	68.81 6±0.39	85.049 ±0.65	74.944 ±0.39	68.896 ±0.82
8	97.648 ±0.76	87.896 ±0.21	71.467 ±0.65	87.558 ±0.65	87.782 ±0.52	81.135 ±0.76	98.641 ±0.98	86.890 ±0.36	76.963 ±0.33	99.661 ±0.33	86.896 ±0.36	76.964 ±0.92
9	-	98.309 ±0.46	79.370 ±0.12	96.245 ±0.25	96.980 ±0.89	89.515 ±0.66	-	98.450 ±0.35	87.171 ±0.32	-	97.433 ±0.31	87.181 ±0.62
10	-	-	89.763 ±0.32	-	-	96.567 ±0.96	-	--	99.678 ±0.42	-	-	93.675 ±0.22
11	-	-	98.357 ±0.39	-	-	-	-	-	-	-	-	98.513 ±0.42

Table 4: release kinetics studies of the formulations

Batch no	Release model										
	Zero order		First order		Higuchi matrix		Koresmeyer-peppas			Hixson-crowell	
	K0	R0	K1	R1	KH	RH	n	kk	rk	Ks	Rs
F-I	12.67	0.9883	-0.310	0.8729	30.00	0.9666	0.727	20.31	0.9961	-0.071	0.9548
F-II	11.38	0.9880	-0.28	0.8564	28.51	0.9677	0.763	17.76	0.9994	-0.06	0.9525
F-III	9.18	0.9895	-0.22	0.8330	25.25	0.9595	0.831	13.18	0.9958	-0.05	0.9407
F-IV	11.13	0.9947	-0.31	0.7789	27.72	0.9524	0.823	15.45	0.9976	-0.06	0.9170
F-V	11.28	0.9881	-0.27	0.8640	28.24	0.9662	0.738	18.32	0.9973	-0.06	0.9528
F-VI	10.23	0.9925	-0.26	0.8323	26.86	0.9585	0.837	14.22	0.9979	-0.05	0.9433
F-VII	11.51	0.9689	-0.429	0.677	26.09	0.8470	2.36	1.00	0.948	-0.07	0.8520
F-VIII	10.21	0.9760	-	-	24.60	0.8604	2.27	0.9561	0.948	-0.07	0.779
F-IX	9.08	0.9770	-	-	22.99	0.858	2.22	0.83	0.946	-0.06	0.7709
F-X	11.36	0.9695	-0.27	0.8213	25.78	0.8493	2.52	0.768	0.9557	-0.06	0.9043
F-XI	10.60	0.9774	-	-	25.59	0.8652	2.27	0.9853	0.951	-0.07	0.8153
F-XII	9.58	0.9834	-	-	24.42	0.8772	2.13	1.07	0.9505	-0.06	0.8022