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Research Article

Preparation and Evaluation of Ketoprofen Loaded Mucoadhesive Microspheres

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Abstract

The aim of the present study was to prepare and evaluate Ketoprofen loaded microspheres fabricated with sodium alginate and Carbopol 934 by ion gelation method which enhances the drug residence time into the stomach by adhering to the mucus layer of and control the rate of drug release for longer period of time. Ketoprofen is a nonsteroidal anti-inflammatory drug (NSAID) that is commonly used for its analgesic, anti-inflammatory, and antipyretic (fever-reducing) properties. It belongs to the propionic acid class of NSAIDs and is available in various formulations, including oral tablets, capsules, topical gels, creams, and as an injectable solution. In present study ketoprofen incorporates in mucoadhesive drug delivery system for utilizing its controlled drug delivery up to 12 hrs. In present study prepared microspheres were evaluated for- particle size, entrapment efficiency, percentage yield, morphology, mucoadhesive property, *in-vitro* drug release property.

Keywords: Mucoadhesive microspheres, NSAID, ion gelation method, ketoprofen

INTRODUCTION

A mucoadhesive microsphere is a small particle or sphere that is designed to adhere to the mucosal surfaces of the body, such as the gastrointestinal tract, nasal cavity, or ocular surfaces. These microspheres are typically composed of biocompatible polymers that have adhesive properties, allowing them to interact with the mucosal surfaces and remain attached for an extended period of time.

Mucoadhesive microspheres have gained significant attention in the field of drug delivery due to their ability to provide sustained and localized drug release. By adhering to the mucosal surfaces, they can overcome various barriers, such as rapid clearance, enzymatic degradation, and the need for frequent dosing associated with conventional drug formulations. These microspheres can be loaded with a variety of drugs, including small molecules, peptides, proteins, and nucleic acids, and can be formulated to release the drug in a controlled manner over an extended period of time. The mucoadhesive properties of the microspheres ensure prolonged contact with the mucosal surfaces, facilitating enhanced drug absorption and bioavailability [1,2,3].

Ketoprofen helps relieve pain by inhibiting the synthesis of prostaglandins, which are chemical messengers involved in pain and inflammation. By blocking the action of cyclooxygenase (COX) enzymes, ketoprofen reduces the production of prostaglandins, thereby reducing pain sensation. Ketoprofen exhibits anti-inflammatory effects by reducing the release of inflammatory mediators such as prostaglandins, leukotrienes, and histamines. By suppressing inflammation, it helps alleviate symptoms associated with inflammatory conditions like arthritis, tendinitis, and gout [4]. Ketoprofen is available as a topical gel or cream for localized application on painful or inflamed areas. When applied to the skin, it penetrates the underlying tissues, providing localized pain relief and reducing inflammation in the affected area [5].

Ketoprofen inhibits both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, although it has a higher affinity for COX-1. COX-1 is involved in various physiological processes, including maintaining the integrity of the stomach lining and regulating blood platelets. COX-2, on the other hand, is induced during inflammation and plays a role in pain and swelling [6]. Ketoprofen can lower fever by inhibiting the production of prostaglandins in the hypothalamus, which is the part of the brain that regulates body temperature. By reducing the production of prostaglandins, ketoprofen helps bring down elevated body temperatures [7].

MATERIALS AND METHODS

Ketoprofen was obtained from Infinity Chemicals Pvt. Ltd, Mumbai, India, Carbopol 934P was purchased from Loba chemical Pvt Ltd, Sodium alginate was purchased from Nice chemicals Pvt Ltd.

Preparation of Mucoadhesive microsphere [8, 9]

1. Ketoprofen, Carbopol 934P, Sodium alginate were pass through 60 no. sieve.
2. Required quantities of Carbopol 934P (mucoadhesive polymer), Sodium alginate were dissolved in purified water and a homogenous polymer solution was made.
3. Ketoprofen was added to the polymeric solution and mixed thoroughly by the help of the magnetic stirrer.
4. The drug-polymeric solution was then added into the calcium chloride solution (2%) drop wise by syringe through needle (size no-18).
5. The resulting droplets were kept into calcium chloride solution up to 15 minutes to obtain its rigidness.
6. Then the prepared microspheres were separated from the solution by filtration.
7. Prepared microspheres were washed and dried at 45^{0}C for 12 hours.

Following table represents the composition of mucoadhesive microspheres.

Table 1: Composition of Ketoprofen loaded mucoadhesive microspheres.

INGREDIENTS	FORMULATION CODES				
	F1(mg)	F2(mg)	F3(mg)	F4(mg)	F5(mg)
Ketoprofen	100	100	100	100	100
Carbopol934P	500	600	400	300	350
Sodium-Alginate	300	200	400	500	450
Calcium carbonate (%)	2	2	2	2	2

Characterization of microspheres

Particle size determination

Particle size of prepared microsphere was determined by optical microscopy. Optical microscopy involves observing microspheres under a microscope and measuring their sizes directly [10].

Drug encapsulation efficiency

Drug encapsulation efficiency (EE) of each formulationwas determined by following formula. It is a measure of the amount of drug that is successfully encapsulated within microspheres during the formulation process. It is an important parameter in drug delivery systems, as it directly influences the therapeutic efficacy and dosage accuracy of the microsphere formulation. Drug encapsulation efficiency can be calculated using the following formula [11].

EE (%) = (Amount of drug encapsulated / Total amount of drug initially added) × 100

Percentage yield

The percentage yield of microspheres was determined by the following formula. It is referring to the efficiency of the microsphere synthesis process. It indicates the proportion of the desired microspheres obtained compared to the theoretical yield, which is the maximum amount that could be produced under ideal conditions.

Use the following formula to calculate the percentage yield [12].

Percentage yield = (Actual yield / Theoretical yield) × 100

Morphology

The morphology of prepared microspheres was determined by scanning electron microscopy (SEM) [13].

Flow properties

The flow properties of prepared microspheres were determined by porosity, angle of repose, Carr's index, Hausner's ratio [14, 15].

$$\text{Carr's index} = \frac{TD - BD}{TD} \times 100$$

$$\text{Hausner's ratio} = \frac{TD}{BD}$$

TD= Tapped density, BD=Bulk density

Mucoadhesive properties

The degree of swelling of mucoadhesive microspheres refers to the extent to which these microspheres increase in size when exposed to a surrounding medium, typically biological fluids or mucosal surfaces. To measure the degree of swelling, the microspheres were placed in acid buffer and allowed to swell to equilibrium. The weight of the microspheres is measured at the initial dry state (W_I) and then again after swelling to a certain time point (W_F). Following formula is used to calculate the Degree of swelling [16].

$$\text{Degree of swelling} = \frac{WF - WI}{WI} \times 100$$

W_I= Initial weight of microspheres before swelling, W_F= Final weight of microspheres after swelling

In-vitro drug release studies

In-vitro drug release study of Ketoprofen loaded mucoadhesive microspheres were carried out in USP type II dissolution apparatus. Prepared microsphere was introduced into 900 ml of 0.1 N HCl buffer solutions and allowed to rotate at 50 rpm at 37±0.5^{0}C for up to 12 hours. Samples were withdrawn after 1-hour intervals and replace with fresh buffer solution for maintaining the sink condition. Then the samples were analyzed under UV spectrophotometer at- 260 nm [17].

RESULT AND DISCUSSION

Particle size determination

The particle sizes of ketoconazole loaded mucoadhesive microsphere were observed by optical microscopy and the range of the particle size was between 64-71mm. Among them F4 formulation was having the smaller sizes (Table 2 and Figure 1).

Table 2: Particle size of microspheres

Formulation code	Particle size (mm)
F1	66
F2	68
F3	69
F4	64
F5	71

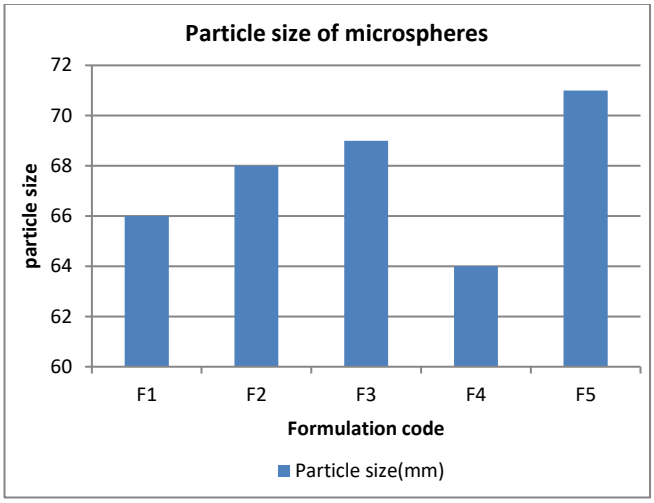

Figure 1: Particle size of microspheres

Drug encapsulation efficiency

By using particular formula drug encapsulation efficiency was calculated and the range was found between 58-85 % (Table 4 and Figure 2).

Table 3: Drug Encapsulation efficiency

Formulation code	Drug encapsulation efficiency (%)
F1	84
F2	74
F3	83
F4	85
F5	58

Percentage yield

The percentage yield of prepared microsphere was calculated and among all formulations F4 showed highest percentage yield (Table 4).

Table 4: Percentage yield

Formulation code	Percentage yield (%)
F1	63
F2	59
F3	72
F4	76
F5	68

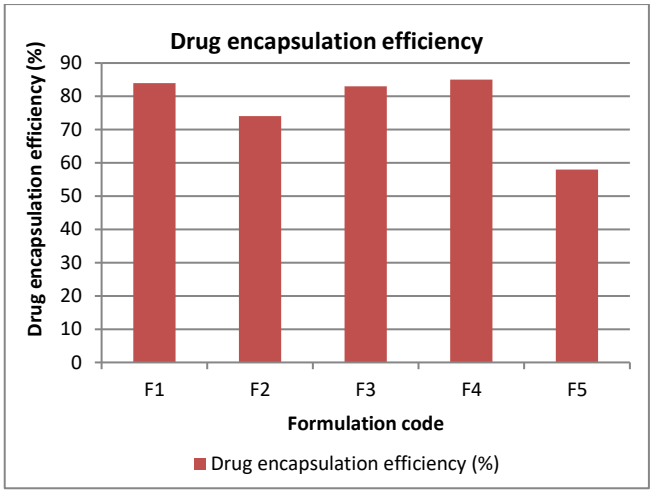

Figure 2: Drug encapsulation efficiency

Morphology

The morphology of prepared microspheres was determined using SEM. All the microspheres were spherical and rough in surface. The graphical representation of the size of the prepared microspheres i.e. the ketoconazole loaded mucoadhesive microspheres were shown in Fig 1.

Flow properties

Angle of repose, Carr's index, Hausner's ratio was determined for study the flow property of prepared microspheres. Among all batches, F4 shows good flow property (given below in table 5).

Table 5: Flow properties

Formulation code	Angle of repose (degrees)	Carr's index (%)	Hausner's ratio
F1	26	12	1.16
F2	31	14	1.15
F3	28	13	1.15
F4	26	11	1.12
F5	27	15	1.14

Mucoadhesive properties

The range of swelling index of prepared mucoadhesive microsphere was between 1.22-1.85 % (given in table 6 and figure 3).

Table 6: Swelling index

Formulation code	Weight of microspheres before swelling (mg)	Weight of microspheres after swelling (mg)	Swelling index (%)
F1	70.26	71.12	1.22
F2	71.19	72.25	1.48
F3	68.24	69.46	1.78
F4	69.36	70.65	1.85
F5	67.21	68.17	1.42

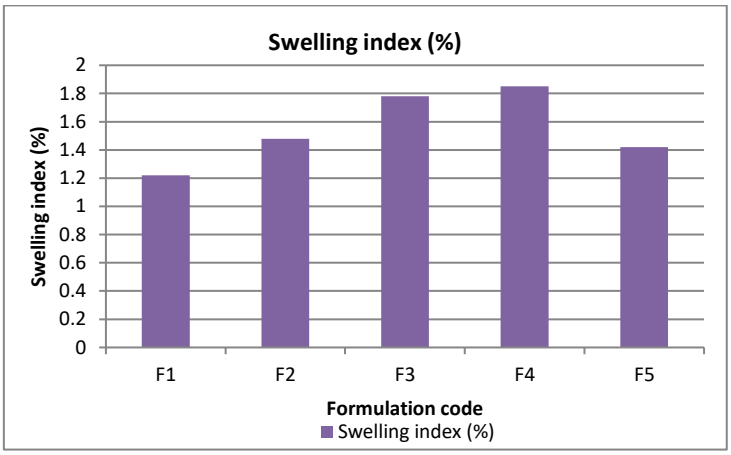

Figure 3: Swelling Index (%)

***In-vitro* drug release studies**

Ketoprofen loaded prepared mucoadhesive microspheres undergo the *in-vitro* dissolution test. In 900 ml of 0.1N HCl, the test was carried out up to 12 hrs and the % CDR were calculated for each formulation. The table 7 and figure 4 show the result and among all formulation batches F4 shows the best % CDR.

Table 7: Cumulative amount of Drug Release

Time	F1 (%CDR)	F2(%CDR)	F3(%CDR)	F4(%CDR)	F5(%CDR)
1	10	12	19	25	26
2	19	22	33	42	32
3	28	30	41	54	43
4	36	39	47	59	58
5	42	46	50	65	64
6	47	52	60	72	78
7	51	58	67	78	84
8	54	61	74	84	87
9	58	66	82	89	91
10	63	72	84	92	92
11	65	79	90	96	94
12	78	86	94	97	96

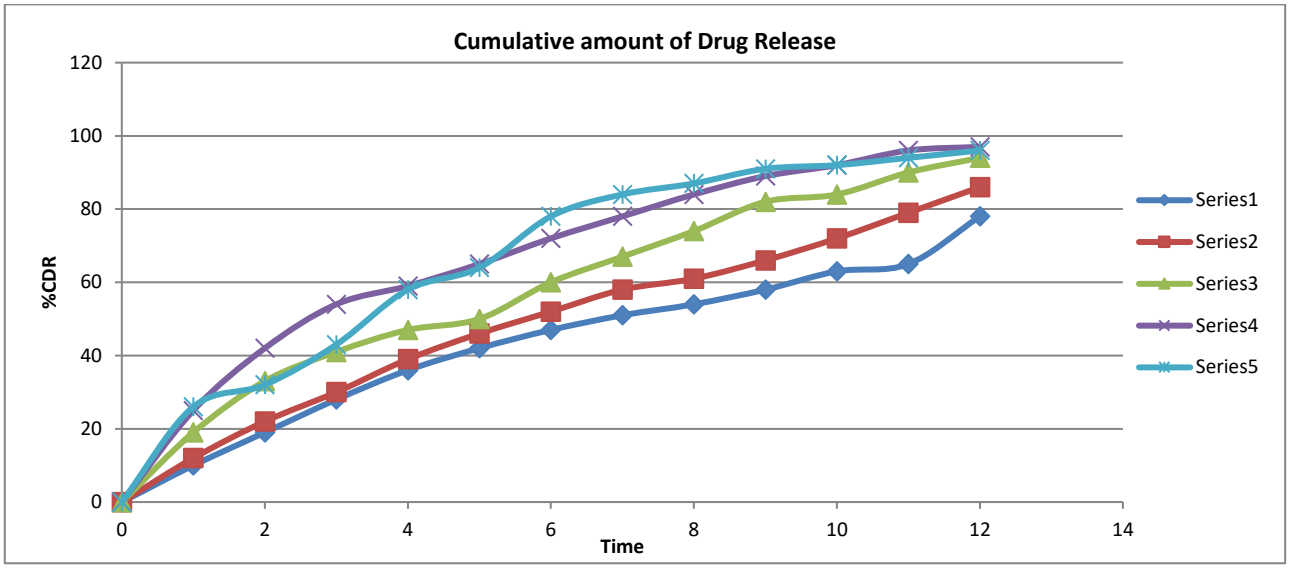

Figure 4: Cumulative amount of Drug Release

DISCUSSION

Ketoprofen loaded microspheres were prepared by ion gelation method by using carbopol934P, sodium alginate, calcium carbonate. After successful preparation they are allowed for different evaluation test like- particle size determination, drug encapsulation efficiency, percentage yield, morphology, flow properties, mucoadhesive properties, *in-vitro* drug release studies. Prepared mucoadhesive microspheres were found spherical and the range particle size was between 64-71 mm, drug encapsulation efficiency was between 58%-85%, percentage yieldwas between 59%-76%, and swelling index was between1.22-1.85% and the, *in-vitro* drug release was up to 94% during 12 hrs in acid buffer.

CONCLUSION

Prepared ketoprofen loaded mucoadhesive microspheres were spherical in shape and showed good flow property as well except that, the microspheres were showed the result of all evaluation test within acceptable range. Among all the formulationsF4 was the best formulation in terms of particle size, drug encapsulation efficiency, percentage yield, flow properties, mucoadhesive properties, *in-vitro* drug release studies.

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