

## Formulation and Characterization of Meloxicam Loaded Microspheres Intended for the Treatment of Rheumatoid Arthritis

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**Abstract:** The present work was to prepare and evaluate colon specific meloxicam loaded microspheres for the treatment of rheumatoid arthritis. Sodium alginate microspheres were prepared by using emulsification method using different ratios of sodium alginate (1:1, 1:2, 1:3 and 1:4). Prepared microspheres were coated with eudragit S100. The microspheres were characterized for different physical parameters such as particle size, particle size distribution, shape, percent entrapment efficiency, FTIR studies, in vitro drug release studies and stability studies. The SEM studies of coated microspheres showed smooth spherical surface and size ranged from 584-890nm. The release studies of coated microspheres were performed and showed good release retardation in 0.1N HCl (2hr), pH 4.5 (2hr) and had a controlled released in pH 7.4 (up to 24hr).

**Keywords:** Emulsification method, Eudragit microspheres, Meloxicam microspheres, NSAID microspheres, Sodium alginate microspheres.

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### I. Introduction

Rheumatoid arthritis, an auto immune disorder is a present day prevailing disease for which complete cure was not yet discovered. Medications for treating immune responses are of main use for chronic arthritis patients but inflammation conditions can only be treated by NSAIDS, which gives symptomatic relief. Though it will not cure the disease it will be a necessary adjunctive therapy for symptomatic relief of chronic patients causes the mobility and relieves the pain. As NSAIDS have severe disadvantages, it becomes a study to invent the ways to effectively deliver them avoiding the difficulties associated with them. One such approach is the polymeric microspheres, a novel drug delivery system which overcomes almost all the problems associated with meloxicam<sup>[1, 2]</sup>. The choice of polymer should be based on the disadvantages associated with API for e.g. if the drug is extremely irritant to gastric mucosa the polymer should be gastro resistant material. Factors such as repetitive dosing and unpredictable absorption lead to the concept of oral sustained release (SR) drug delivery systems. Release of a drug after lag time i.e. chronopharmacotherapy, of disease which show circadian rhythm in their pathophysiology<sup>[3]</sup>. The present investigation is to prepare meloxicam microspheres to reduce the toxic effect of the drug, avoid repetitive dosing and delay release of drug to treat rheumatoid arthritis. The short half life and the low single administration dose make meloxicam a very good candidate for the formulation of sustained release<sup>[4]</sup>.

### II. Materials And Methods

Meloxicam is a gift sample from TRIDENT pvt ltd, Hyderabad, India. Sodium alginate, calcium chloride, acetone, iso propyl alcohol was purchased from SD fine chemicals. Eudragit S100 was purchased from Himedia laboratories. All other materials used were of pharmaceutical grade.

#### 2.1 Method of Preparation

The colon specific microspheres of meloxicam were prepared by emulsification method using sodium alginate as a polymer. 100mg of meloxicam was dispersed in 4%w/v of sodium alginate solution and emulsified in liquid paraffin oil containing (1%v/v) span80 at 70<sup>0</sup>C using a mechanical stirrer at 1000rpm for about 1hr to form a stable w/o emulsion. 5%w/v calcium chloride solution was added drop wise using a syringe in the formed emulsion at the rate of 2ml/min, maintained stirring (1000rpm) for more 10min at 70<sup>0</sup>C. The formed solution was cooled rapidly to about 15<sup>0</sup>C and then added to 50ml acetone. Microspheres were collected by filtration and washed 4-5 times with cyclohexane to remove excess liquid paraffin. Finally the microspheres were dried at room temperature<sup>[5]</sup>.

## **2.2 Encapsulation of Core (Meloxicam) Microspheres**

Varying the core to coat ratio different formulations of coated meloxicam microspheres were prepared. Core microspheres were dispersed in 10% w/v of eudragit S100 solution (solvent used was methanol and dichloromethane in 1:4 ratio). The eudragit S100 solution and core microspheres dispersed were emulsified in liquid paraffin containing 1% v/v of span80 by a mechanical stirrer at 1000rpm and stirring was continued for about 2hrs until the solvent evaporates. The coated microspheres were separated by filtration and washed 4-5 times with cyclohexane to remove liquid paraffin and dried at room temperature <sup>[6]</sup>.

## **2.3 Evaluation of Meloxicam Microspheres**

### **2.3.1 Particle Size**

Average particle size determination of the prepared meloxicam microspheres were carried out by optical microscopy using eye piece micrometer (previously calibrated with stage micrometer). Microspheres were suspended in distilled water and 2-3 drops of the suspension was spread on a clean glass slide and average sizes of 100 microspheres were determined in each formulation.

### **2.3.2 Angle of Repose**

Angle of repose of prepared meloxicam microsphere was determined by employing fixed fennel method <sup>[7]</sup>, using the following equation:

$$\text{Angle of repose } (\phi) = \tan^{-1}(h/r) \quad (1)$$

Where h = height of the pile.

r = radius of the pile.

### **2.3.4 Percentage Yield**

The total weight of the prepared microspheres was taken and considered as practical yield. The total weight of the drug, polymer and all other nonvolatile components used in the preparation of microspheres were considered as theoretical yield. The percentage yield was calculated by using the formula :

$$\% \text{ yield} = \frac{\text{Practical yield} \times 100}{\text{Theoretical yield}} \quad (2)$$

### **2.3.5 Entrapment Efficiency**

In 50ml volumetric flask 50mg of crushed microspheres were taken and dissolved in methanol and the volume was made up to the mark with pH 7.4 and stirred for 12hr. After stirring, the solution was filtered through whatman filter paper <sup>[8]</sup>. From the filtrate appropriate dilutions were made and absorbance was measured at 337nm (using shimadzu UV spectrophotometer).

### **2.3.6 Infrared Spectroscopy**

FTIR spectra of meloxicam, sodium alginate, eudragit S100, empty microspheres and prepared microspheres were recorded using IR spectrometer.

### **2.3.7 Scanning Electron Microscopy**

Scanning electron microscopy was carried out to study the shape and surface morphology of the prepared microspheres. Microspheres were coated with gold about 100Å<sup>0</sup> under an argon atmosphere and micrographs were observed.

### **2.3.8 In Vitro Release Study**

Drug release study for the prepared microsphere were performed using USP dissolution test apparatus (apparatus 1, RPM-100, 37±0.5<sup>0</sup>C) for first 2hr in 0.1NHCl (900ml). Then for another 2hr in pH 4.5 (by adding 1.7gm of potassium dihydrogen phosphate and 2.225gm sodium biphospate and adjusting pH by using 1 M NaOH until it is adjusted to pH 4.5). After 2hr, release study was performed in pH 7.4 (adjusted by 1M NaOH) and continued for 24hr. Samples were withdrawn at regular time intervals filtered, diluted and assayed for meloxicam content released, at λ<sub>max</sub> of 337nm using double beam UV-spectrometer. Three trials were carried out for all formulations. From the data percentage drug release was calculated.

### **2.3.9 In Vitro Drug Release Kinetics**

The cumulative drug release data obtained from the optimized formulation was used to calculate the release kinetics i.e. zero order, first order, higuchi's square root of time equation plot and korsmayer-peppas power law equation model <sup>[9]</sup>.

### 2.3.10 Stability Studies

The stability studies for optimized formulation was performed at temperature of  $4\pm 1^{\circ}\text{C}$  in refrigerator, at ambient temperature  $25\pm 2^{\circ}\text{C}$  and  $60\pm 5\%$  RH and in incubator  $40\pm 2^{\circ}\text{C}$  and  $75\pm 5\%$  RH for 3 months.

## III. Results And Discussion

In an attempt to fulfill the objectives of the project, sodium alginate microspheres loaded with meloxicam were prepared and coated with eudragit S100 and were evaluated. The results are as follows.

Under the task of preformulation studies drug characterization, solubility studies and drug excipient incompatibility studies were carried out. The drug sample procured was analyzed for organoleptic properties, melting point and particle size.

### 3.1 API Characterization

#### 3.1.1 Organoleptic Evaluation

Colour: yellow

Odour: odourless

Texture: fine crystalline powder

Melting point:  $242^{\circ}\text{C}$

#### 3.1.2 Solubility Profiles

Solubility of meloxicam was determined by shake flask method in various dissolution media and organic solvents. From the solubility studies it was concluded that meloxicam has more solubility in chloroform and methanol. It is practically insoluble in water.

Table: 1 Solubility Profile of Meloxicam

Medium/Solvent	Solubility (mg/ml)
Acetone	Slightly soluble
Methanol	Slightly soluble
DMSO, DMF	Freely soluble
Ethanol	Slightly soluble
Water	Insoluble

#### 3.1.3 FTIR Studies

The FTIR spectrum of meloxicam in formulations was shown in figures 1 and 2. The spectrum revealed the presence of peaks at  $3287\text{cm}^{-1}$  for  $\text{NH}_2$  stretching,  $2997\text{cm}^{-1}$  for C-H stretch, aromatic,  $2922\text{cm}^{-1}$  for C-H stretch, aliphatic,  $1180\text{cm}^{-1}$  for S=O stretching,  $1618\text{cm}^{-1}$  for  $\text{NH}_2$  scissoring,  $1549\text{cm}^{-1}$  for  $\text{C}\equiv\text{N}$  stretch respectively, indicating that there is no interaction between the drug and excipients used in the study.



Fig 1. FTIR Spectrum of Meloxicam

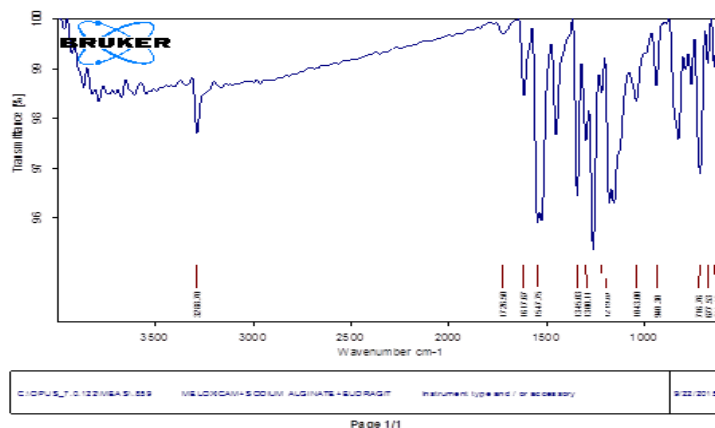


Fig. 2. FTIR Spectrum Of Meloxicam Microspheres

3.1.4 Evaluation of Microspheres on the Basis of Entrapment Efficiency and Percent Yield

Table 2: Percent Yield and Percent Entrapment Efficiency of Prepared Formulations

Formulation Code	Percent Yield	% Entrapment Efficiency	Particle Size
F1	92.2	79	736
F2	92.6	82	740
F3	93.2	86	790
F4	93.8	87	800
F5	95.4	92	830
F6	96.7	90	834
F7	97.3	78	-
F8	97	78.8	-

Percent yield of the prepared microspheres increased with the increase in the polymer concentration from F1 to F8 starting from 92.2% to 97%. The increase in yield may be due to increase in particle size that resulted in efficient filtration. The highest yield observed is 97% but % drug entrapped increased from F1 to F6 but decreased in the case of F7 and F8 may be due to high viscosity because of the increase of the polymer and also that the microspheres formed in F7 and F8 was irregular in size and shape.

3.1.5 Particle size analysis

Particle size analysis was done for the prepared microspheres through optical microscopy, results showed an increment with the increase in polymer concentration but the particle size increase was not much significant.

3.1.6 SEM studies

Optimized formulation was studied for surface characteristics of the particles. SEM studies showed that the shape of the particles varied from spherical to oval shape and showed smooth surface.

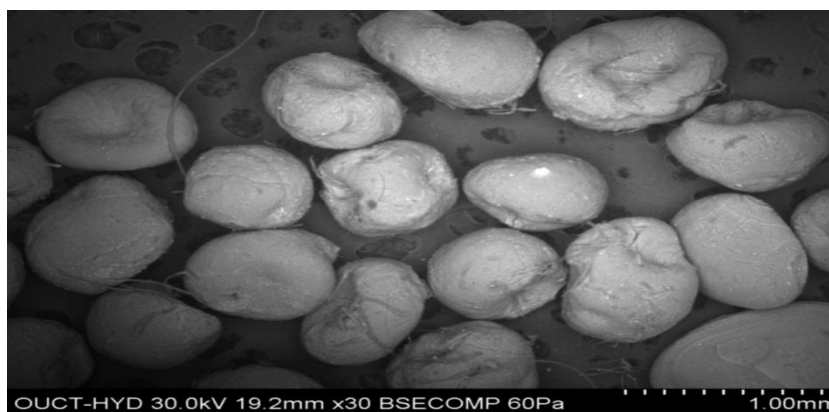


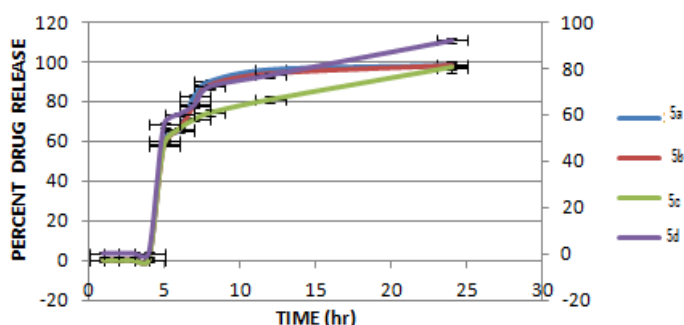
Fig 3. SEM Picture of Optimized Formulation

### 3.1.7 In Vitro Drug Release Study

The drug release study for coated formulations was carried out using dissolution test apparatus.

**Table.3 Cumulative Drug Release from Coated Microspheres**

Time(hr)	F5a	F5b	F5c	F5d
<b>0.1N HCl</b>				
1	0.014±0.01	0.010±0.1	0.00±0.01	0.00±0.0
2	0.020±0.01	0.018±0.01	0.00±0.01	0.00±0.0
<b>pH4.5 Buffer</b>				
3	0.022±0.1	0.021±0.2	0.01±0.0	0.01±0.02
4	0.030±0.1	0.027±0.1	0.04±0.1	0.01±0.01
<b>pH7 Phosphate Buffer</b>				
5	60.07±0.6	58.26±0.2	57.91±0.2	55.62±0.4
6	65.32±1.2	66.13±0.5	66.17±0.7	60.15±0.5
7	82.67±1.6	78.26±1.3	70.98±0.9	64.07±0.8
8	90.02±1.2	88.34±1.6	74.26±1.9	72.16±0.9
12	96.07±1.4	94.27±1.7	80.94±1.8	77.12±1.4
24	98.20±2.10	98.36±2.0	97.29±3.0	92.06±3.0



**Fig 4. Graph Showing Drug Release Profile**

In vitro drug release studies for F5a, F5b, F5c and F5d was performed in 0.1N HCl (2hr), pH4.5 (2hr) and pH7 (up to 24hr). All the four formulations showed very little to no drug release in 0.1NHCl and in buffer pH 4.5. The percent drug release of all formulations showed from 92% to 98% for 24hr, in phosphate buffer of pH7 but F5c was optimized formulation because it had controlled drug release compared to other formulations.

### 3.1.8 Study of Drug Release Kinetics

Different kinetics models were applied to the release kinetics of formulations to determine the drug release kinetics based on the regression coefficient obtained and the obtained data was tabulated. From the obtained regression coefficient, the release kinetics of formulations was determined, which followed the first order release owing to the matrix of polymer. According to the obtained correlation coefficients, it is observed that the release from almost all formulations followed Higuchi kinetics and thus it could be said that the mechanism of release was diffusion rate limited. Based on the Korsmeyer Peppas n value all formulations were found to follow non-Fickian diffusion which infers that release was by both diffusion from polymer and polymer erosion.

### 3.1.9 Accelerated Stability Testing

The stability studies for optimized formulation was performed at temperature of 4±1°C in refrigerator, at ambient temperature 25±2°C and 60±5% RH and in incubator 40±2°C and 75±5% RH for 3 months. Samples were collected at the end of 1 month, 2 month and 3 month and assayed to determine % drug degraded. There is no considerable degradation during the three months period of stability testing.

## IV. Conclusion

The designed site specific delivery of meloxicam from the system may reduce the side effects of the drug caused by its absorption from the upper part of the GI tract when given in conventional dosage forms such as tablets and capsules. The experimental results demonstrated that eudragit S100 coated alginate microspheres have the potential to be used as a drug carrier for an effective colon specific delivery system.

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