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Research Article

Preparation and Evaluation of Mefenamic Acid Loaded Microspheres Using Eudragit by Solvent Evaporation Technique

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ABSTRACT

The aim of the present investigation is to prepare mefenamic acid loaded Eudragit microsphere by solvent evaporation technique. Total seven formulations were prepared by altering drug to polymer. The obtained microspheres were evaluated for drug content, entrapment efficiency, loading capacity and surface morphology. *In vitro* dissolution profile of all the seven formulation was compared. Among all the formulations F3 formulation was found to be the best formulation with a product yield pf 83%, drug content of 87%,. The entrapment efficiency and loading capacity was observed as 93% and 79% respectively. In a time period of 12 hrs 98.5% of drug was released from F3 formulation.

INTRODUCTION

Microsphere are defined as "structure made up of continuous phase of one or more miscible polymer in which drug particles are dispersed at the molecular or macroscopic level. It has a particle size of (1-1000nm). [1, 2]

The drug has to be delivered for a prolonged period of time and many medicines have to be taken simultaneously in case of chronic patients. Frequent administration of drug is necessary when those have shorter half – life and all these leads to decrease in patient's compliances [3, 4] The controlled release dosage form maintain relatively constant drug level in the plasma by releasing the drug at a predetermined rate for an extended period of time [3,4].

Microsphere can be prepared by various natural and synthetic materials. A number of drugs have been encapsulated into microsphere including anticancer drugs, antibiotics, antidebatics, NSAID, hormones, proteins/peptides and tissues. There are two types of microsphere; microcapsules and micromatrices , which are described as, microcapsules are those in which entrapped substances in distinctly surrounded by distinct capsule wall and micromatrices in which entrapped substances is dispersing throughout the microsphere matrix.

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Solid microspheres incorporating a drug dispersed or dissolved through particle matrix has the potential for the controlled release of drug [5, 6].

Microsphere, as carrier for drug is one approach which can be used in a sustained controlled release fashion. The range of technique for the preparation of microsphere offers a variety of opportunities to control drug administration issue.

One such microsphere as carrier of drug becomes an approach of controlled release dosage form in novel drug delivery system [7].

Mefenamic acid has prescribed as NSAID and used as first line therapy for the treatment of ailments such as Arthritis and Dysmenorrheal and its half-life t1/2 1.5-2hrs. It is considered to be a BCS Class II drug (low soluble and high permeable). Mefenamic acid binds the prostaglandin syntheses receptors COX-1 and COX-2, inhibiting the action of prostaglandin synthesis. As these receptors have a role as a major mediator of inflammation, the symptoms of pain are temporarily reduced. Eudragit is non-biocompatible, non-biodegradable. Mefenamic acid has biological life of 1.5-2hrs. Because of its short half life mefenamic acid is a suitable candidate for drug delivery [8, 9].

Controlled release refers to the delivery of drug with the objective of releasing the drug into the

patient at a predetermined rate at specific times or with a specific release profile. Microspheres of biodegradable or non biodegradable polymers have been investigated depending upon final application. Biodegradable polymers have many advantages that they degrade in biological fluids. They can be injected, implanted and inserted into the body. They are non- toxic and surgical removal of the polymer skeleton is not required [10, 11].

Need and Objective of the Study

The treatment for arthritis is to reduce pain and improve the function of joints. The drug used in the investigation is mefenamic acid. Mefenamic acid is a widely prescribed NSAID and used s first line therapy for the treatment of ailment such as Arthritis and Dysmenorrhea. MA is available as tablets, capsules and suspensions. MA has a wide range of gastrointestinal disorder, like gastrointestinal bleeding and gastric upset, hypertension. MA biologically half-life is 1.5-2hrs; frequent administration of drug to maintain the desired steady state level is required. Its usual dose is 200-400mg twice day [12, 13].

MATERIALS AND METHODS

Materials

Drug: Mefenamic acid was supplied as a gift sample from Sigma Aldrich Chemicals Pvt. Ltd., Bangalore

Polymer: Eudragit s100.

Organic solvent: Isopropyl alcohol.

Methodology

Preparation of Mefenamic Acid Microspheres by Solvent Evaporation Method

Various parameters were optimized for the preparation of microsphere such as organic solvents (isopropyl alcohol), stirring speed (700rpm) , organic solvent to aqueous phase ratio (1:10) . Eudragit was dissolve in isopropyl alcohol to form a homogenous solution. Mefenamic acid was taken in a homogenous solution and mixed thoroughly. Dispersion was then added as a thin steam to 100ml of aqueous mucilage of 0.5% sodium cmc contained in 250 ml beaker while being stirring at 700rpm to emulsify. Then solvent was removed by continuous stirring at room temperature for three hours to produce spherical microsphere. Then the microspheres were collected by filtration and were air dried [14, 15].

Table 1: List of formulations

Formulation	Ratio
F1	1:1
F2	1:1.5
F3	1:2
F4	1:2.5
F5	1.5:1
F6	2:1
F7	2.5:1

Characterization and Evaluation of Microspheres

The microspheres prepared by the above techniques were characterized for

1) Particle size.
2) Percentage yield.
3) Drug content.
4) Entrapment efficiency.
5) Invitro drug release.

Scanning Electron Microscopy (SEM)

Suspension was made to obtain Photomicrographs of the mefenamic acid loaded microspheres using the SEM Scanning Electron Microscopy is used to determine the shape, size and surface morphology of the microspheres**.**

Percentage Yield

The yield of the prepared formulations was calculated as the percentage of the weight of the dried product at room temperature compared to the theoretical amount. Product yield is calculated by using the following Equation.

$$\textbf{Product yield=} \frac{\text{Weight of the product}}{\text{Weight of raw material}} \times 100$$

Drug Content

Accurately weighed microsphere samples. The powdered microspheres were dissolved in adequate quantity of isopropyl alcohol in two necked round bottomed Flask. With the help of mechanical stirrer allow it to stir for 3 hours and then filter. The UV absorbance of the filtrate was measured using a UV spectrometer at 285nm [16].

$$\textbf{Drug Content} = \frac{\text{Practical drug content}}{\text{Theoretical drug content}} \times 100$$

Entrapment Efficiency

The prepared formulations were examined for entrapment efficiency. 10mg of the prepared formulation was taken in equivalent quantity of

Table 2: Percentage yield, Drug content, Entrapment efficiency and Loading capacity of all formulations.

Formulation	Percentage yield	Drug content	Entrapment efficiency	Loading capacity
F1	71%	85%	89%	29%
F2	80%	81%	91%	34%
F3	83%	87%	93%	59%
F4	72%	70%	90%	48%
F5	76%	73%	90%	47%
F6	81%	66%	92%	42%
F7	50%	73%	91%	39%

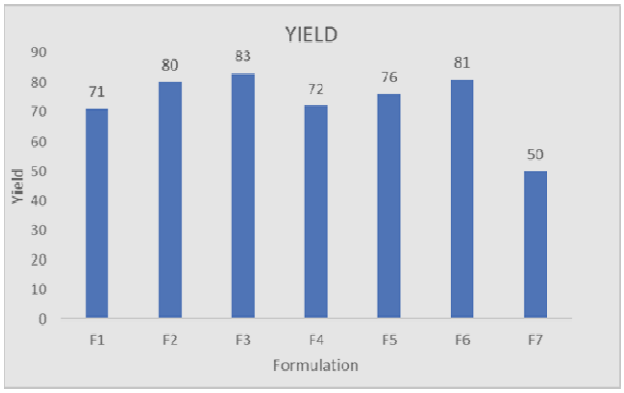

Figure 1: percentage yield of mefenamic acid loaded eudragit s100 microsphere.

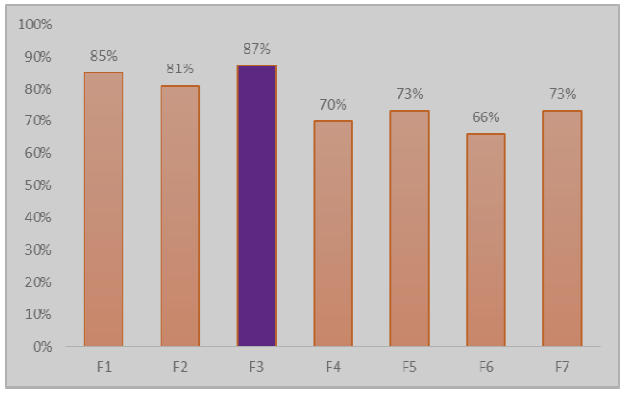

Figure 2: Drug content of mefenamic acid loaded eudragit s100 microsphere.

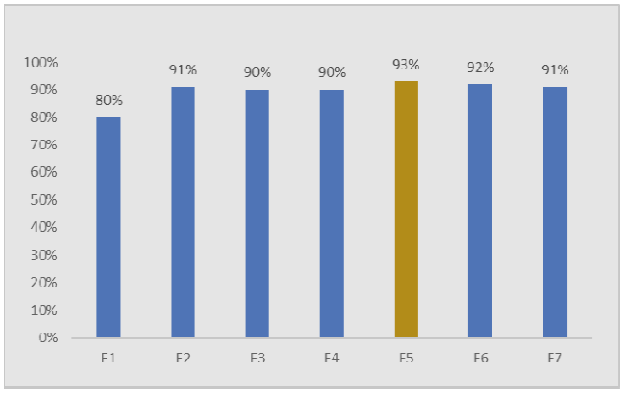

Figure 3: Entrapment efficiency of mefenamic acid loaded eudragit s100 microsphere

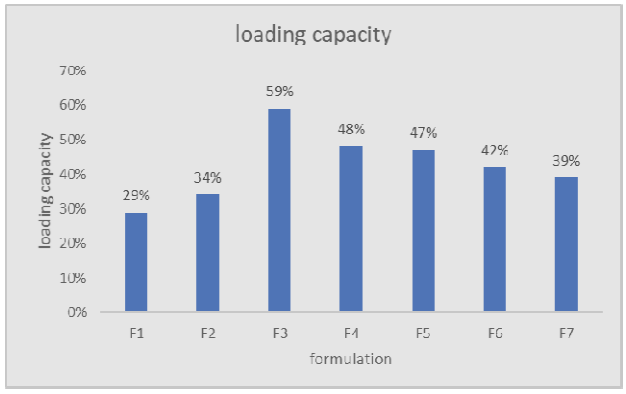

Figure 4: Loading capacity of mefenamic acid loaded eudragit s100 microsphere

7.4 phosphate buffer. The suspension is ultra-centrifuged at 17240rpm for 40 minutes [17].

EE= Total amount of drug- Amount of drug in supernatant / Total amount of drug × 100

In vitro Dissolution Release Study

The dissolution rate testingapparatus was employed to study thedrug release of mefenamic acid using phosphate buffer pH 7.4 as a dissolution medium.25mg equivalent of mefenamic acid microsphere was taken in a dissolution test was carried out at 50rpm maintained at 37ºC±0.5ºC.1ml of sample were withdrawn at specific time interval for 12hrs. The sample volume was replaced by equal volume of fresh medium. The concentration was determined in spectrophotometer at 285nm.The same procedure was repeated for other formulations.

RESULTS AND DISCUSSION

The prepared microspheres using eudragit as a polymer seven formulations F1, F2, F3, F4, F5, F6 and F7 were evaluated for product yield, drug content, entrapment efficiency, and *in vitro* drug

release. The drug content results for F1, F2, F3, F4, F5, F6 and F7 was found to be 85%, 81.1%, 87%, 70%, 73%, 66%, 73% among all the seven formulation F3 was found to be 87%. Entrapment efficiency and loading capacity of F1, F2, F3, F4, F5, F6, F7 was found to be 89%, 91%, 90%, 90%, 93%, 92%, 91% and 79%, 74%, 77%, 63%, 68%, 61%, 66%. Among all seven formulations F5 was found to be 93% and loading capacity of F1 was found to be 79%. And *In vitro* drug release study for F1, F2, F3, F4, F5, F6, F7 was found to be 63.57%, 62.58%, 98.75%, 72.55%, 86.64%, 91.09%, 84.87%. Among all the formulation of microsphere F3 formulation was found to be best by 98.75% at 12hrs.

Percentage Yield

The prepared formulations were evaluated for percentage yield. The percentage yield of prepared seven formulation F1, F2, F3, F4, F5, F6 and F7 was found to be 71%,80%,83%,72%,76%81%, 50% respectively. Among all F3 formulation was showing highest percentage yield.

Drug Content

The prepared formulations were evaluated for drug content. Drug content of F1, F2, F3, F4, F5, F6 and F7 was found to be 85%, 81.1%, 87%, 70%, 66%, 73% respectively. Among all F3 formulation was showing highest drug content.

Entrapment Efficiency

The prepared formulations were evaluated for entrapment efficiency. Entrapment efficiency of F1, F2, F3, F4, F5, F6 and F7 was found to be 80%, 91%, 93%, 90%, 90%, 92%, and 91% respectively. Among all F3 formulation was showing highest entrapment efficiency.

Loading Capacity

The prepared formulations were evaluated for loading capacity. Loading capacity of F1, F2, F3, F4, F5, F6 and F7 was found to be 29%, 34%, 59%, 48%, 47%, 42%, and 39% respectively. Among all F3 formulation was found to be showing highest loading capacity.

***In vitro* Release Studies**

In vitro drug release studies were performed for all the formulation by orbital shaking method. Weighed quantity of microsphere was dissolved in 25ml of phosphate 7.4PH buffer. They were kept in orbital shaker at 100rpm at 37ºC for 12hrs. 2.5ml aliquots were withdrawn at 30mins, 1hr, 2hr, 3hr, 4hr, 5hr, 6hr, 7hr, 8hr, 9hr, 10hr, 11hr, 12hr replaced by buffer each time. Then the withdrawn samples were analysed in U.V. spectrophotometer at 285nm with necessary dilutions.

Cumulative % of drug release profile of the formulation prepared by solvent evaporation method:

All the 7-formulationprepared by solvent evaporation method i.e., F1, F2, F3, F4, F5, F6, F6, F7 were compared for drug release profile.

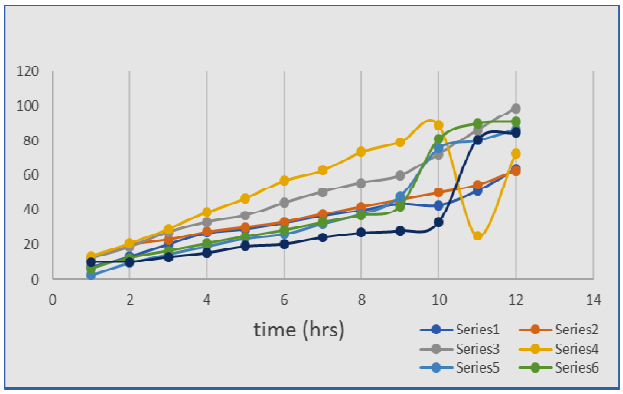

Figure 5: comparative invitro drug release of mefenamic acid loaded eudragit microsphere formulation.

In vitro drug release of F1, F2, F3, F4, F5, F6, F7, was found to be 63.5%, 62.58%, 98.7% , 72.5%, 86.6%, 91.0%, 84.8% respectively. Among all formulation F3 formulation was found to be sustained for 12hrs with 98.7% drug release rate.

Comparison of Best Formulation with Various Kinetics Models

Several plots (zero order plot, first order plot, higuchi plot and peppas plots) were drawn in order to known the release kinetics and drug release mechanism.

Table 4: Kinetic parameter of mefenamic acid loaded Eudragit microspheres

Formulation	Zero order plot (R^2)	First order Plot (R^2)	Higuchi plot (R^2)	Peppas plot (n)
F3	0.9762	0.6116	0.9177	0.8041

From the result, it was concluded that the drug release was following zero order kinetic with fickian diffusion mechanism.

Table 3: *In vitro* drug release data for microsphere using Eudragit s100 polymer

S. no	% cumulative Drug release	Log % remaining	Log % cumulative drug release	Time (hrs)	Log t	T1/2
1	12.50	1.942	1.096	1	0	1
2	18.75	1.909	1.273	2	0.30	1.414
3	27.34	1.861	1.436	3	0.477	1.732
4	33.07	1.825	1.519	4	0.602	2
5	36.85	1.800	1.566	5	0.698	2.236
6	44.16	1.746	1.645	6	0.778	2.449
7	50.39	1.695	1.702	7	0.845	2.645
8	55.77	1.645	1.746	8	0.903	2.828
9	59.77	1.604	1.776	9	0.954	3
10	72.18	1.444	1.858	10	1	3.162
11	86.02	1.145	1.934	11	1.041	3.316
12	98.75	0.0969	1.994	12	1.079	3.464

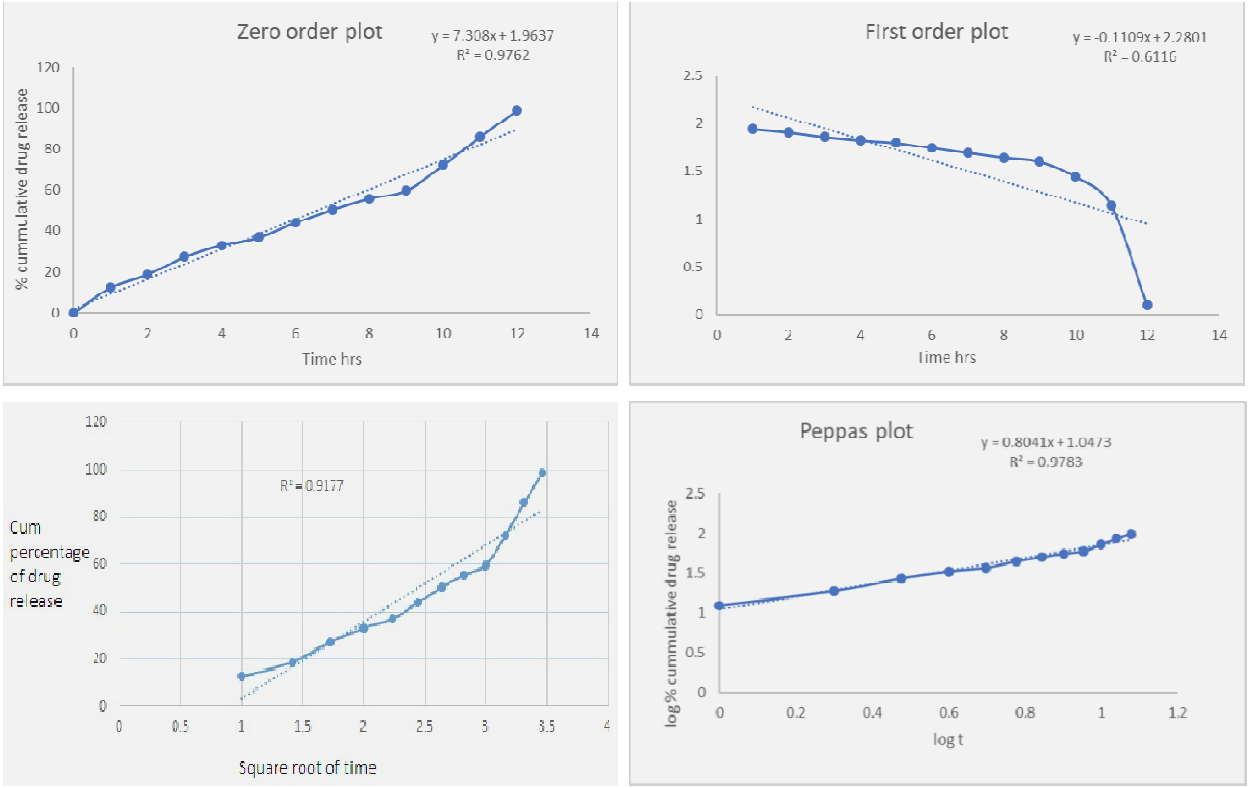

Figure 6: Kinetic plots of best formulation of mefenamic acid loaded eudragit S100 polymer.

CONCLUSION

Microsphere has been prepared by solvent evaporation method using Eudragit as synthetic polymer. Process parameters have been optimized as organic: aqueous ratio, different organic solvent, different speed. Seven formulations were prepared by varying drug: polymer ratio. Out of seven formulation F3 formulation i.e.,(1:2) drug :polymer ratio was found to best formulation with the product yield pf 83%, drug content of 87%,. The entrapment efficiency and loading capacity was observed as 93% and 79% respectively. In a time period of 12 hrs 98.5% of drug was released from F3 formulation.

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