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In vitro Evaluation of Controlled Release Containing Aceclofenac Microspheres

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Abstract

Abstract: the objective of the present study was to microencapsulate Aceclofenac by cross-linking technique using gelatin as polymer; Microspheres were prepared with different polymer and gluteraldehyde concentration. The microsphere was prepared so as to provide control release preparation andto reduce the frequency of medication. The microsphere so prepared were characterized by micromeretic analysis, particle size analysis, Scanning electron microscopy (SEM) and in vitro drug release profile studies. Prepared microsphere was free flowing, non aggregate and slightly yellowish due to sesame oil. Aceclofenac loaded microspheres having a fairly high yield (60-88.39%) were obtained with different polymer ratio.

Key words: *Aceclofenac, microsphere, gelatin , gluteraldehyde , cross linkage*

Introduction :

Aceclofenac is newer derivative of diclofenac belonging to class Non Steroidal Anti Inflammatory drugs (NSAID's) use in treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis having less GIT complication, the short biological half-life 4 h, and dosing frequency more than one time make it an ideal candidate for modified release multiple unit preparation[1,2,3]. To reduce the frequency of administrations and to improve patient compliances, Aceclofenac is suitable for making sustain release dosage form. The microsphere formulation can be use to control the release of

formulation, to increase patient compliance, to overcome various drawbacks of conventional dosage form and to decrease dosing frequency.

Natural polymers such as gelatin were widely used for the preparation of particulate drug delivery. Use of gelatin in pharmaceutics was particularly attractive by virtue of its bicomtability and biodegradability along with a total absence of toxicity and allergic problem.[4] It has been utilized in fabrication of both injectable and oral drug delivery system. Being a soluble polymer, gelatin has to be chemically crosslinked to become insoluble at 37°c. Aldehyde derivative such as formaldehyde, gluteraldehyde or other bifunctional reactants have been used to produce insoluble biodegradable gelatin microsphere. Gluteraldehyde is used as a cross-linking agent to obtain rigid microsphere. Gluteraldehyde is expected to produce cross-linked between gelatin molecules and thereby to slow down the rate of release from microspheres. In this method, it is important that to remove excess oil by washing the particle with solvent such as acetone. Otherwise, the oil retained in microsphere may cause aggregation and alter the morphological properties of the microsphere[5,6]

Material and method:

Aceclofenac was supplied by Emcure Pharmaceutical, Pune while gelatin and Gluteraldehyde was supplied by Qualigens Fine Chemicals, Mumbai. All other chemical used was of analytical grade.

Method of preparation

The microsphere containing aceclofenac were prepared by cross-linking technique using gelatin as polymer. For microsphere preparation as drug & gelatin were dissolved in 10 ml distilled water. The solution was added drop wise to 50 ml sesame oil with 1% v/v span 80 as emulsifying agent as the external phase while being stirrer use magnetic stirrer at 300rpm**.** Then 10% gluteraldehyde (v/v) was added to harden or crosslinked the microsphere. Microspheres were prepared with different polymer and gluteraldehyde concentration; the formulation was stirred at a constant 300 RPM. The prepared microspheres were filtered and washed with distilled water. The crosslinked microsphere was filtered, washed with acetone and dried at room

temperature overnight. Till further use they were stored in a desiccator. Detail of microsphere formulation is given in table below:

Batch Code	Drug: Polymer Ratio(mg)	Gluteraldehyde concentration (%)
F1	200:500	10
F2	200:600	10
F3	200:700	10
F4	200:800	10
F5	200:800	5
F6	200:800	10
F7	200:800	15
F8	200:800	20

Percentage yield: The percentage yield values of microspheres was calculated from the ratio of the total dried and solidify microspheres amount (A) to the totals solid material amount in dispersed phase (B) –

Percentage yield value = [A / B] X 100

Particle size and size distribution

To determine the particle size and particle size distribution, microspheres were taken on a glass slide and sizes of 200 microspheres were measured using eye piece micrometer in microscope. The eye piece micrometer was calibrated with help of stage micrometer average particle size was calculated and results were tabulated.

Formulation	Drug: polymer (mg)	Particle Size (µm)		**Percentage yield (%)**	**Entrapment efficiencies (%)**
		Mean Diameter (dIn)	Surface Diameter (dSn)		
F1	200:500	219.91	227.73	86.77	50.61
F2	200:600	220.45	230.19	75.32	52.43
F3	200:700	228.02	239.47	66.45	55.78

F4	200:800	233.88	243.39	60.03	58.23
F5	200:800	237.80	247.46	55.05	56.36
F6	200:800	233.88	243.39	60.35	58.23
F7	200:800	227.77	238.97	62.32	61.32
F8	200:800	221.25	229.34	65.32	65.62

Micromeretic properties

The micromeritics property of microsphere was shown in table below. The flow property represented in term of angle of repose, hausner ratio, Carr's index shown good flow property. Bulk property of microsphere were range in 0.511 to 0.542g/ml , and angle of repose less than 34° show the good flow property. Micromeritic property indicates that prepared microsphere free flowing and good morphology property.

Angle of repose:

Angle of repose of different formulations was measured according to fixed funnel standing method[4]

$$\theta = \tan^{-1} h / r$$

where θ is the angle of repose, *r* is the radius, and *h* is the height.

Bulk density & Tapped density:

Bulk and tapped densities were measured by using 10 ml of graduated cylinder. The sample poured in cylinder was tapped mechanically for 100 times, then tapped volume was noted down and bulk density and tapped density were calculated. Each experiment for micromeritic properties was performed in triplicate manner and reported.

Carr's index:

Compressibility index (Ci) or Carr's index value of microparticles was computed according to the following equation:

$$\text{Carr (\%)} = \frac{(\text{Tapped density} - \text{Bulk density})}{\text{Tapped density}} \times 100$$

Hausner's ratio:

Hausner's ratio of microparticles was determined by comparing the tapped density to the bulk density using the equation:

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table below shows the Micromeritics Properties of different formulation of Microspheres:

S. no.	Formulation	Bulk Densiy (gm/ml)	Tapped Density (gm/ml)	Hausner Ratio	Carr's Index	Angle of Repose(°)	Type of flow
1	F1	0.533	0.627	1.18	15.99	33°96'	Good
2	F2	0.523	0.634	1.21	17.58	34°32'	Good
3	F3	0.511	0.614	1.20	17.78	29°78'	Good
4	F4	0.497	0.597	1.20	17.01	31°53'	Good
5	F5	0.527	0.609	1.15	14.46	28°35'	Good
6	F6	0.533	0.627	1.18	15.99	33°96'	Good
7	F7	0.542	0.634	1.17	15.51	31°37'	Good
8	F8	0.511	0.637	1.18	17.68	28°93'	Good

SCANNING ELECTRON MICROSCOPY

Scanning electron microscopy was carried out in order to characterize surface morphology of the microspheres. In this study the morphological observations were carried out to study the surface morphology of microspheres[7].SEM micrographs and typical surface morphology of the microspheres are given in fig. 1(a-c). It was

observed that microspheres of formulation F1 (a&b) are spherical in shape. Photographs of formulation F5 (c) are have smooth surface, smooth surface allow free flowing characteristic to the microparticles[8]

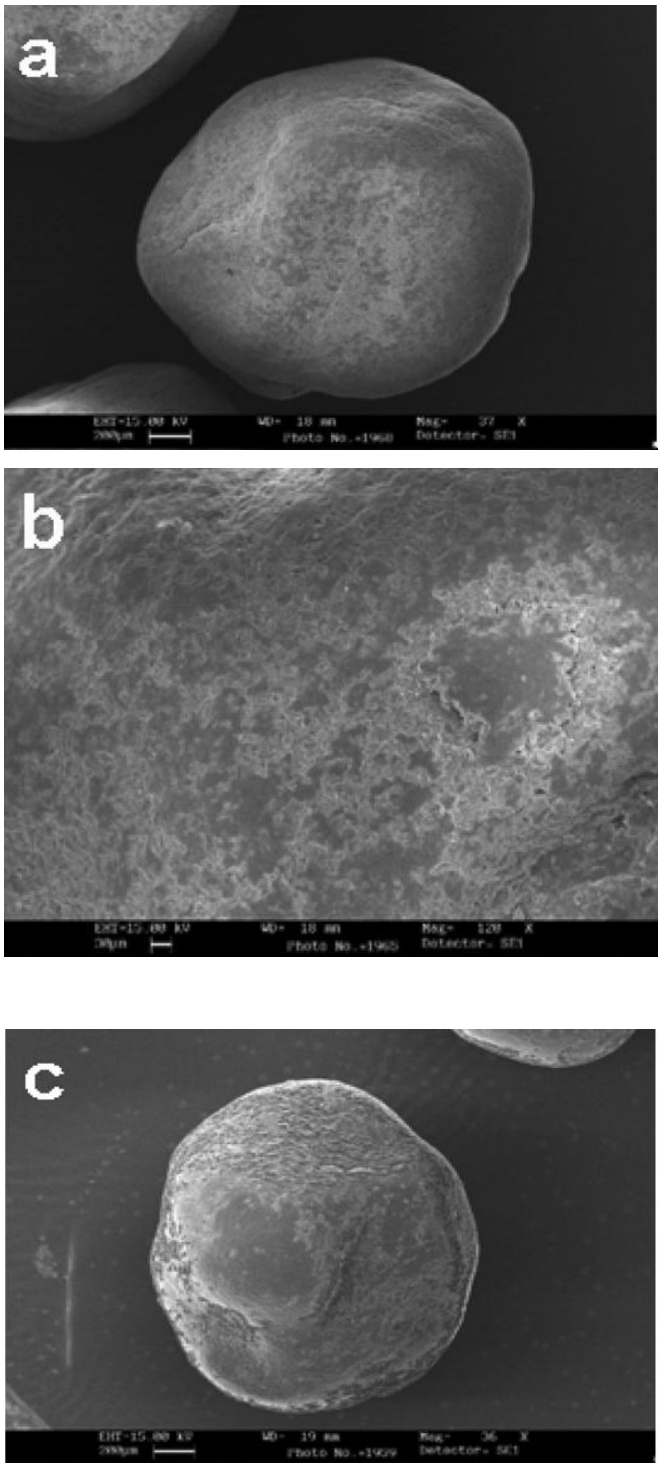

Fig. 1 (a-c) SEM PHOTOGRAPHS

IN VITRO RELEASE STUDY OF GELATIN MICROSPHERES:

Profile of drug release from the prepared microsphere was studied using a USP dissolution tester. The known amount of microsphere filled in capsule and then drop in 900 ml of acidic medium pH1.2 for 2 hrs and then in phosphate buffer medium at pH at 6.8 & 7.4. The media were agitated at 100 rpm, while maintaining temperature at 37°C. 5ml sample withdrawn from the dissolution medium at the regular time intervals and replaced with fresh medium. Absorbance of the withdrawn sample was measured spectrophotometrically at 274nm mentioned above.

Drug release from microsphere used paddle apparatus *in-vitro* dissolution method. In order to investigated the influence of crosslinking on the drug release profile of microsphere dissolution test applied for 12 hrs. The amount of drug release was determined by spectrophotometric determination (at the 274nm) of the sample solution[9,10].

Fig. below show the release of Aceclofenac from the gluteraldehyde crosslinked microsphere with the various ratio of polymer. The results indicate that the release rate decreased with increased in concentration of gluteraldehyde and increased in polymer quantity. The burst effects of drug release also depend on polymer concentration.

Fig. below showed that increased the concentration of polymer from 500mg to 800mg with 10% gluteraldehyde crosslinked, the rate of drug release decrease. In first 2hrs release of drug is 18-24% but after this the burst effect was obtained 30.79-52.21% drug released in 2-6 and then the drug release constantly with in 12 hrs. Formulation F1 prepared with 500mg polymer concentration released show about 89% and formulation F4 prepared with 800gm polymer concentration while drug released show about76%, this drug release decrease due to increase in polymer concentration..

Gelatin microspheres are known to swell in aqueous environment due to hydration. Swelling of microsphere may result in mobility of gelatin chain, facilitating rapid release rates of drug by diffusion through the polymer[11]. Since gluteraldehyde was responsible for formation of cross-linked, increased in the amount of crosslinking will increase the polymer density, resulting in reduction of the macromolecular chain mobility, and formation of the more stable and rigid sphere that show a lower

tendency to swell. The finding of this study is in agreement with Reedy and coworkers, in which they reported that release from albumin microsphere, could be extended by increasing the crosslinking degree of microsphere.

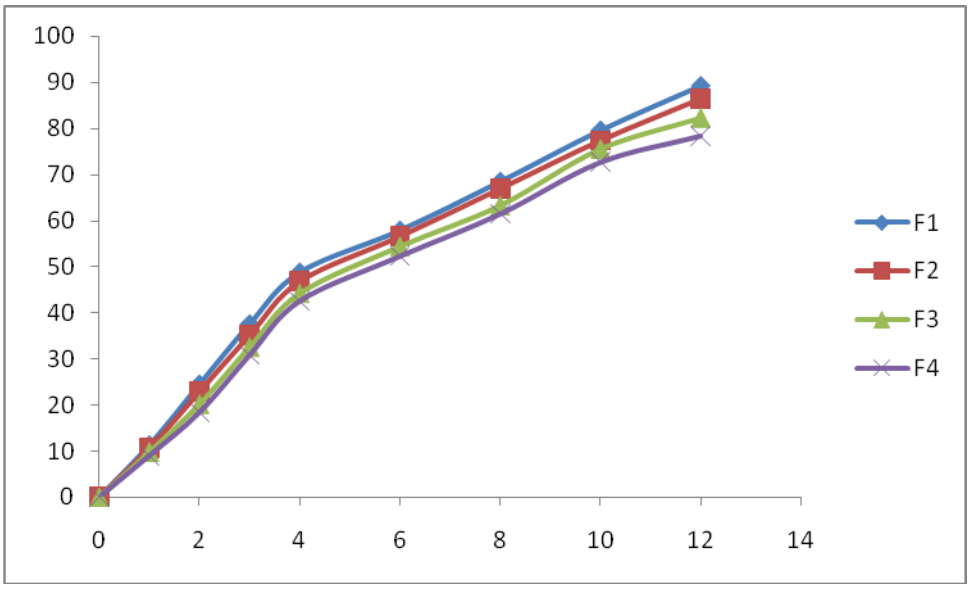

Fig.2 : The *in vitro* drug release of gelatin microspheres F1 to F4 containing Aceclofenac

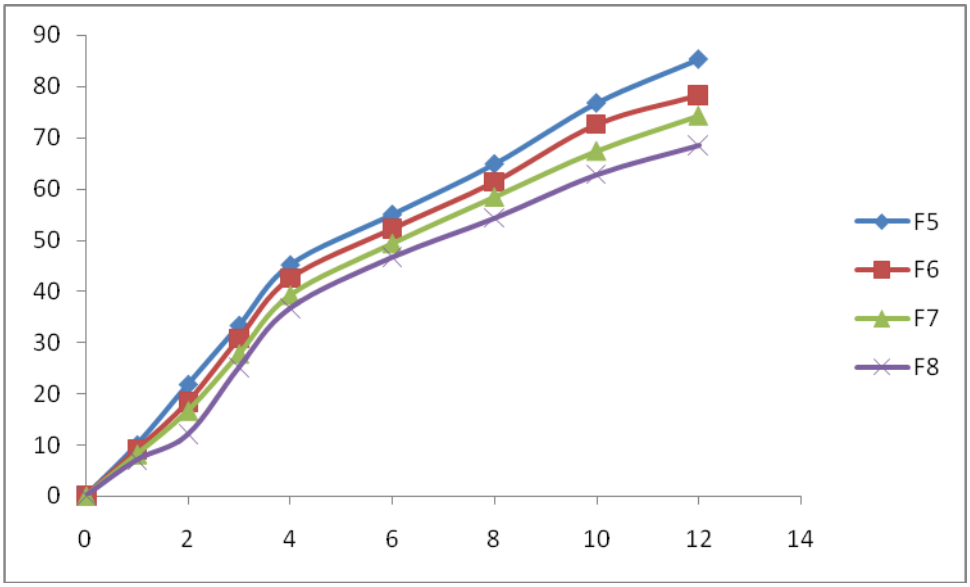

Fig. 3: The *in vitro* drug release of gelatin microspheres F5 to F8 containing Aceclofenac

Result:

Microsphere of Aceclofenac from the gluteraldehyde crosslinked microsphere with the various ratio of polymer were formulated. Aceclofenac loaded microspheres having a fairly high yield (60-88.39%) were obtained with different polymer ratio.

It was seen that In- vitro release of prepared microsphere with different gluteraldehyde concentration (5%-20%) was decreased with increased in gluteraldehyde concentration. Formulation F5 showed drug release about 85.29% while formulation F8 showed about 68.56% in 12 hrs. This result showed that decrease in release rate due to increased in crosslinking concentration i.e. In F5 21.78% drug released in 2hrs but in F8 12.02% drug released on microsphere. After burst effect the release in 6hrs F5 showed 54.97% and F8 showed 46.68%. As the increased in the crosslinked concentration burst effect of microsphere were decreased continuously.

Conclusion:

Gelatin microspheres were prepared successfully by polymerization or crosslinking technique. Gelatin microspheres were prepared by altering polymer ratio and crosslinked with gluteraldehyde. The effect of gelatin cross linking and polymer concentration on aceclofenac microsphere was studied relatively to various physico-chemical characteristics such as micromeritic property, drug entrapment, particle size. Prepared microsphere were free flowing, non aggregated and size range approximately between 100µm to 250µm. Increase in polymer concentration increase the particle size due to increase in the viscosity of medium and as increase the polymer concentration increase in drug entrapment efficiency.

Scanning electron microscopy (SEM) photographs of prepared microsphere was showed spherical size with irregular shape and rough surface.

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