

RESEARCH ARTICLE

FORMULATION AND EVALUATION OF MICROSPHERES CONTAINING IMATINIB MESYLATE USING SODIUM ALGINATE BY CHEMICAL CROSS LINKING METHOD***Senthil S Periasamy¹, Nagesh R Sandu², Senthilkumar K Loganathan²**¹The Erode College of Pharmacy and Research, Veppampalayam, Erode, Tamilnadu, India.²Padmavathi College of Pharmacy, Dharmapuri, Tamilnadu, India**Corresponding Author's E-Mail: senthilumasenthil@yahoo.co.in, Phone: +91 - 94433 03975*

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ABSTRACT:

The present research deals with formulation of microspheres containing an Anti-cancer drug Imatinib mesylate reduce the side effects and frequency of dosing. It is currently registered and used for two indications, Chronic Myeloid Leukemia (CML) and Gastrointestinal Stromal Tumors (GISTs). Imatinib mesylate loaded microspheres was formulated by using Sodium Alginate polymer by Chemical CrossLinking method to develop a sustained release dosage form. The effect of concentration of polymer ratio on the microspheres properties like percentage of drug loading, biodegradability, drug release kinetics, particle size, encapsulation efficiency, angle of repose, bulk density, SEM, DSC and XRD were investigated in our study. Moreover, the kinetics of Imatinib Meyslate released from different formulations of microspheres were analyzed using four different theoretical models, that is Zero order, First order, Peppa's and Higuchi models. Microspheres prepared with Glutaraldehyde showed different release kinetics. Increasing the polymer concentration decreased the release rate of Imatinib Meyslate from microspheres because of formation of greater structural strength and more tightly texture with the drug. Besides, microspheres gave an adequate fit to either zero order or first order kinetic models, depending on the extent of cross linking reaction between drug and the cross linking agent.

Key Words: Sodium Alginate, Imatinib Mesylate, microsphere, chemical cross linking, release kinetics.**INTRODUCTION**

Microspheres are defined as homogenous, monolithic particles in the size range of about 1.0 – 1000 μm and are widely used as drug carriers for Sustained release. Administration of the drug in the form of microspheres usually improves the action by providing the localization of the active substance at the site of action and by sustaining the release of drugs. Glutaraldehyde was used as cross-linking agent to extent the release of the drug from the formulation. It may have more advantage to deliver this drug in a sustained release dosage form. The present study was focused on development of sustained release Imatinib mesylate using Chemical Cross linking method. Imatinib Mesylate is currently registered in adults for two indications: (a) monotherapy in Chronic Myeloid Leukemia (CML) and (b) Metastatic Gastrointestinal Stromal Tumors (GISTs).

EXPERIMENTAL**Materials**

Imatinib Mesylate^{1,2} was procured as a gift sample from Natco Pharma Limited, Mumbai (India). Sodium Alginate³⁻⁶ was obtained from Safe Pharma, Narasaraopet as gift sample. All chemicals were of analytical grade and were used without further purification.

Method of preparation⁷⁻⁹

A 4.0% (w/v) Polymer solution in aqueous acetic acid (5.0%) was prepared. This dispersed phase was added to continuous phase (100 mL) consisting of light liquid paraffin and 25ml of Petroleum ether containing 2.0ml of Span 80 in a beaker at room temperature. Stirring was continued at 2000 rpm using a 3 - blade half moon paddle

for 5 minutes. A drop-by-drop solution of a measured quantity (2.5 mL each) of aqueous glutaraldehyde (25% v/v) saturated with toluene was added at 15, 30, 45, and 60 minutes. Stirring was continued for 2.0 hours and separated by centrifugation and washed, first with petroleum ether (60°C - 80°C) four times, once with acetone and then thrice with distilled water to remove the adhered liquid paraffin and glutaraldehyde, respectively. The microspheres were then finally dried at room temperature and stored in vacuum desiccators.

Compatibility studies^{10,11}

One of the requirements for the selection of suitable carrier for pharmaceutical formulation was compatibility. Therefore in the present work a study was carried out by using FTIR spectrophotometer to find out if there are any possible chemical interactions between Imatinib mesylate, sodium Alginate.

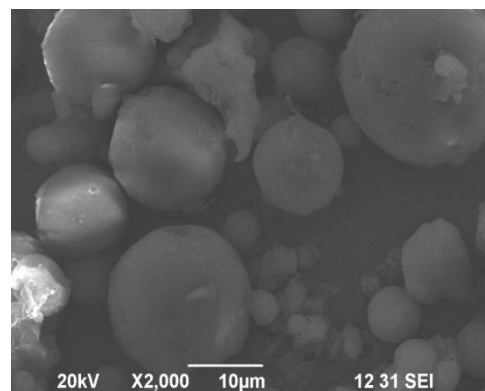


Figure 1: FCC3 Optimised formulation

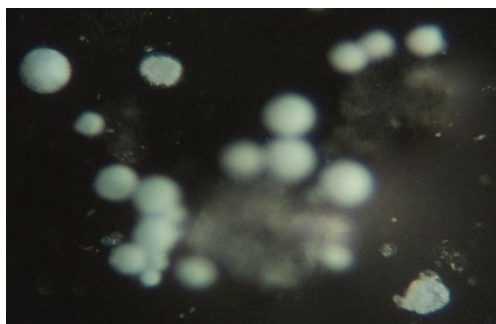


Figure 2: FCC3 Optical microscopic photo

Particle size analysis¹²⁻¹⁴

The microsphere size distribution was determined by the optical microscopy method using a calibrated stage micrometer (μm).

Angle of repose

The fractional force in the loose powder can be measured by the angle of repose. Angle of repose was calculated by static method using fixed funnel method. This was the maximum angle possible between the surfaces of the site of the powder to the horizontal plane.

Determination of bulk density

The bulk density was determined by 3-tap method. Bulk density is defined as, "the mass of powder divided by the bulk volume". The packing characteristics of the powder play an important role in determining physical properties of product.

Table 1: Micromeritic Evaluation of Microspheres

Formulation Code	Particle size	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio
FCC1	100.45 \pm 1.906	21.59 \pm 1.073	0.845 \pm 0.010	0.965 \pm 0.012	12.40 \pm 0.928	1.27 \pm 0.240
FCC2	102.88 \pm 3.042	21.59 \pm 1.532	0.850 \pm 0.002	0.970 \pm 0.021	12.34 \pm 2.068	1.14 \pm 0.027
FCC3	105.08 \pm 1.981	23.11 \pm 0.587	0.846 \pm 0.016	0.970 \pm 0.028	12.64 \pm 4.117	1.15 \pm 0.052
FCC4	104.28 \pm 1.825	23.01 \pm 0.907	0.853 \pm 0.008	0.969 \pm 0.023	9.82 \pm 1.376	1.11 \pm 0.016
FCC5	107.62 \pm 2.385	23.15 \pm 0.530	0.831 \pm 0.020	0.955 \pm 0.014	12.91 \pm 3.443	1.14 \pm 0.044

Determination of drug content

Accurately weighed microspheres equivalent to 25mg of Imatinib mesylate, crushed in glass mortar and pestle and the powdered microspheres were suspended in 100 mL of 0.1N HCl. After 24 hours, the solution was filtered and the filtrate was analyzed for the drug content.

Encapsulation efficiency¹⁵

Encapsulation efficiency was calculated using the following formula;

$$\text{Encapsulation Efficiency} = \frac{\text{Estimated Drug Content}\%}{\text{Theoretical Drug Content}\%} \times 100$$

In-vitro dissolution studies¹⁶

The drug release study was performed using USP XXIII dissolution test apparatus, the capsules filled with equivalent amount of Imatinib Meyslate 100 mg was placed in a basket. The instrument was set at 100 - rpm rotation and at 32°C, 900 mL of 0.1N HCl was filled as dissolution medium for first 2 hours and phosphate buffer pH 7.4 for remaining period. Samples were withdrawn at predetermined intervals, from 0.5 – 24 hours filtered and analyzed spectrophotometrically at 230 nm using corresponding medium as blank. After each withdrawal, the same quantity of fresh medium was replaced immediately.

Kinetic characteristics of the drug release¹⁷⁻¹⁹

To know the mechanism of the drug release from the microspheres, the results obtained from the In-vitro dissolution process were fitted into different kinetic equations as follows:

1. Zero - order drug release: Cumulative % drug release Vs Time.

2. First order drug release: Log cumulative % drug retained Vs Time.

3. Higuchi's classical diffusion equation: Cumulative % drug release Vs Square root of time.

4. Peppas's Korsmeyer Exponential equation: Cumulative % drug release Vs Log time.

'n' values can be used to characterize diffusion release mechanism.

Stability studies²⁰

The Optimised preparation was divided into 3 sets and was stored at 4°C (refrigerator), room temperature and 40°C (thermostatic oven). After 15, 30, 60, 90 drug content and SEM of the formulation was determined.

RESULTS AND DISCUSSION

We formulated 5 formulations using sodium alginate with different ratios. The characterisation of formulations were studied in particle size, angle of repose, bulk density, tapped density, percentage yield, drug content, Hausner's ratio, carr's index and cumulative percentage of drug release. The sustained release microspheres of all batches were found to be spherical and free flowing nature based on the SEM analysis. FTIR studies said that there were no incompatibility between drug and polymer. Formulated microsphere particle size showed the range from 107.62 (FCC5) - 100.45 (FCC1). The angle of repose for the formulated microspheres found to be within the range 23.15-21.59 and showed moderate to good flow in nature. The formulation shows the bulk density values are from 0.970-0.955 indicating moderate flow characteristics of

microspheres. The percentage yield of the formulations were 81.35 (FCC1) - 86.42 (FCC3). The drug content was started from 22.18 (FCC3) to 19.61 (FCC1). The drug encapsulation efficiency was found to be 789.05 - 87.12 and said that drug polymer blend was good to made

microspheres. Stability studies stated that there was not much difference in the drug content and slight difference in the SEM analysis. The In-vitro drug release for all formulation was found to follow Non-Fickian diffusion release kinetics.

Table 2: Evaluation of Microspheres

Formulation Code	% yield	Encapsulation Efficiency	Drug Content	In-vitro Release	'n' Value	R ² Value
FCC1	81.35±0.579	79.05±0.540	19.61±0.374	99.01±0.273	0.637	0.993
FCC2	84.05±0.912	83.71±0.665	20.85±0.692	99.38±0.209	0.615	0.996
FCC3	86.42±0.290	87.12±1.378	22.18±0.470	99.60±0.238	0.615	0.992
FCC4	83.70±0.461	79.47±0.506	21.73±1.070	97.64±0.422	0.540	0.944
FCC5	84.33±0.494	81.37±0.865	20.21±0.420	98.65±0.349	0.630	0.995

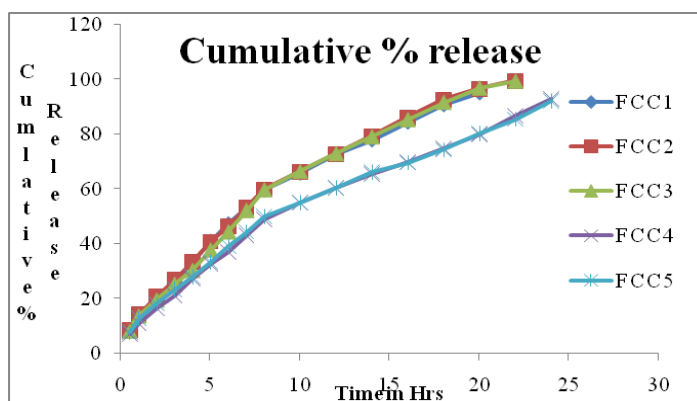


Figure 1: Cumulative % release of Microspheres

CONCLUSION

From our study, it was concluded that the Imatinib Mesylate (α -form) loaded microspheres prepared by cross-linking agent Glutaraldehyde with Sodium Alginate with different ratios showed decreased in the release rate of drug from the formulation depending on the concentration of the polymers. The concentration of the polymers influenced the drug release pattern and polymer impregnation depending upon cross-linking agent. The formulation with drug and polymers in 1:3 ratio (FCC3) with cross linking agent maximum concentration was considered best because, it showed retard drug release in pH 7.4 buffer was found to be 99.60% almost complete and uniform after the 24-hour release study. Drug encapsulation efficiency for formulation (FCC3) was

87.12% w/w and all the remaining parameters were within the prescribed limit. Stability studies showed that the optimised formulation not much altered the drug content and SEM report. Optimised formulations toxicological study was done and observed data were showed that no significance of toxicological difference. As per the results concluded the formulation FCC3 fully satisfy in all expectation.

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