International Journal of Research
Available at http://internationaljournalofresearch.org/
p-ISSN: 2348-6848
e-ISSN: 2348-795X
Volume 02 Issue 03
April 2015

# Development and Evaluation of Alginate Microspheres Paracetamol: Effect of Different Concentrations of Crosslinking Agent and Coating(Scmc &Sodium Alginate)

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**Abstract**

The objective of the present study was to design the alginate microspheres of paracetamol (modeldrug) using calcium chloride as a crosslinking agent by inotropic gelation method. The study focused on the effect of different concentrations of crosslinking agent and coating on the dissolution profile of microspheres using sodium carboxymethylcellulose (SCMC) as coating agent. Microspheres were prepared by using 2% sodium alginate aqueous solution with three different concentrations (5%, 10%, 15% w/v) of crosslinking agent (CaCl2), followed by coating with 2% sodium carboxymethylcellulose (low viscosity grade). Uncoated microspheres were evaluated for micromeritic properties like angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and for drug content. The in vitro drug release study was done for both uncoated and coated microspheres. The bulk density values were found in between 0.78 to 1.45 and tapped density values were found in between 0.82 to 1.48. Angle of repose was found to be less than 200, which shows excellent flow properties. The values of Carr's index were in between 5.05 to 6.22 and Hausner's ratio was in between 1.01 to 1.05 for uncoated microspheres. It was concluded that microspheres formulated with lower concentration of crosslinking agent showed the higher drug release while the coated microspheres showed prolongedor extended release drug release.

**Key words:** Paracetamol, Microspheres, Sodium alginate, Calcium chloride, Sodium carboxymethylcellulose.

## INTRODUCTION

Microspheres are free flowing polymeric micro particles loaded with biologically active drugs intended for providing constant and prolonged therapeutic effect thus reducing the dosing frequency and thereby improving the patient compliance [1]. They not only used for prolonged release but also for targeting drug to specific site for minimizing the side effects [2-4] Coating of microspheres with a suitable coating material is an additional important technique in microsphere formulation taken for modification of characteristics of microspheres especially in-vitro release profile. Paracetamol is a mild "aniline"analgesic with weak COX enzyme

inhibiting activity. It is used primarily as antipyretic and analgesic drug. It has a short biological half life (2.5h) and about 98% of the drug gets eliminated after a single dose thus requiring a high dosing frequency [5, 6]. Therefore, the present study aims to develop the alginate microspheres of paracetamol prepared with three different concentrations of crosslinking agent (CaCl2) followed by their coating with sodium carboxymethylcellulose (coating agent) for modifying the dissolution profile and providing a sustained release of drug leading to reduce dosing frequency. The prepared microspheres (uncoated and coated) were subjected to evaluation. The uncoated microspheres were subjected to evaluation for various micrometric properties along with the drug content and in vitro drug release. On the other hand the coated microspheres were subjected to in vitro drug release study.

## MATERIALS AND METHODS

Paracetamol was obtained as a gift sample from Wings Pharm. Ltd. Mumbai. Sodium alginate, sodium carboxymethylcellulose and calcium chloride were purchased from Himedia Ltd. Mumbai. All other chemicals were of analytical grade.

### Method of preparation of alginate microspheres and its coating

The microspheres of paracetamol were prepared by ionotropic gelation method using sodium alginate as polymer and calcium chloride as crosslinking agent (Table 1). A 2% sodium alginate solution was prepared by dissolving weighed amount of sodium alginate in 100 mL distilled water with stirring on a
magnetic stirrer (Remi 5MLH, India).

**Table 1: Composition of uncoated microspheres of paracetamol**

| Formulation | PARACETAMOL(mg) | Sodium alginate %( w/v) | Calcum chloride %(w/v) |
|---|---|---|---|
| A1 | 500 | 2% | 5% |
| A2 | 500 | 2% | !0% |
| A3 | 500 | 2% | 15% |

Weighed amount of paracetamol was dispersed in the sodium alginate solution. Crosslinking solutions of various concentrations (5, 10, 15 %w/v) were prepared by dissolving calcium chloride in distilled water. Sodium alginate solution was filled in the syringe and dropped into the solutions of crosslinking agent from a height of 6 inches with speed of about 50 drops per minute. Microspheres were prepared due to the crosslinking of the polymer by the calcium ions. The prepared microspheres were collected by decantation followed by centrifugation of the solutions, air dried overnight and then stored in vacuum desiccator. For the coating of prepared microspheres a fraction of uncoated microspheres were subjected to the process of coating with 2% sodium carboxymethylcellulose solution (in water). The prepared microspheres were dipped into the coating solution for 30 minutes and then the coated microspheres were collected by decantation followed by centrifugation, air

dried for overnight and then stored in vacuum desiccators until the characterization. The coated microspheres prepared with different concentrations (5, 10 and 15%) of crosslinking agent were coded as formulations CA1, CA2 and CA3.

## EVALUATION

**Drug content**

An amount of microspheres containing a quantity equivalent to 100 mg paracetamol were weighed, crushed and dissolved into 100mL of distilled water using magnetic stirrer for 24 h. Sample was withdrawn after 24h, diluted appropriately and analyzed spectrophotometrically (Double beam UV-Vis spectrophotometer, AU2701, Systronics Ltd. India) at 257nm for determination of the drug content.

**Density determination**

Bulk density: A weighed amount of microspheres were filled into a measuring cylinder and the volume (V0) occupied by the microspheres was noted and the bulk density was calculated as followed [7], Bulk Density =Mass of the microspheres (W)/Initial volume of the microspheres (V0). Tapped density: A weighed quantity of microspheres were filled in a measuring cylinder and the cylinder was tapped against a wooden surface at regular interval for 100 times, then the volume occupied by the microspheres was noted down and tapped density was calculated as followed [7], Tapped Density = Mass of the microspheres (W)/Tapped volume of the microspheres (Vf).

**Flow properties**

Carr's compressibility index and Hausner's ratio were calculated for the uncoated microspheres using the following equations [7] Carr's index = Tapped density- Bulk density/
Tapped density

**Table 2 : Evaluation of uncoated microspheres of paracetamol**

| Formulation | Drug content (%) | Bulk density (g/mL) | Tap density (g/mL) | Angle of repose ($^0$) | Carr's index | Hausner's ratio |
|---|---|---|---|---|---|---|
| A1 | 96.78±0.05 | 0.78±0.02 | 0.82±0.3 | 6.78±0.05 | 5.05±0.05 | 1.05±0.09 |
| A2 | 96.61±0.08 | 1.45±0.07 | 1.48±0.07 | 7.35±0.08 | 6.22±0.07 | 1.02±0.04 |
| A3 | 96.06±0.04 | 0.91±0.09 | 0.91±0.05 | 15.27±0.09 | 5.36±0.11 | 1.01±0.03 |

Hausner's ratio = Tapped density/ Bulk Density

Angle of repose: It is a measure of resistance to flow and calculated by funnel method. A weighed quantity of microspheres was passed through the funnel and the heap was formed on the paper. The area of the heap was encircled and diameter of the circle and the height of the heap were measured and the angle of repose was calculated as followed [7], TanΦ = 2H/D H = Height, D = diameter of heap formed, 2H/D = surface area of the heap formed.

**In Vitro drug release studies**

In Vitro release studies was carried out in USP type II dissolution apparatus (Veego, 8DR, India) using 900mL of acid buffer pH 1.2 (upto 3h) and phosphate buffer pH 6.8 (after 3h) as dissolution mediums maintained at 37±0.50C and 50 rpm. A quantity of microspheres equivalent to 100 mg of paracetamol was used for the

dissolution study. Samples (5mL) were withdrawn at different intervals and an equal volume of the fresh dissolution medium was introduced into the apparatus. Each sample was diluted suitably with dissolution medium and analyzed with UV spectrophotometer at 257nm for determining the drug release.

## RESULTS AND DISCUSSION

In the present study the alginate microspheres prepared by ionotropic gelation technique using three different concentrations (5, 10, 15 %) of crosslinking agent (CaCl2) leading to three different formulations (A1, A2, A3). These microspheres were subjected to the evaluation for drug content, micrometric properties (like bulk density, tapped density, compressibility index and Hausner's ratio) and in vitro drug release studies. A1, A2, and A3 formulations were coated with 2% SCMC (low viscosity grade) and the effect of coating on in vitro drug release were also studied. Drug content for different microsphere formulation was in the range of 96.06 to 96.78 %. Microsphere formulation A1 (5% CaCl2 as crosslinking agent) showed highest drug content of 96.78%. The rank order of drug content for all formulation was as follows A1> A2>A3. The micromeritic properties such as bulk density, tapped density, angle of repose, Carr's index and Hausner's ratio were determined for uncoated microspheres (Table 2). The various microsphere formulations showed angle of repose less than 200 indicating good flow properties which might be due to lesser friction between the microspheres. The values of Carr's index ranging from 5.05 to 6.22 and Hausner's ratio ranging from 1.01 to 1.05 indicated excellent flow properties. Bulk density for all the formulation was in the range of 0.78 to 1.45g/mL and tapped density value was in between 0.82 to 1.48g/mL. In Vitro release studies of all the microspheres were done in USP type II apparatus using acid buffer pH1.2 and phosphate buffer pH 6.8 as mediums at 257nm. The % cumulative drug release for all uncoated microspheres formulations at the end of 12h were found to be in between 55.56 to 73.38% and for all coated microspheres were found in the range of 47.61 to 57.52% (Fig. 1). The formulation A1 (prepared with 5% crosslinking agent) showed the highest drug release while the A3 (prepared with 15% crosslinking agent) showed the lowest drug release. It was evident from the study that the higher degree of crosslinking decreased the drug release as supported by previous study Yapel et al. (1996) also reported that for epinephrine release from albumin microspheres, the releaserate was dependent on degree of crosslinking [8- 10]. Coating with 2% SCMC solution increased the diffusional path length for the drug release leading to a slower release as shown by CA1, CA2 and CA3. The different kinetic models (first order, Higuchi model) were also studied for all the formulations and it was found that drug release from the microspheres followed the matrix diffusion process [10-13].

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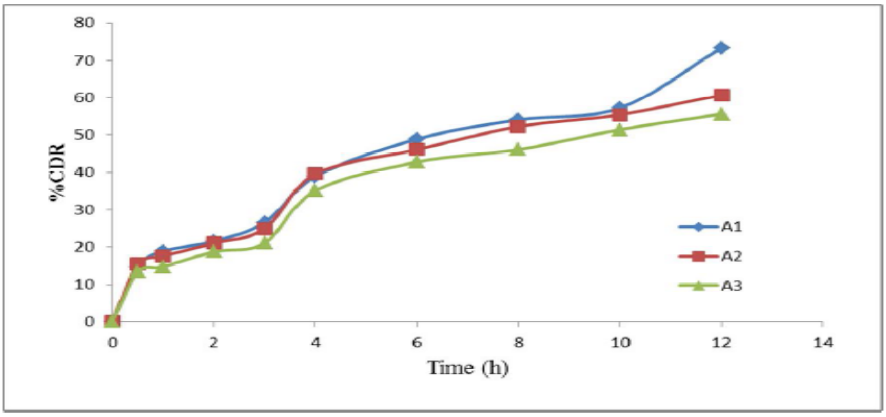
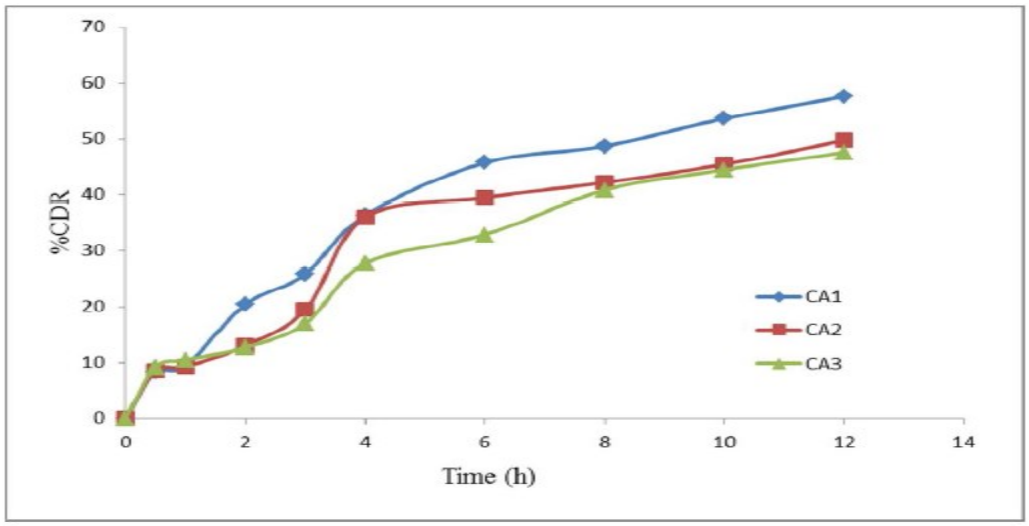



**Fig. 1: In Vitro drug release study of uncoated microspheres of Paracetamol**
(Alginate microspheres A1, A2 and A3 were prepared with 5, 10 and 15% concentration of crosslinking agent)

**Fig. 2: In Vitro drug release study of SCMC coated microspheres of paracetamol**
(Alginate microspheres CA1, CA2 and CA3 were prepared with 5, 10 and 15% concentration of crosslinking agent and were coated with 2% Sodium caboxymethylcellulose)




## CONCLUSION

The alginate microspheres were prepared by ionotropic gelation technique using three different concentrations (5, 10, 15%) of crosslinking agent (CaCl2) and these three different formulations were coated with sodium carboxymethylcellulose. It can be concluded that all the uncoated microspheres showed satisfactory percent drug content, excellent flow properties and good drug release. The microspheres

prepared with lower concentration of crosslinking agent showed the higher drug release therefore, modulating the concentration of crosslinking agent may be a critical factor for modulating the drug release. The coated microspheres prolonged and extended the drug release. Therefore, these coated microspheres can be used to control and prolong the drug release effectively and reducing the dosing frequency of Paracetamol.

## ACKNOWLEDMET

The authors sincerely thanks to D.S.T.S college of pharmacy solapur Maharashtra, India for providing experimental facilities to carry out this work

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