

Formulation and *in vitro* study of Ibuprofen loaded crosslinked sodium alginate and gellan gum microspheres

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Abstract

Ibuprofen loaded microspheres were prepared using sodium alginate and gellan gum and were cross-linked by maleic anhydride, aluminium chloride. The resulting microspheres were evaluated by *in-vitro* release study, swelling index, microscopic analysis and entrapment efficiency. DSC study shows there was no interaction between drug and excipients. Entrapment was found good in all the formulations while the maximum entrapment (97.6%) was recorded in formulation cross-linked by aluminium chloride and their average particle size were 150 to 160 μm . Approximately 50% of drug was released by the formulation cross-linked by aluminium chloride (F2) over a period of 6 hours. From this experiment, it is observed that the formulation with cross-linked by aluminium chloride is the better formulation among others due to good release profile and entrapment efficiency.

Keywords: Microspheres, gellan gum, drug release.

1. Introduction

Microsphere are spherical shell that is usually made of biodegradable polymer, that has a very small diameter usually in micrometer or nanometer range and that is often filled with a substance (drug) for release as the shell is degrade [1]. Microspheres are small spherical particles, with diameters in the micrometer range (typically 1 μm to 1000 μm). Microspheres are sometimes referred to as microparticles. Natural polymer can also be used form microspheres preparation like Albumin, Gelatin etc. [2].

Among naturally occurring biodegradable polymers, sodium alginate and gellan gum are widely used polymer candidates for the designing and development of various drug delivery systems. Alginate is now known to be a whole family of linear copolymers containing blocks of (1,4)-linked β -D-mannuronate (M) and α -L-guluronate (G) residues. Alginates are easily gelled in presence of a divalent cation as calcium ion. The gelation or crosslinking

is due to the stacking of the glucuronic acid blocks of alginate chains [3].

Gellan gum is water-soluble linear anionic polysaccharide obtained as a fermentation product by a pure culture of *Pseudomonas elodea* [3,4]. Gellan gum consists of linear structure of repeating saccharide units of glucose, glucuronic acid and rhamnose in a molar ratio of 2:2:1[5]. The physical gelation ability of gellan gum makes it suitable as structuring and gelling agent in foods and toothpastes, binders, and as a sustained release matrix [6].

Ibuprofen is chemically (RS)-2-[4-(2-methylpropyl) phenyl] propanoic acid, as a non-steroidal anti-inflammatory drug (NSAID) with short half-life (2-4 h), treatment of pain and inflammation. It is also used in the treatment of analgesic, antipyretic, arthritis, osteoarthritis, rheumatoid arthritis. They are indicated in soft tissue injuries, fractures, vasectomy, tooth extraction, postpartum and postoperatively: suppress swelling and inflammation.

Ibuprofen is reported to produce side effects like gastric irritation, ulcer etc. as result of prolong treatment. They are not to be prescribed to pregnant women and should be avoided in peptic ulcer patient. Due to its short half-life, its recommended dose is considered as 400 mg daily in divided doses [7]. To reduce dosing frequency and adverse effects during prolong treatment, sustained release dosage of Ibuprofen to deliver Ibuprofen at a slow release rate over an extended period of time is essential. Therefore, the attempt to design Ibuprofen-loaded sodium alginate and gellan gum microspheres using maleic anhydride and/or aluminium chloride as cross linking agent.

2. Materials and methods

2.1 Materials required:

Ibuprofen was obtained from Yarrow Chem. Gellan Gum was procured from Hi Media Lab Pvt Ltd. Maleic anhydride and Aluminium chloride were obtained from Loba chemine, Mumbai. All chemicals and reagents used were of analytical grade.

2.2 Methodology

2.2.1 Study of physical interaction between drug and excipients

Differential Scanning Calorimetry (DSC) thermograms were taken by scanning the samples of (i) pure drug (Ibuprofen), (ii) pure excipients (gellan gum and sodium alginate) (iii) formulation (microsphere) using DSC (Pyris Diamond TG/DTA, PerkinElmer, SINGAPORE) in nitrogen atmosphere (150ml/min). Platinum crucibles were used with alpha alumina powder as reference.

2.2.2 Preparation of Ibuprofen microsphere [8]

The ibuprofen loaded microspheres were prepared by polymer matrix of sodium alginate and gellan gum.

Cross linking agent used for the microspheres was various combination of malic anhydride, aluminium chloride. Sodium alginate, 500 mg, was accurately weighed and dissolved in 40 ml of warm water with the help of magnetite stirrer. Gellan gum was also accurately weighed on a digital balance and dissolved in 40 ml of warm water. The temperature of the solution maintained (50⁰ C) and was rotated at 200 rpm until dissolved. Upon complete dissolution of two polymers, they were mixed together and became bubble free or uniformly mixed. In separate beaker 500 mg of accurately weighed ibuprofen was added in few ml of chloroform and mixed thoroughly. Then after complete dissolution of the drug in water, the drug solution was mixed in the polymer mix to form a drug-polymer solution. The drug-polymer was rotated at 200 rpm until it became homogeneous mixture. On another separate beaker, the counter ion solution was prepared by weighing maleic anhydride, aluminium chloride at ratio and mixed in 50 ml of water. When the mixture is complete, the drug polymer mix was pipette out and dropwise in the counter ion solution with the help of pipette maintaining a minimum distance from the tip of pipette and the surface of counter ion solution. The droplet of the drug polymer mix cross link with the counter ions and form microspheres. After 15 minutes of curing, the microspheres were strained and washed thoroughly with water to remove the traces of excess counter ion solution from the surfactant of the microspheres and hardens of the microsphere. The microspheres were collected on a Petridis and kept to dry under room temperature. Different microsphere formulations along with percentage of polymers, drug (ibuprofen) and cross-linkers were shown in Table 1.

Table 1: Composition of different formulation of ibuprofen microsphere

Formulation code	Sodium alginate [%w/v]	Gellan gum [%w/v]	Ibuprofen [%w/v]	Malic anhydride [%w/v]	Aluminium chloride [%w/v]
F1	0.5	0.5	0.5	1	
F2	0.5	0.5	0.5		1
F3	0.5	0.5	0.5	1	1

2.2.3 Drug entrapment efficiency: [9]

Drug entrapment efficiency is the amount of drug physically entrapped by polymer in the microsphere. Accurately weighed 100 mg of microspheres were triturated

$$\text{Entrapment efficiency (\%)} = \frac{\text{actual drug content in microsphere}}{\text{theoretical drug content in microsphere}} \times 100$$

2.2.4 Swelling behaviour: [10]

Swelling behaviour is carried out by placing the microspheres in the dissolution apparatus type 2 in phosphate buffer 6.8 at temperature of 37±1°C under 50

rpm. The beads were removed at different time intervals by filtration and blotted carefully to remove excess surface water. The swollen beads were weighed.

$$\text{Swelling index} = \frac{\text{weight of microspheres after swelling} - \text{Dry weight of microspheres}}{\text{Dry weight of microspheres}} \times 100$$

2.2.5 In vitro release studies: [11]

In vitro dissolution studies were performed using USP Type II dissolution test apparatus (Paddle) rotate at 50 rpm and the microspheres were placed in the basket and immersed in the dissolution media containing 900 ml of phosphate buffer 7.2 at temperature of $37 \pm 0.5^\circ \text{C}$ for a period of 6 hours. At intervals of 15 minutes, 5 ml aliquots were withdrawn and added by 5 ml fresh media. The same volume of dissolution medium was replenished after each sampling. The sample were diluted ten times by taking 1 ml of sample and diluting it by adding 9 ml of phosphate buffer of pH 7.2. The absorbance of the withdrawn samples

was assayed by UV-spectrophotometry at the wavelength of maximum absorbance (221 nm).

2.2.6 Particle size determination: [11]

The diameter of micro particle of each formulation was measured by spreading a thin layer of micro particles on a glass slide and an ocular micrometre was previously attached and the particles were placed on a slide and their size was measured. Each sample was measured at three times and an average particle size was articulated as mean diameter. After collection of data, the data was divided in size ranges and the frequency was calculated by this formula.

$$\text{frequency (\%)} = \frac{\text{Number of particles in each size range}}{\text{Total number of particles}} \times 100$$

3. Results and discussion

3.1 Differential Scanning Calorimetry

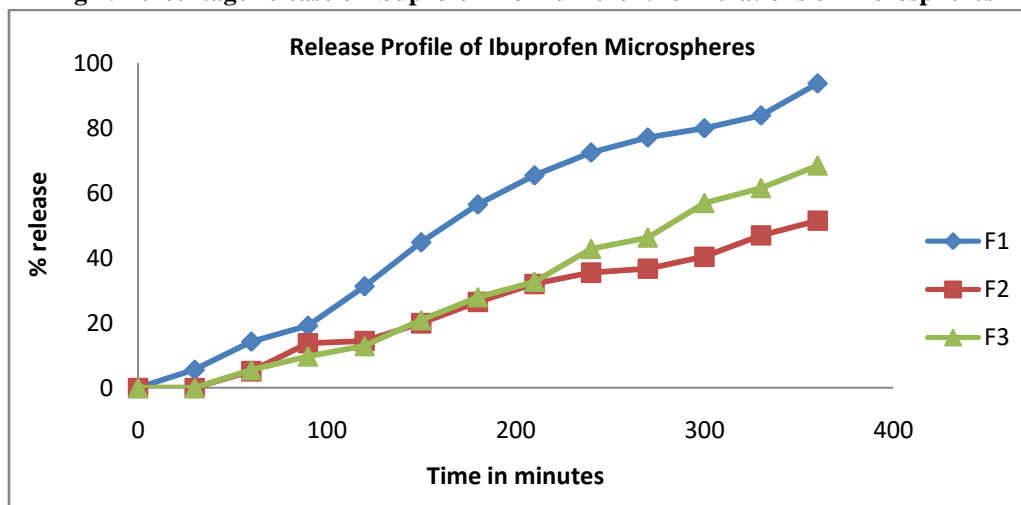
The pre formulation study of drug-excipients interaction was carried out by DSC, which showed no interactions of the drugs and excipients.

3.2 In vitro release studies

In vitro release studies were carried out for the formulations of microspheres containing ibuprofen as drug and gellan gum and sodium alginate as polymer, cross-linked with counter ion solutions of maleic anhydride and aluminium chloride in various ratios in buffer for 6 hours. Drug released from different formulations showed a lag phase in the release pattern. The lag phase indicates that better cross-linking and drug entrapment resulting in

sustained release behaviour. The *in vitro* release profiles are shown in the figure 1. Better cross-linking was observed in the formulations cross-linked with 1% aluminium chloride. Maleic anhydride alone was insufficient as a cross-linking agent having sustained action for a short period (F1), but combining maleic anhydride with aluminium chloride improved the results. Approximately 50% of drug was released by the formulation cross-linked by aluminium chloride (F2) over a period of 6 hours. Thus it can be safely said that the drug Ibuprofen exhibited sustained activity by cross-linking with aluminium chloride (F2) while cross-linking was poor for formulation cross-linked by maleic anhydride (F1).

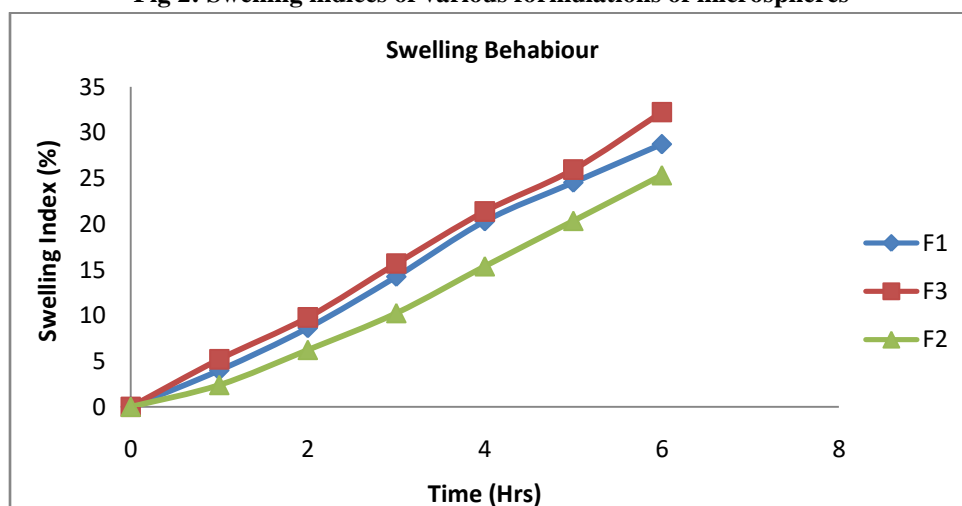
Fig 1: Percentage release of Ibuprofen from different formulations of microspheres



3.3 Swelling Index

Swelling behaviour of the formulations was shown in figure 2. From the figure, it was seen that maximum swelling property is exhibited by the formulation cross-linked by maleic anhydride (F1) and combination of both maleic anhydride & aluminium chloride (F3) and least

swelling by formulation cross-linked by aluminium chloride (F2) respectively. Swelling of formulations cross-linked by aluminium chloride and maleic anhydride is greater than individual swelling percentages of aluminium chloride and maleic anhydride.

Fig 2: Swelling indices of various formulations of microspheres

3.4 Microscopic Analysis

Microscopic analysis of Ibuprofen reveals that the size range of ibuprofen microspheres lies between 120 μm to 190 μm . Microspheres cross-linked by 1% w/v aluminium chloride (F2) exhibited maximum frequency of size in 150 μm to 160 μm . Microspheres cross-linked by maleic anhydride (F1) exhibited maximum frequency of size range in 120 μm to 190 μm . Microspheres cross-linked by 1% maleic anhydride and aluminium chloride exhibited maximum size range in 150 μm 170 μm .

3.5 Entrapment Efficiency

The percent entrapped was shown in table 2. Drug entrapment in the formulations was found to be fairly good, the maximum entrapment being exhibited by the formulation cross-linked by aluminium chloride (F2). The formulation cross-linked by the combination of two cross-linking agents also showed good entrapment efficiency. The probable reason for the high entrapment efficiency of formulation F2 might be due to cross-linking reaction of aluminium chloride and ibuprofen. Due to strong bonding of the drug and polymer and counter-ion polymers, entrapment of the drug in the polymer matrix is high.

Table 2: % Entrapment different formulations
(Mean \pm SD, n=3)

Code	% Entrapped
F1	82.7 \pm 0.81
F2	97.6 \pm 0.35
F3	88.4 \pm 0.69

4. Conclusions

The objective of project was to exploit the activity of Ibuprofen as a model drug by attempting to prolong release for a longer period of time. To achieve the design of sustained delivery of Ibuprofen, microspheres were prepared from where the rate of release was reduced by the

incorporation of sodium alginate and gellan gum as polymer and maleic anhydride and aluminium chloride served as counter ion solutions for cross-linking of the drug. Cross linking occurs by formation of covalent bonds between two or more molecules. The cross linking agents contain two or more reactive ends to chemically attach with functional groups. This phenomenon is known as cross-linking.

After the formulation of microspheres, they were evaluated to estimate their microscopy, swelling index, entrapment and release. From this experiment, we have come to know that the formulation with aluminium chloride as a cross linker (F2) is the better formulation than the rest formulated. Swelling of F2 was least while the entrapment was the maximum. 97.6% entrapment efficiency was recorded by the formulation F2. Release profile of the formulations revealed the sustained design of the drug, particularly formulation F2 releasing approximately 50% over 6 hours. It was also observed that on increasing the counter ion solutions, the release rates were also improved. Long term stability study is requiring for future development of this formulations.

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