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Original Article

# Design and Characterization of Ibuprofen Loaded Alginate Microspheres Prepared by Ionic Gelation Method

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ABSTRACT

**Introduction:** Ibuprofen is a non-steroidal anti-inflammatory drug. Ionotropic gelation technique is used for the preparation of Ibuprofen microspheres which is a controlled released drug delivery system. This process where the drug is enclosed in a microscopic particle by the formation of wall coating around it is called microencapsulation. **Material and Methods:** The drug is dissolved in sodium alginate and different polymers for the preparation of a suspension. 10% w/v calcium chloride solution is used as a cross linking agent in which the suspension is added drop- wise to form a microsphere. Na-CMC, Ethyl cellulose, HPMC, and Carbopol 940 are the different polymers which are used along with sodium alginate to form the suspension. The characterization of the prepared microspheres is done using different evaluation parameters such as like flow properties, swelling index, drug content and in vitro drug release. **Result and Discussion:** It was observed from the evaluation that the formulation having the polymer HPMC i.e. the formulation 7 may be a better choice of drug for site specific delivery as it gives the maximum release. **Conclusion:** Therefore, one can assume that the Ibuprofen microspheres are promising pharmaceutical dosage forms by providing controlled release drug delivery systems.

**Keywords:** Controlled-release, Ibuprofen, Cross-linking agent, Ionotropic gelation, Microencapsulation.

## 1. INTRODUCTION

Microspheres are generally biodegradable in nature and have a characteristic of free flowing. They are mainly consisting of proteins or synthetic polymers. Microspheres are mainly intended for the controlled release drug delivery system which improves the bioavailability of such drugs because of its smaller size and spherical shape, although it undergoes extensive first-pass metabolism[1]. Particle size of these microspheres is ideally less than 1000µm. Microspheres are widely spread in gastrointestinal tract because of its small

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particle sizes. It enhances drug absorption and helps in reducing the side effects as there is localized action of irritating drugs [2].

This process of enclosing solids, liquids or gases in microscopic particles by formation of wall coatings around the drug is known as microencapsulation[1]. One of the extensively used methods is by inotropic gelation which works on the principle of coalescence. Micro particles are formed by the inotropic gelation of two oppositely charged ions i.e. anionic sodium alginate and cationic calcium ions. Then the colloidal polymer particles are fused into homogenous matrix. Once the matrix is formed, the coating and drying process is done the colloidal polymer particles fuse into homogenous film [3].

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID). The drugs of this class leads to gastric irritation. Ibuprofen has short biological half-life and can cause gastric irritation so due to this it can be used for preparing controlled release products which also gives prolonged action[4]. Ibuprofen is also used as anti- pyretic drug which is used in the treatment of rheumatism and arthritis and also used to treat primary dysmenorrheal. In terms of chiral characteristics ibuprofen is the most researched drug and it is a mixture of S (+) – ibuprofen and R (-) – ibuprofen[5].

Alginate when taken orally is considered to be nontoxic and it protects the mucous membrane from irritation. The acid sensitive drugs are incorporated into microspheres as they had a property of reswelling in environmental pH so the incorporation protects them from gastric juice. Thus ibuprofen in form of microspheres helps to overcome the potential problems caused by such NSAIDs in gastrointestinal tract leading to the reduction of their adverse effects [6]. This study was to develop Ibuprofen microspheres by ionic gelation technique using different polymers so as to make it sustain released system in order to improve patient capacitance and reduce the frequency of dosing[1].

## 2. MATERIALS AND METHODS

### Materials

We obtained Ibuprofen from Yarrow Chem Products Manufacturer. The other chemicals required were Sodium Alginate, Ethyl Cellulose, Sodium Carboxy Methyl Cellulose (Na-CMC), Hydroxy Propyl Methyl Cellulose (HPMC), Carbopol 940, Calcium Chloride which was all purchased from Loba Chemie.

### Method of Preparation

Orifice inotropic gelation method was used for the preparation of alginate microspheres using polymers such as EC, Na-CMC, HPMC and Carbopol 940. A homogenous polymer solution was prepared by dissolving Sodium alginate (1g) and the polymers (1g) in purified water (32 ml). Then Ibuprofen (1g), the active substance was added to the polymer solution and stirred thoroughly to form a viscous dispersion. 10% w/v calcium chloride solution was prepared which has been used as a cross linking agent. The prepared dispersion was then manually added drop wise into calcium chloride (10% w/v) solution (40 ml) with the help of a syringe having a needle of size no.18. The calcium chloride solution having the droplets was then allowed to stay for 15 minutes for the curing reaction to take place and produce spherical rigid drug loaded spheres. The spheres obtained after the reaction were then collected and washed repeatedly with water. After washing, it is required to dry the spheres properly at $45^0$C for 12 hours [10].

**Table 1: Composition of Formulations**

| Ingredients | F1 (gm) | F2 (gm) | F3 (gm) | F4 (gm) | F5 (gm) | F6 (gm) | F7 (gm) | F8 (gm) | F9 (gm) |
|---|---|---|---|---|---|---|---|---|---|
| Ibuprofen | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Na-Alginate | 1 | 1 | 0.8 | 1 | 0.8 | 1 | 0.8 | 1 | 0.8 |
| EC | - | 1 | 0.2 | - | - | - | - | - | - |
| Na-CMC | - | - | - | 1 | 0.2 | - | - | - | - |
| HPMC | - | - | - | - | - | 1 | 0.2 | - | - |
| Carbopol 940 | - | - | - | - | - | - | - | 1 | 0.2 |
| CaCl2 | 10% w/v | 10% w/v | 10% w/v | 10% w/v | 10% w/v | 10% w/v | 10% w/v | 10% w/v | 10% w/v |

### Characterization

### Flow properties

### Bulk density

To measure bulk density a 10 ml graduated cylinder is used. The sample is poured in the cylinder and the volume is measured. Bulk density is calculated by using the formula: (weight of microspheres / bulk volume).

### Tapped Density

It is also performed in a 10 ml graduated cylinder. Once the sample is poured in cylinder it is been tapped mechanically for about 100 times and the tapped volume is noted. Tapped density is measured using formula: (weight of microspheres / tapped volume).

### Carr's Index

Carr's index is calculated according to the following equation: Carr's index (%) = [(Tapped density - Bulk density) / Tapped density] * 100.

Hausner's Ratio Hausner's ratio is measured by determining the ratio of tapped density to the bulk density. Hausner's ratio = Tapped density / Bulk density.

### Angle of Repose

The maximum angle possible between the horizontal plane and the surface of the pile is known as angle of repose. It is calculated using the equation: $\tan \theta = h / r$, where h = height of pile and r = radius of the base of pile. Thus angle of repose, $\theta = \tan^{-1} (h / r)$.

### Swelling Index

The weight of the microspheres is taken first and then dissolved in phosphate buffer (pH 7.2) for 24 hrs. The excess liquid is removed using blotting paper and the weight of the swollen microspheres is taken. Swelling index is thus calculated using following formula, Swelling index = [(weight of swollen microspheres – weight of dried microspheres) / weight of swollen microspheres] [10].

**Drug Content**

About 1 gm of sample was taken and dissolved in 100 ml distilled water in a beaker. After 24 hrs the sample was filtered and suitable dilution is done. Then the absorbance of the solution is measured at 221 nm and drug content is calculated [6].

**Dissolution Study**

The 500 ml of distilled water was placed in vessel the dissolution apparatus (USP apparatus type-II paddle method) was assembled. The sample was then placed in the vessel and the apparatus was operated for 4 hrs. at 50 rpm. The definite time interval, 5 ml was withdrawn from the vessel and another 5 ml of the blank was added to the vessel. The withdrawn fluid is then filtered and suitable dilution was done. Samples are then analyzed under UV Spectrophotometer at 221 nm[10].

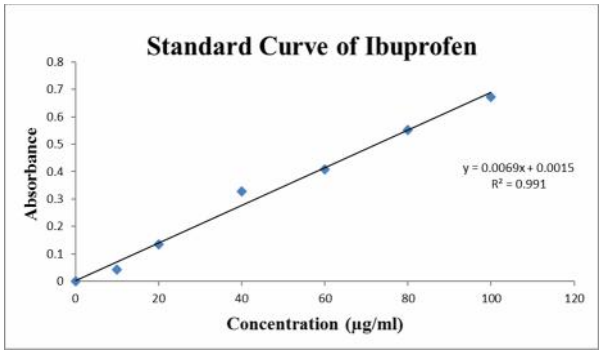


**Fig 1: Standard Curve of Ibuprofen**

## 3. RESULT AND DISCUSSION

Ibuprofen microspheres were prepared using sodium alginate and other polymers such as Na- CMC, Ethyl cellulose, HPMC and Carbopol 940 using the method inotropic gelation technique.

**Flow Properties**

Microspheres are spherical in shape which has a characteristic of free flowing. All the formulations showed good and excellent flow of the system as the angle of repose, Carr's index and Hausner's Ratio values are very less. The angle of repose ranges from 3-10° where the formulation 3 i.e. the formulation containing ethyl cellulose has the highest angle of repose. Carr's index is ranging from 13-20% where the highest value is observed in formulation 2 having ethyl cellulose as polymer and the lowest of all has been shown by formulation 8 having carbopol 940 as the polymer. The flow characteristic showed Hausner's ratios of <1.35 where the formulation containing Na-CMC i.e. formulation5 gave the highest Hausner's ratio.

**Table 2: Flow Properties of Microspheres**

| Formulations | Angel of Repose | Bulk Density | Tapped Density | Carr's Index | Hausner's Ratio |
|---|---|---|---|---|---|
| 1 | 7.125 | 0.500 | 0.526 | 14.94 | 1.052 |
| 2 | 3.814 | 0.500 | 0.625 | 20.00 | 1.250 |
| 3 | 9.926 | 0.500 | 0.526 | 14.94 | 1.052 |
| 4 | 4.899 | 0.500 | 0.588 | 14.96 | 1.176 |
| 5 | 3.814 | 0.625 | 0.833 | 14.97 | 1.333 |
| 6 | 3.814 | 0.500 | 0.714 | 19.97 | 1.328 |
| 7 | 8.530 | 0.588 | 0.769 | 13.54 | 1.308 |
| 8 | 9.462 | 0.666 | 0.769 | 13.39 | 1.155 |
| 9 | 5.079 | 0.769 | 0.909 | 15.40 | 1.182 |

**Swelling Index**

It refers to the amount of phosphate buffer absorbed by the microspheres after dissolving them in buffer. It has been observed that formulation 5 i.e. the formulation containing Na-CMC gives the highest swelling index.

**Drug Content**

After determination of drug content of the following microsphere formulations, it was found to be in between 22.33% and 34.47%. It has been observed that formulation 7 containing polymer HPMC gives the highest drug content whereas formulation 4 containing polymer Na-CMC gives the lowest drug content.

**Table 3: Swelling Index & Drug Content of Microspheres**

| Formulations | Swelling Index | Drug Content |
|---|---|---|
| F1 | 69.69 | 27.04 |
| F2 | 75.00 | 25.10 |
| F3 | 77.27 | 31.24 |
| F4 | 80.76 | 22.33 |
| F5 | 88.88 | 23.53 |
| F6 | 84.84 | 30.32 |
| F7 | 88.09 | 34.47 |
| F8 | 88.23 | 27.77 |
| F9 | 83.33 | 34.39 |

**In-vitro Release Study**

In vitro release study of Ibuprofen microspheres was done for 4 hours in phosphate buffer. The microspheres demonstrated controlled release of the drug. It has been observed from the study that the formulation containing HPMC i.e. the formulation 7 gives the highest release of 67.53% and formulation 2 having polymer Ethyl cellulose gives the lowest release of 29.20%. Thus, from this study it can be concluded that the Ibuprofen microspheres provides a better carrier system for controlled delivery of drugs.

**Table 4: In-vitro Release Study of Ibuprofen Microspheres**

| Time (min) | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0000 |
| 15 | 1.8356 | 1.8653 | 2.1570 | 2.5043 | 2.0446 | 3.3349 | 7.9960 | 1.1135 | 3.0110 |
| 30 | 6.4576 | 7.3571 | 25.5793 | 26.6335 | 5.2502 | 8.6978 | 23.5995 | 2.0758 | 4.0090 |
| 60 | 14.0685 | 10.5965 | 33.8421 | 30.3691 | 5.4962 | 9.6883 | 31.0810 | 6.3697 | 5.9307 |
| 90 | 31.6906 | 17.3037 | 37.9036 | 33.5656 | 6.2822 | 17.5446 | 37.9479 | 16.9686 | 15.0761 |
| 120 | 39.8723 | 19.4382 | 40.1067 | 39.7387 | 7.9794 | 27.1304 | 43.6622 | 31.8271 | 23.5597 |
| 150 | 43.2667 | 22.0587 | 40.5960 | 42.9964 | 18.8612 | 28.8627 | 49.2426 | 42.9352 | 29.7608 |
| 180 | 46.9243 | 23.6481 | 41.5111 | 45.5002 | 21.6944 | 31.2018 | 54.1560 | 45.7999 | 33.2795 |
| 210 | 55.5675 | 25.9630 | 53.7069 | 49.6945 | 29.3103 | 32.1901 | 57.8957 | 50.9161 | 44.7343 |
| 240 | 60.9418 | 29.2069 | 64.0925 | 55.1002 | 31.7704 | 37.2682 | 67.5397 | 60.9612 | 49.3643 |

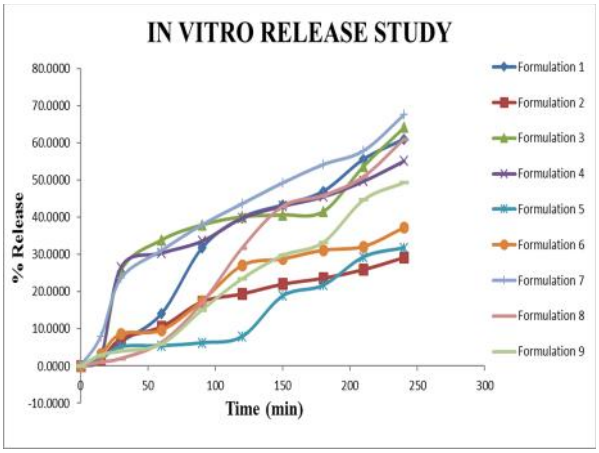


**Fig 2: In-vitro Release Study of Ibuprofen Microspheres**

## 4. CONCLUSION

Controlled release formulations of Ibuprofen microspheres were successfully prepared using sodium alginate in combination with Na-CMC, Ethyl cellulose, HPMC and Carbopol 940 by inotropic gelation technique. The in vitro release data showed controlled release of the formulation up to 4 hours. The microspheres were prepared without the use of organic solvents. The flow characteristic showed Hausner's ratios of <1.35 and Carr's index of 13-20 % indicating good and excellent flow of the systems. The surface morphology of drug-loaded microspheres prepared with sodium alginate and Na-CMC, Ethyl cellulose, HPMC and Carbopol 940 were spherical in shape and has large bridges observed on the outer surface. The entire process is feasible in an industrial scale and demands pilot study. The optimized formulation, drug + Na-alginate + HPMC microspheres demonstrated controlled release of the drug 67.53% for 4 hours. The spherical and free flowing microspheres could be successfully prepared by inotropic gelation technique with better drug content 34.47%. From this study it is concluded that the Ibuprofen microspheres can provide a better carrier system for controlled delivery of drugs. Therefore, one can assume that the Ibuprofen microspheres are promising pharmaceutical dosage forms by providing controlled release drug delivery systems.

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