

PREPARATION AND EVALUATION OF MUCOADHESIVE MICROCAPSULES OF IBUPROFEN FOR CONTROLLED RELEASE

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ABSTRACT

The aim of this study was to prepare and evaluate microcapsules containing ibuprofen employing sodium alginate in combination with mucoadhesive polymers namely methylcellulose, Hydroxypropylmethylcellulose and sodiumcarboxymethylcellulose. The microcapsules were prepared by orifice-ionic gelation method. The microcapsules prepared are spherical, discrete, free flowing and were of multinucleate and monolithic type. Microencapsulation efficiency was in the range of 77.81-91.41 %. The *in vitro* drug release of the microcapsules carried out in phosphate buffer pH7.2 and drug release from the microcapsules was slow over 12 h and depends on core:coat ratio, wall thickness and size of the microcapsules. The drug release from all the microcapsules followed non-fickian diffusion. Microcapsules of alginate-methylcellulose gave relatively fast release when compared to others. The order of release rate observed with various microcapsules was sodiumcarboxymethylcellulose < Hydroxypropylmethylcellulose < methylcellulose. Results of our present study suggest that ibuprofen microcapsules can be successfully designed to develop controlled drug delivery, which can improve compliance by reducing dosing frequency.

KEYWORDS: Ibuprofen, Microcapsules, Controlled release.

INTRODUCTION

Ibuprofen, α -methyl-4-(2-methylpropyl)-benzene acetic acid is a non-steroidal anti-inflammatory, antipyretic and analgesic drug. This drug is used for the relief of pain and inflammation in conditions such as dysmenorrhea, migraine, postoperative pain, dental pain. It is also used in chronic disorders as ankylosing spondylitis, osteoarthritis and rheumatoid arthritis for all of which a sustained release is desirable¹. The usually oral dose of drug is 1.2 to 1.8 g divided in different administrations. The drug is readily absorbed from the gastrointestinal tract, and peak plasma concentrations occur about 1 to 2 h after ingestion²⁻³. Unfortunately, ibuprofen causes a certain irritation in the gastrointestinal mucous membrane and possesses a bitter taste and aftertaste. The half-life of the drug in plasma is about 2h. Due to short half life, drug is eliminated from body immediately. So ibuprofen a very good candidate to formulate into controlled release formulations to maintains the therapeutic concentration for prolonged period⁴⁻⁶. At the same time, great attention has been devoted on the possibility to prepare ibuprofen microcapsules in order to formulate oral controlled release systems, to protect the gastric mucous membrane from drug irritation or to mask its unpleasant taste.

Microcapsules are one of the microparticulate systems and are prepared to obtain prolonged or controlled drug delivery, to improve bioavailability or stability and to target drug to specific sites. Microcapsules can also offer advantages like controlling fluctuations within therapeutic range, reducing side effects, decreasing dosing frequency and improving patient compliance. They spread out more uniformly in the GI tract, thus avoiding exposure of the mucosa to high concentration of drug and ensuring more reproducible drug absorption. The risk of dose dumping also seems to be lower than with a single unit dosage form⁷⁻⁹. In this study, ibuprofen microcapsules were prepared by a novel technique, called orifice-ionic gelation method.

MATERIALS AND METHODS

Ibuprofen was obtained as gift sample from M/s Micro Lab. Ltd., Pondichery. Methylcellulose was obtained from Qualigens, Mumbai (having a methoxyl content of 28.32% by weight and viscosity of 65 cps in 0.5% w/v aqueous solution at 25°C), Hydroxypropyl methylcellulose (HPMC), having a viscosity of 50 cps in a 2% by weight aqueous solution at 20°C), Sodium carboxy methylcellulose (Sodium CMC, having a viscosity of 1500 – 3000 cps in a 1% by weight aqueous solution at 25°C) was gift samples from M/s Natco

Pharma Ltd., Hyderabad. Sodium alginate was obtained from SD Fine Chemicals, Mumbai. Calcium chloride was obtained from Qualigens, Mumbai. The other chemicals were of analytical grade and distilled water was used for all experiments.

PREPARATION OF MICROCAPSULES

Sodium alginate (1.0 g) and the mucoadhesive polymer (1.0 g) were dissolved in purified water (32 ml) to form a homogenous polymer solution. The core material, ibuprofen (1.0 g) was finely powdered and passed through mesh No. 120 which was then added to the polymer solution and mixed thoroughly to form a smooth viscous dispersion. The resulting dispersion was then added drop wise into calcium chloride (10% w/v) solution (40 ml) through a syringe with a needle size No. 16. The added droplets were retained in the calcium chloride solution for 15 min to complete the curing reaction and to produce spherical rigid microcapsules. The microcapsules were collected by decantation and the product thus separated was washed repeatedly with water and dried at 45°C for 12 hrs. The microcapsules prepared along with their compositions are listed in Table.1.

EVALUATION OF MICROCAPSULES

The microcapsules prepared were evaluated for the following

Drug content and microencapsulation efficiency

Drug release kinetics

Mechanism of drug release

Drug content

Ibuprofen content in the microcapsules was estimated by the UV spectrophotometrically at 221nm. From each batch of microcapsules, 50 mg each of sample of were taken into 25 ml volumetric flasks and 10 ml methanol was added. The mixture was shaken thoroughly for about 30 min while warming in a hot water bath to extract the ibuprofen from the microcapsules. The solution was then made up to volume with methanol. The methanolic solution was subsequently diluted with phosphate buffer of pH 7.2 and determined for ibuprofen content.

Microencapsulation Efficiency¹⁰

Microencapsulation efficiency was calculated using the formula,

$$\text{Encapsulation efficiency} = \frac{\text{Estimated percent drug content in microcapsules}}{\text{Theoretical percent drug content in microcapsules}} \times 100.$$

Drug Release study

Release of ibuprofen from various microcapsules was studied using a 6-Station Dissolution Test Apparatus (MDA-8/D, microprocessor Marrison's New Delhi, India)

with a basket stirrer over a period of 12 hours. Phosphate buffer of pH 7.2 (900ml) was used as dissolution fluid as prescribed in the drug release test for ibuprofen. A sample of microcapsules equivalent to 200 mg of ibuprofen, a stirrer with speed of 50 rpm and a temperature of 37±0.5°C were employed in each test. Samples (5ml) of dissolution fluid were withdrawn through a filter (0.45µ) at different time intervals and were assayed at 221 nm for ibuprofen. At the end of the experiment the remaining microcapsules were collected and the amount of ibuprofen remaining in the microcapsules were estimated and used in calculating the percent ibuprofen released at various times. Each drug test is repeated three (n=3) times. The percent of ibuprofen released at various times was calculated and plotted against time. The results are given in Fig.1.

RESULTS AND DISCUSSION

Microcapsules of ibuprofen with a coat consisting of sodium alginate and a mucoadhesive polymer namely methyl cellulose, HPMC and sodium CMC in 1:1 and 1:2 ratios could be prepared by the orifice-ionic gelation method. Microcapsules with a coat of mucoadhesive polymer alone could not be prepared because of their water soluble nature. Low coefficient of variation values (<1.0%) in percentage drug content indicated that uniformity of drug content in each batch of microcapsules. The microencapsulation efficiency was in the range of 77.81% - 91.41% shown in Table 2. The microcapsules were found to be discrete, spherical and free flowing. The nature of the method of preparation indicated that the microcapsules were of multinucleate and monolithic type. SEM photographs (Fig.2) indicated that the microcapsules were spherical with smooth surface and completely covered with the polymer coat.

Ibuprofen release from the prepared microcapsules was studied in phosphate buffer P^H 7.2 (900 ml). The drug release profiles are shown in Fig.1 and drug release parameters are summarized in Table.2. Ibuprofen release from all the coated microcapsules was slow and spread over a period of 12 h. Release data were analyzed as per zero order, first order, Higuchi, Peppas equation models to assess the drug release kinetics and mechanism from the microcapsules. The correlation coefficient (r²) values in the analysis of release data as per different kinetic models are given Table3. The analysis of release data as per zero and first order kinetics models indicated that ibuprofen release from the microcapsules followed zero order kinetics. Correlation coefficient (r²) values were higher in the zero order model than those in the first order model with these microcapsules. When the release data were analyzed as per the Peppas equation, the release exponent (n) was in the range of 0.5425- 0.7716

in all microcapsules indicating that the release mechanism from these microcapsules was by non-Fickian diffusion. Ibuprofen release from the microcapsules was slow and dependent on the composition of the coat. Microcapsules of alginate-MC gave relatively fast release when compared to others. The order of release rate observed with various microcapsules was alginate-NaCMC < alginate-HPMC < alginate-MC. The drug released from microcapsules was diffusion controlled, as of amount released versus the square root of time were found to be linear ($r^2 > 0.8906$). Ibuprofen release from microcapsules OMC6 was slow and extended over a period of 12 hours and these microcapsules were found suitable for oral controlled release formulation.

CONCLUSION

It may be concluded that Ibuprofen microcapsules prepared using HPMC, MC and NaCMC as drug release modifiers by orifice ionic gelation technique is inexpensive, free from any organic solvents with low manufacturing cost. The study also indicates that release of drug from the coated microcapsules obeyed diffusion controlled process and zero order release rate kinetics. Finally from the study it may be concluded that mucoadhesive microcapsules of ibuprofen is considered to be promising pharmaceutical dosage forms by providing controlled release drug delivery systems and avoiding the dose related side effects in the entire physiological region and may improve the bioavailability.

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Table1: List of mucoadhesive microcapsules of ibuprofen

S.No	Coat composition	Core: Coat	Code
1	HPMC+Sodium alginate (1:1)	1:1	OMC 1
2	MC + Sodium alginate (1:1)	1:1	OMC 2
3	NaCMC + Sodium alginate 1:1)	1:1	OMC 3
4	HPMC +Sodium alginate(1:1)	1:2	OMC 4
5	MC+ Sodium alginate(1:1)	1:2	OMC 5
6	NaCMC + Sodium alginate (1:1)	1:2	OMC 6

HPMC- Hydroxy propyl methyl cellulose, MC-Methyl Cellulose, NaCMC-sodium caboxy methyl cellulose

Table 2: Drug Content, Encapsulation Efficiency and Release Characteristics of mucoadhesive Microcapsules of Ibuprofen

Micro-capsules	Core: Coat	Drug content (mean \pm SD)	Encapsulation efficiency	K_0 (mg/ h)	K_1 (h^{-1})	'n' in Peppas equation
OMC1	1:1	43.73 \pm 0.256	81.21	13.052	0.198	0.6342
OMC2	1:1	48.36 \pm 0.137	91.41	16.648	0.227	0.5425
OMC3	1:1	50.00 \pm 0.101	85.21	10.185	0.148	0.7581
OMC4	1:2	49.60 \pm 0.561	79.21	8.251	0.097	0.7516
OMC5	1:2	49.59 \pm 0.266	77.81	9.362	0.115	0.6911
OMC6	1:2	49.44 \pm 0.551	90.12	5.948	0.046	0.7716

Values are given as mean \pm SD of n=3 determinations

Table 3: Correlation Coefficient (r^2) Values of Mucoadhesive Microcapsules of Ibuprofen as per Various Kinetic Models

Microcapsules	Correlation coefficient (r^2) values			
	Zero order	first order	Higuchi	Peppas
OMC 1	0.9652	0.8767	0.9863	0.988
OMC 2	0.9501	0.8348	0.9545	0.9371
OMC 3	0.9836	0.8651	0.9239	0.8975
OMC 4	0.9814	0.8718	0.9271	0.969
OMC 5	0.9614	0.7473	0.8963	0.9288
OMC 6	0.9692	0.8452	0.8906	0.9775

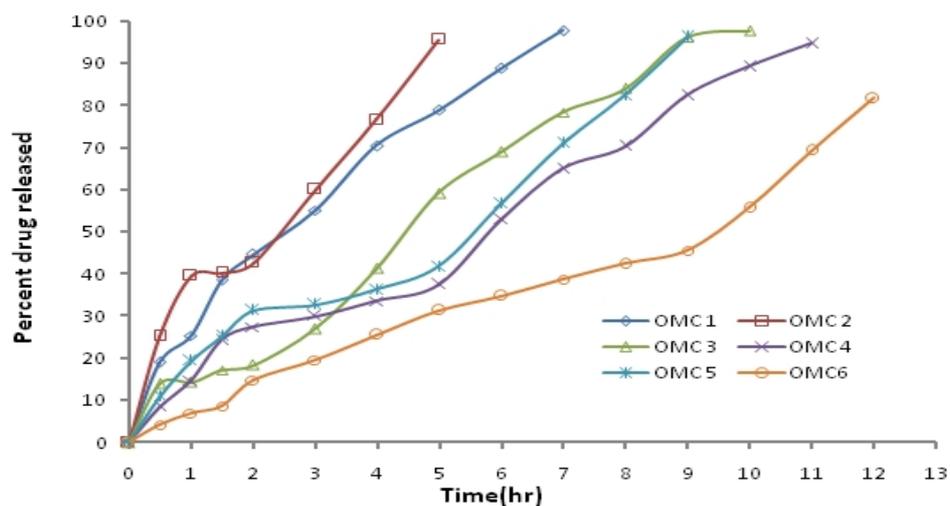


Fig 1: Drug release profiles of mucoadhesive microcapsules of ibuprofen

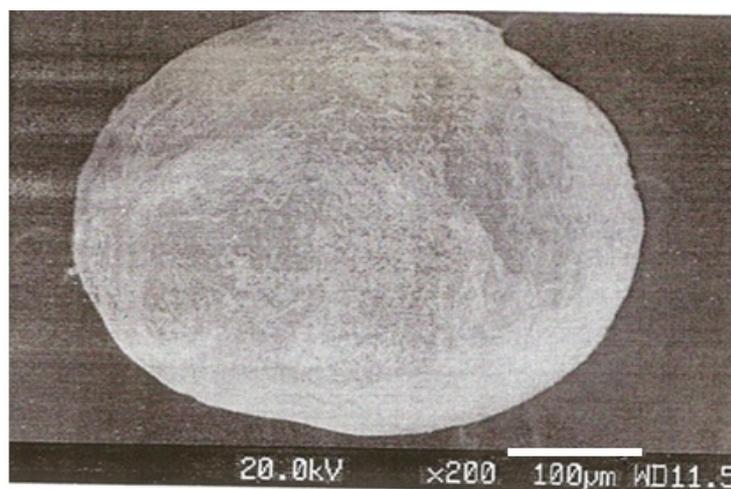


Fig 2: SEM photograph of mucoadhesive microcapsules of ibuprofen

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