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Research Article

Formulation and In Vitro Evaluation of Ibuprofen Loaded Ethyl Cellulose Microspheres

Lakshmanarao.R*, Pavani Priya.G, Saikishore.V
Department of pharmaceutics,
Bapatla college of pharmacy, Bapatla, Guntur, Andhra Pradesh, India
*rapakalakshmanarao@gmail.com

ABSTRACT

Microspheres are well accepted technique to control the drug release from the dosage form to improve bioavailability, reduce absorption difference in patients, reduce the dosing frequency and adverse effects during prolong treatment. The main objective of the present study is to prepare and evaluate ibuprofen microspheres by solvent evaporation method, with water insoluble polymers such as Ethyl cellulose and sodium carboxymethyl cellulose as suspending agent, using as carrier for oral administration in view to achieve oral sustained release of the drug. Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) used for relief of signs and symptoms of rheumatoid arthritis, osteoarthritis and is used in chronic and acute conditions of pain and inflammation. Its biological half-life is 2 ±0.5 hrs. Due to its low biological half-life (2 hrs), it requires frequent administration to maintain plasma concentration. This causes inconvenience to the patient and also leads fluctuations in plasma drug concentration that may cause inferior therapeutic effects or toxic effects. There-fore, development of controlled release dosage forms would clearly be beneficial in terms of decreased dosage requirements, thus increase patient compliance. The formulations were evaluated for particle size distribution analysis, flow properties like Angle of repose, bulk density, tapped density, Hausner's Ratio, Carr's index, Encapsulation efficiency, Scanning electron microscopy, optical electron microscopy and invitro release studies. The optimized formulation showed good invitro sustained release activity of the drug ibuprofen.

Keywords: Ibuprofen, Microspheres, solvent evaporation method, Ethyl cellulose, In vitro drug release

INTRODUCTION

Ibuprofen (*p*-Isobutylhydratropic acid) is a potent non-steroidal anti-inflammatory (NSAID), analgesic and antipyretic drug[1]. It is used in the long term treatment of rheumatoid arthritis, osteoarthritis. Because of shorter biological half-life, ibuprofen should be given frequently to maintain its therapeutic activity. Side effects result in gastrointestinal mucosal damage, irritation and bleeding[2]. It is practically insoluble in water and so possesses poor solubility and subsequent poor GI absorption and bioavailability. Microspheres can be defined as solid, approximately spherical particles ranging from1to1000µm, containing dispersed drug in either solution (or) microcrystalline form. Microspheres are sometimes referred to as microparticles. Microspheres can be manufactured from various natural and synthetic materials. Microspheres are characteristically free-flowing powders consisting of proteins/synthetic polymers that are biodegradable in nature. Microspheres have been of particular interest from the pharmaceutical point of view providing the possibility to achieve sustained

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and controlled drug release. Controlled drug delivery using biodegradable polymeric carries has gained increasing interest in last two decades. Microspheres are small and have large surface-to-volume ratio. At the lower end of their size range they have colloidal properties. The interfacial properties of microspheres are extremely important, often indicating their activity. Microspheres can also offer advantages like limiting fluctuation within therapeutic range, reducing side effects due to decrease in dosing frequency and improving patient compliance. Advantage of Microspheres provide constant and prolonged therapeutic effect[3-9].

Methods of Preparation:

Preparation of microspheres should satisfy certain criteria.

1. The ability to incorporate reasonably high concentrations of the drug.
2. Stability of the preparation after synthesis with a clinically acceptable shelf life.
3. Controlled particle size and dispersability in aqueous vehicles for injection.
4. Release of active reagent with a good control over a wide time scale.
5. Susceptibility to chemical modification.

Ibuprofen is a potential anti-inflammatory and analgesic activity and this is the only approved NSAIDs. Because of shorter biological half-life, ibuprofen should be given frequently to maintain its therapeutic activity. Side effects result in gastrointestinal mucosal damage, irritation and bleeding. It has been reported that in the preparation of the modified release microspheres of the drug, the selection of the proper microencapsulation technique and of the excipients, like polymers and emulsifying agents, play a very important role. Thus, the present research objective was to develop a sustained release formulation containing ibuprofen loaded microspheres.

MATERIALS AND METHOD

MATERIALS:

Ibuprofen (Dr.Reddy's labs Pvt.Ltd, Hyderabad), Ethyl cellulose (Himedia Lab's Pvt Ltd, Mumbai), sodium carboxy methyl celluose. All other chemicals, reagents and solvents were used are of A.R. Grade.

METHOD:

PREPARATION OF MICROSPHERS:

Ibuprofen microspheres were prepared by solvent evaporation method. In this method, the internal phase containing of drug and polymer dissolved in organic solvent like chloroform. Thus the prepared internal phase was added to external phase consisting of sodium carboxy methyl cellulose 200-300cps (NaCMC) 0.5%as suspending agent in distilled water. The mixture was continuously stirred for 2 hours in order to evaporate solvent. After that, the rigidized microspheres formed were collected by filtration and washed three times with 20 ml of water each. Microspheres were dried at room temperature for 24 hrs. Evaluation of the effect of drug: polymer ratio on the physical characteristics of microspheres different ratios of drug to Ethyl cellulose(1:1,1:1.5,1:2 and 1:3) were tried .Formula for different batches of ibuprofen microspheres were shown in below table.2.

EVALUATION OF MICROSPHERES

Calibration curve of ibuprofen :

Stock solution of 1000 µg/ml is prepared by taking 10mg of ibuprofen and dissolve it in methanol and make up with 6.8 pH buffer and prepare further dilutions of 2, 4, 6, 8, 10µg/ml. Calibration curve was shown in Figure: 1

Flow properties of microspheres

The prepared microspheres were evaluated for Angle of repose, Bulk density, Tapped Density, Carr's Index, Hausner's Ratio[10].

Size Distribution and Particle Size Analysis

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The particle size of microspheres was determined by using optical microscopy method in which 100 particles were measured using light microscope[11].

Estimation of ibuprofen content (drug content)

The drug content in each formulation was determined by triturating 100mg microspheres and powder equivalent to average weight was added in 100ml of 6.8 pH phosphate buffer, followed by stirring. The solution was filtered, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 221 nm using 6.8 pH phosphate buffer as blank[12].

Entrapment Efficiency

Entrapment efficiency was calculated using the formula[13].

$$\text{Entrapment efficiency} = \frac{\text{Amount of drug entrapped in microspheres}}{\text{Total amount of drug}} \times 100$$

SEM Analysis

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. The microspheres were then observed with the scanning electron microscope. microspheres size were shown in the figure 2.

Optical Electron microscopy :

The shape of spherical agglomerates is studied by observing them under optical microscope. microspheres shape were shown in the figure 3.

%Yield of Microspheres

Microspheres recovered at the end of preparation were weighed and the yield was calculated as a percentage of the total amounts of polymer and drug added during the preparation of microspheres[14].

$$\%\ \text{Percent yield} = \frac{\text{The Amount of microspheres obtained(g)}}{\text{The theoretical amount (g)}} \times 100$$

Invitro drug release:

The USP dissolution rate testing apparatus was employed to study the release of ibuprofen microspheres of different ratios (F1, F2, F3 and F4) using phosphate buffer PH 6.8 as a dissolution medium.200mg equivalent of ibuprofen containing microspheres was taken a dissolution test was being carried out at 50 rpm maintained at 37°C±0.5°C. 5ml of samples were withdrawn at specific time interval for 8hours. The sample volume was replaced by an equal volume of fresh medium[15]. The concentration was determined spectrophotometrically at 221nm. The percentage of drug release at various time intervals was calculated and plotted against time. Shown in figure: 4.

Stability studies of ibuprofen microspheres

The optimized ibuprofen microspheres were separated in to two groups. Each group of formulations were placed separately in stability chamber which is maintained at 25±5°C/60% RH and 40±5°C/75% RH respectively for three months and every month the formulations from each group were subjected to dissolution studies and % drug release was calculated[16].

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RESULTS AND DISCUSSION

In the present study, it was aimed to develop ibuprofen microspheres using water insoluble polymer as a carrier for oral administration to extend the period of the dosage form.

This process produced uniform microspheres. These microspheres were characterized for size analysis, flow properties, % Drug Content,% Entrapment efficiency. All the formulations offered good flow property. The technique also showed good entrapment efficiency. The micrometric parameters like angle of repose, bulk density and tapped density of all microspheres confirms better flow and packaging properties. All the formulations showed good flow ability represents in terms of angle of repose, Carr's index, and Hausner's ratio. The results are given in Table 3.

The microspheres were found to be discrete, spherical and free flowing. The % yield was found to be in the range of 85%-96%. The mean particle size of the various formulations was found to be in the range of 670-708µm.The results are given in Table 4 and figure 2.

Microspheres prepared with ibuprofen and Ethyl cellulose in 1:1, 1:1.5,1:2 and 1:3 ratios shown sustained drug release for a period of 5 hours,7 hours,8 hours, 9 hours respectively.

The results indicated that the drug release from the microspheres was not changed significantly when stored at varying conditions and the release data was given in table 5, Thus the drug release from microspheres was found be quite stable.

CONCLUSION

Microspheres prepared with ibuprofen and Ethyl cellulose in 1:3 ratio shown sustained drug release for a period of 9 hours. This gave a hope to the possibility of single dose treatment for patients. The formulated ibuprofen microspheres show pharmacotechnical properties in the acceptable range. This study clearly demonstrated that one could develop a sustained release dosage form of a drug having a long biological half-life as a single dose treatment and thus reduce the drug resistance in patients.

Table.1.Calibration curve of ibuprofen

s.no	Concentration(µg/ml)	Absorbance
1	2	0.114
2	4	0.246
3	6	0.323
4	8	0.431
5	10	0.547

R^2:0.9987

Table 2: composition of various formulations of ibuprofen microsperes

Batch code	Ibuprofen (mg)	Ethyl cellulose(mg)	Sodium carboxy methyl cellulose(ml)
F1	500	500	100
F2	500	750	100
F3	500	1000	100
F4	500	1500	100

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Table 3.flow properties of ibuprofen microspheres

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Carr's Index	Hausner's Ratio	Angle of repose
F1	0.276±0.014	0.314±0.013	12.10±0.024	1.137±0.012	26.94±0.021
F2	0.350±0.012	0.408±0.011	14.21±0.022	1.161±0.014	25.6±0.031
F3	0.320±0.020	0.370±0.009	11.89±0.009	1.134±0.017	25.42±0.052
F4	0.331±0.011	0.354±0.024	12.25±0.012	1.122±0.010	25.22±0.046

Table 4.Evaluation Tests of ibuprofen Microspheres Formulated with ethyl cellulose.

Formulation code	Average Particle Size(μ)	% yield	%Encapsulation Efficiency	%Drug content
F1	670	85	88.5	93
F2	682	92	94	91
F3	705	95.4	95.5	92
F4	708	96	95	97

Table:5 Stability studies of best formulation according to ICH guidelines

S.NO	Time (hrs.)	% drug release (mg)						
		Initial	25±5°C/60% RH			40±5°C/75% RH		
			1st month	2nd month	3rd month	1st month	2nd month	3rd month
1	0.5	09.47	09.42	09.13	09.06	08.95	08.87	08.76
2	1	11.09	11.02	10.56	10.44	10.75	10.86	10.62
3	1.5	16.73	16.41	16.22	16.36	16.50	15.69	15.42
4	2	19.82	19.49	19.55	19.06	18.56	18.47	18.35
5	2.5	22.07	22.01	21.68	21.72	21.60	21.55	21.41
6	3	26.27	26.16	26.12	26.08	26.01	25.68	25.54
7	3.5	29.13	29.04	29.02	28.78	28.54	28.41	28.37
8	4	33.08	33.01	32.84	32.72	32.58	32.64	32.44
9	4.5	46.56	46.43	46.31	46.25	46.12	46.09	45.62
10	5	48.91	48.52	48.46	47.81	47.55	47.31	47.26
11	5.5	56.07	55.77	55.62	55.44	55.24	55.13	55.02
12	6	62.23	62.20	62.15	62.08	61.58	61.49	61.42
13	6.5	71.22	71.16	71.01	70.58	70.41	70.33	70.27
14	7	79.24	79.22	79.18	79.15	79.09	78.84	78.56
15	7.5	83.60	83.51	82.46	82.31	81.42	81.37	81.23
16	8	93.91	93.88	93.75	93.68	93.51	93.43	92.88
17	8.5	97.57	97.50	97.42	97.27	96.33	96.46	96.21
18	9	99.63	99.54	99.48	99.35	99.24	99.12	98.56

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Figure:1 standard calibration curve of ibuprofen

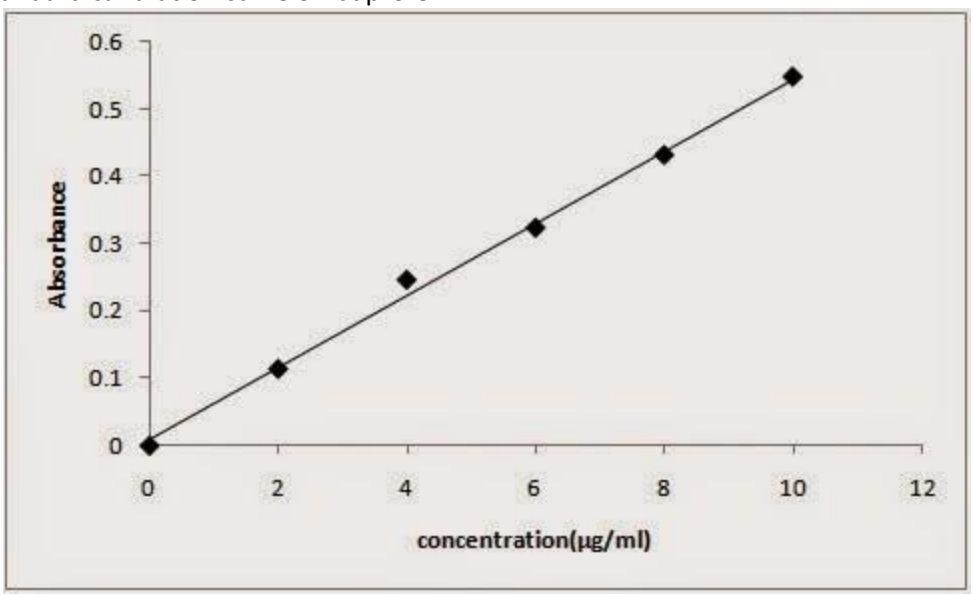

Figure:2 SEM Photograph showing particle size of microspheres

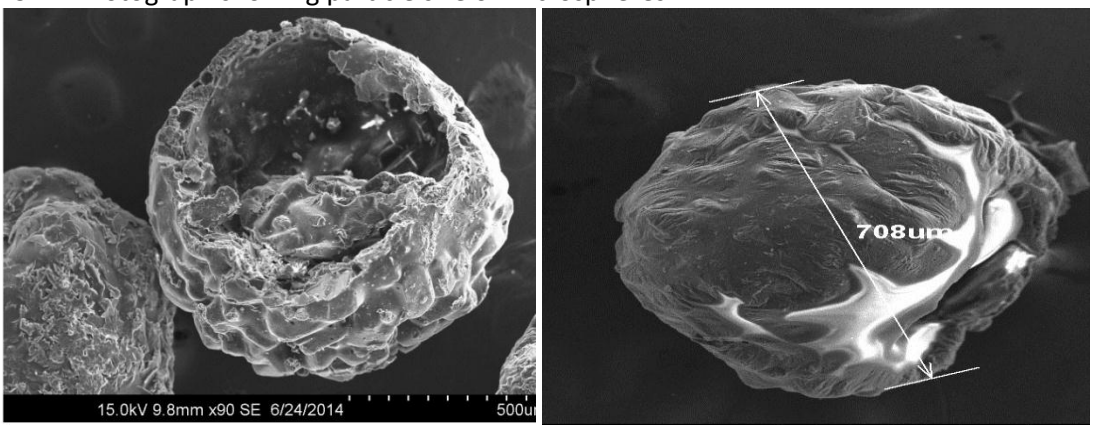

Figure:3 optical electron microscopy Photograph showing particle size of microspheres

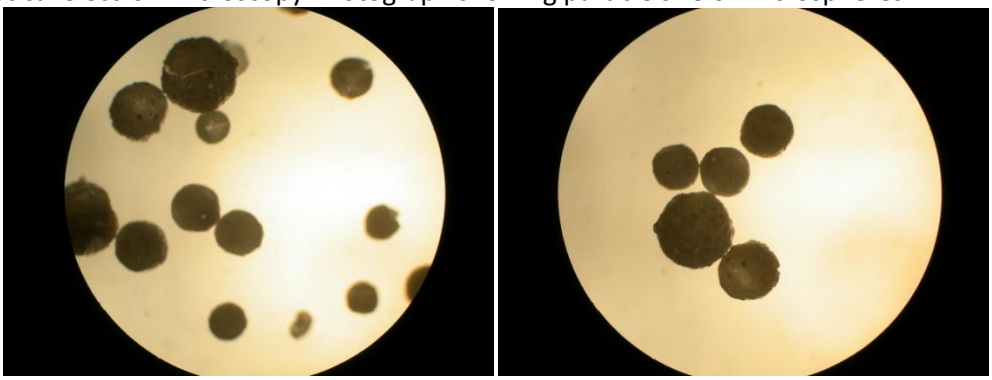

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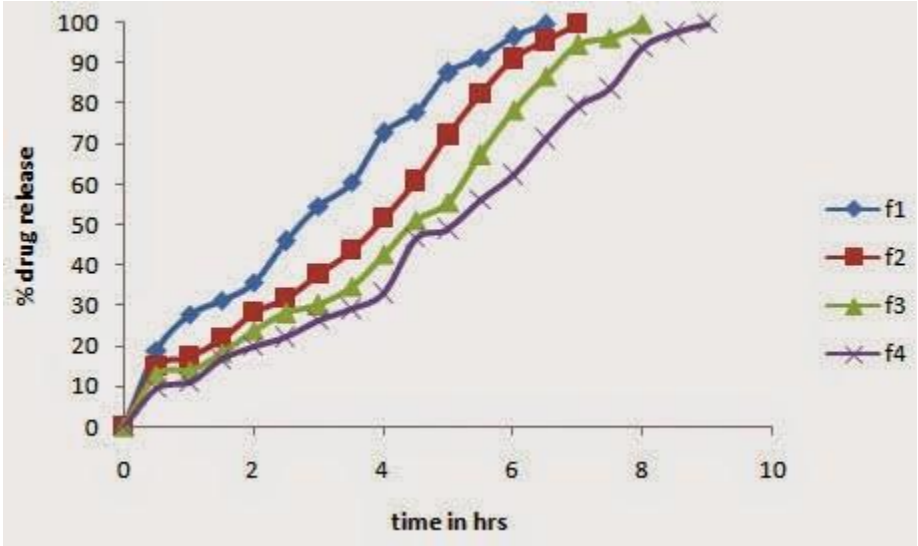
Figure:4 In-vitro Zero order release profile plot of ibuprofen microspheres prepared with Ethyl cellulose in different ratios



F_1: Formulation prepared with 1:1 ratio of drug and polymer.
F_2: Formulation prepared with 1:1.5 ratio of drug and polymer.
F_3: Formulation prepared with 1:2 ratio of drug and polymer.
F_4:formulation prepared with 1:3 ratio of drug and polymer.

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