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FORMULATION AND SYSTEMATIC EVALUATION OF MUCOADHESIVE MICROSPHERES OF IBUPROFEN

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ABSTRACT

Drugs are often required to be administered over a prolonged period which may necessitate high frequency of administration for those with short half-lives. Controlled drug delivery systems allow therapeutic agents to be delivered at predefined rates, locally or systemically, for a specified period. Microspheres have been developed as carriers for delivering therapeutic agents to their target sites in a controlled release manner. Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID), has a short half-life (1–3 hours) and is typically administered 3-4 times daily with subsequent adverse side effects. In the present study, batches of muco-adhesives microspheres of ibuprofen consisting of various combinations of sodium alginate, hydroxypropymethylcellulose and chitosan were prepared by orifice ionic gelation method. Calcium chloride was used as cross-linker and the drug–polymer ratios were varied. Compatibility study between drug and polymer was done by FTIR. Wash off test was carried out to assess muco-adhesive properties. The prepared microspheres were evaluated for particle size, angle of repose, Carr's index, microencapsulation efficiency, percent drug content, drug release, kinetics and mechanism of drug release. The compatibility study showed no interaction between the drug and polymer. The microspheres were discrete, spherical, free flowing with particle size in the range of 736±0.3 - 797±0.4µm. The encapsulation efficiency was found in the range of 56 ± 0.4 – 70 ± 0.7%. All the microspheres showed good muco-adhesive properties, gave prolonged release which followed first order kinetics with non-fickian release mechanism that was dependent on nature and concentration of polymers. The present study demonstrated that ibuprofen can be considered for mucoadhesive drug delivery containing HPMC and chitosan as mucoadhesive polymers for controlled release of the drug over a period of minimum of 10 hours to maximum of over 12 hours which is however dependent on the concentration and nature of polymers for the gradual reduction of pains and fever.

KEYWORDS: Chitosan, Hydroxypropylmethylcellulose, Ibuprofen, Mucoadhesive microspheres, Orifice ionic gelation, Sodium alginate.

1. INTRODUCTION

Over the past three decades oral controlled release dosage forms have been developed and patented due to considerable therapeutic advantages such as ease of administration, patient compliance and suppleness in formulation.[1-4] However, this approach is associated with several physiological difficulties such as inability to restrain and locate the controlled drug delivery system within the desired region of the gastrointestinal tract (GIT) due to variable gastric emptying and motility. Furthermore, the relatively short residence time of the drug in humans which normally averages 2-3 h through the major absorption zone, i.e., stomach and upper part of the intestine, can result in incomplete drug release from the drug delivery system leading to reduced efficacy of the administered dose.[5,6]

Therefore, control of the placement of a drug delivery system in a specific region of the GI tract offers advantages for a variety of important drugs characterized by a narrow absorption window in the GIT or drugs with a stability problem.[7]

These considerations have led to the development of a unique oral controlled release dosage form with gastro-retentive properties. There are numerous approaches which have been adopted to develop gastro-retentive dosage form for prolonging the gastric residence time. Gastro-retentive dosage form may be broadly classified into muco-adhesive systems, floating systems, high density systems, expendable systems, super porous hydrogel systems and magnetic systems.[8-12] These systems enable oral therapy of drugs with narrow absorption window in upper part of GIT, drugs that have

short half-life ($t_{1/2}$ 2-8 h) or drugs with poor stability. Furthermore, the gastro-retentive systems can act locally within the stomach and prolong the intimate contact with the absorbing membrane thus increasing their efficacy. The most common approach to gastro retentive system was based on floating systems. However, floating devices administered in a single-unit form such as hydrodynamically balanced systems (HBS) are unreliable in prolonging gastro-retention owing to their 'all-or-none' emptying process. Thus, they may cause high variation in bioavailability and local irritation due to large amounts of drug delivered at a particular site of the GIT.[13] In contrast, multiple-unit particulate dosage forms (e.g. muco-adhesive microspheres) have the advantages that they pass uniformly through the GIT to avoid the vagaries of gastric emptying and provide an adjustable release, thereby, reducing the inter-subject variability in absorption and risk of local irritation. A multi-particulate system, such as one containing microspheres can become mixed with the food and as a consequence, will usually empty with the food over an extended period of time.[14] Drugs used in the gastro-retentive dosage forms include floating microspheres of aspirin, griseofulvin, p-nitroaniline, ibuprofen, ketoprofen etc.[15] Muco-adhesive delivery system is desirable for drugs with an absorption window in the stomach or in the upper small intestine.[16]

Chitosan, a cationic polymer, is the most extensively investigated for muco-adhesive system. It is the most abundant polysaccharide in the world, next to cellulose.[17] Chitosan is gaining increasing importance due to its good biocompatibility, biodegradability and favorable toxicological properties.[18-23] The linearity of chitosan molecules also ensures sufficient chain flexibility for interpenetration.[24] Whilst chitosan may provide improved drug delivery via a muco-adhesive mechanism, it has also been shown to enhance drug absorption via the paracellular route through neutralisation of fixed anionic sites within the tight junctions between mucosal cells.[25,26]

Ibuprofen, a non-steroidal anti-inflammatory drug (NSAID) acts by reducing hormones that cause inflammation and pain in the body. Ibuprofen is used to reduce fever and treat pain or inflammation caused by many conditions such as headache, tooth, back pain, arthritis, menstrual cramps or minor injury. It is taken 400 – 800 mg/orally every 6 to 8 hours. This dose may be increased to maximum dose of 3200mg based on patient response and tolerance. Ibuprofen is mostly absorbed in the duodenum (small intestine.). It cannot be absorbed through the lining of the stomach acid, since it dissolves in water better at higher pH. Ibuprofen is rapidly metabolized and eliminated in the urine.[27,28,29,30]

The excretion of ibuprofen is virtually complete 24 h after the last dose. The half-life is 1.8 to 2 h. Thus, such controlled delivery of ibuprofenis required for ibuprofen to prolong its duration of action, reduce frequency of administration and thus improve patient compliance. Controlled release products of ibuprofen also avoid the side effect of nausea, dyspepsia, gastrointestinal ulceration due partly to bolus entry of immediate release ibuprofen.[31]

The objective of this study is to develop, characterize and evaluate muco-adhesive microspheres of ibuprofen using muco-adhesive polymers consisting of various combinations of sodium alginate, hydroxypropy methylcellulose and chitosanfor prolonged gastrointestinal absorption and release.

2. MATERIALS AND METHODS

2.1 Materials

Ibuprofen, chitosan was procured from Sigma Aldrich (St. Louis, MO, USA). sodium alginate from Lobachemie, calcium chloride from Thermo fischer Scientific, India PVt Ltd., HPMC from Lobachemie and chitosan from Sigma Aldrich (St. Louis, MO, USA). All other reagents and chemicals are of analytical grades.

2.2 Method of preparation of microspheres

Batches of microspheres were prepared by orifice ionic gelation method which involves reaction between sodium alginate and polycationic ions like calcium to produce a hydrogel network of calcium alginate. Sodium alginate (75 mg) and the mucoadhesive polymer HPMC or chitosan (75 mg) were dispersed in purified water, pH 6.8, (25 mL) to form a homogeneous polymer mixture. The API (ibuprofen) was added to the polymer premix and mixed thoroughly with a stirrer to form a viscous dispersion. The resulting dispersion was then added into a syringe of 22-gauge needle and allowed to fall as droplets into calcium chloride ($10\%^{w}/_{v}$) solution. The droplets were retained in the calcium chloride solution for 15 minutes to complete the curing reaction and to produce rigid spherical microspheres. The microspheres were collected by decantation and the product thus separated was washed repeatedly with purified water to remove excess calcium impurity deposited on the surface of microspheres and then dried. Microspheres were prepared as shown in the formula given in Table 1.

Table 1: Formulation design of mucoadhesive ibuprofen microspheres.

Batch	Drug: Polymer Ratio	Polymer Composition/Ratio/Quantity
F1	1:2	Na Alginate: HPMC (1:2) (50mg : 100mg)
F2	1:3	Na Alginate : HPMC (1:2) (75mg : 75mg)
F3	1:2	Na Alginate : Chitosan (1:1) (75mg : 75mg)
F4	1:3	Na Alginate : Chitosan (1:1) (75mg : 75mg)
F5	1:2	Na Alginate : HPMC : Chitosan (1:1:1) (50mg : 50mg : 50mg)

Table 2: Particle size, Angle of repose, Carr's index, swelling index of mucoadhesive microspheres.

S/no	Formulation	Particle size (µ)	Angle of repose	Carr's index	Swelling index
1	F1	736±0.3	24.8±0.1	10.6	1.50
2	F2	774±0.4	24.6±0.2	11.67	1.48
3	F3	770±0.7	24.5±0.1	10.86	1.40
4	F4	756±0.5	24.8±0.2	11.47	1.64
5	F5	797±0.4	24.4±0.1	10.73	1.53

2.3 Preparation of standard graph of ibuprofen

A spectrophotometric method (Model Cintra 6, Type GBC UV-Visible, GBC, Scientific Equipment Ltd., Victoria, Australia) based on the measurement of absorbance at 238 in a phosphate buffer of pH 6.8 containing 1% SLS was used for the estimation of ibuprofen.

2.2.2 FTIR compatibility studies

FTIR analysis was carried out to analyze the compatibility between drug and polymers used in the formulation i.e. chitosan, hydroypropylmethylcellulose, sodium alginate. The studies were carried out using combination of drug and polymers and drug alone. The samples were characterized using infrared spectrophotometer (Shimadzu IR Prestige 21, China) in the range of 400 to 4000 cm^{-1} using at least 64 scans with 8 cm^{-1} resolution in the spectral range 4000cm^{-1}.

2.3 Evaluation of microspheres

2.3.1 Size analysis

The size of the microspheres was determined using the Olympus optical microscopy. The diameter of 100 micro-spheres was determined.[32]

The average diameter was calculated using the following formula:

$$\text{Average diameter} = \Sigma\, nd/n \times C.F \text{----------(1)}$$

Where n = number of microspheres

d = diameter of microcapsules

C F = calibration factor

2.3.2 Carr's index

Carr's index was calculated using the formula.[33]

$$\text{Carr's index(c)} = \frac{\text{Bulk density-Tapped density}}{\text{Tapped density}} \times 100\text{--(2)}$$

2.3.3 Bulk and Tap density

2.3.3.1 Evaluation of Ibuprofen muco-adhesive microspheres

Ibuprofen microspheres (30g) were placed in a 100mL clean, dry measuring cylinder and the bulk volume Vb occupied without tapping was determined. After 40 taps on a flat horizontal surface, the tapped volume Vt occupied was also determined. The bulk and tapped were calculated as the ratio of weight to volume (Vb and Vt respectively).

***2.3.3.2 Angle of repose.*[33]**

A funnel was fixed in a stand in such a way that the top of the funnel was at a height of 2 cm from the surface. The microspheres were passed through the funnel so that they form a heap. The height and the radius of the heap were measured and the angle of repose was calculated using the equation:

$$\Theta = \text{Tan}^{-1}\,(h/r) \text{----------(3)}$$

***2.3.3.3 Swelling index of microspheres.*[34]**

Swelling index was determined by measuring the extent of swelling of microspheres in the given buffer to ensure the complete equilibrium. Exactly 1mL of microspheres bed was allowed to swell in a phosphate buffer (pH 6.8) inside a 10mL measuring cylinder. The excess surface liquid drops were removed by blotting and the swollen microspheres were weighed by using a chemical balance. The microspheres were then dried in an oven at 60^{o}C for 5 h until there was no change in the dried mass of sample. The swelling index of the microspheres was calculated using the formula:

Swelling index = (mass of swollen microspheres - mass of dry microspheres) × 100-------(4)

2.3.3.4 Percent drug content

Ibuprofen microspheres were estimated by UV spectroscopic method based on the measurement of absorbance at 238 nm in phosphate buffer of pH 6.8. From each batch 20 mg of microspheres were crushed to fine powder in a mortar, extracted with 10 ml of methanol for half an hour, the methanolic solution was subsequently diluted with phosphate buffer of pH 6.8 and assayed for Ibuprofen by measuring absorbance at 238 nm. Ibuprofen content of microspheres was calculated using the calibration curve shown in Figure 1.[33]

Microencapsulation efficiency

Microencapsulation efficiency was calculated using the following formula.

$$\text{Microencapsulation efficiency} = \frac{\text{Estimated \% drug content}}{\text{Theoretical \% drug content}} \times 100\text{---------(5)}$$

***In vitro* wash-off test for microspheres[35]**

The muco-adhesive properties of the microspheres were evaluated by *in vitro* wash-off test. A 1-cm by 1-cm piece of rat stomach mucosa was tied onto a glass slide (3-inch by 1-inch) using thread. Microspheres (50) were spread onto the wet, rinsed, tissue specimen, and the prepared slide was hung onto one of the groves of a USP tablet disintegrating test apparatus. The disintegrating test apparatus was operated such that the tissue specimen was given regular up and down movement in a beaker containing saline. At the end of 5 hrs the percentage

muco-adhesion was calculated by the following equation:

% Mucoadhesive =

Number of microsphere adhered X 100---(6)

Number of microspheres

Preparation of standard graph of ibuprofen

A spectrophotometric (Shimadzu IR Prestige 21, China) method based on the measurement of absorbance at 238 nm in a phosphate buffer for pH 6.8 containing 1% sodium lauryl sulphate (SLS) was used in the present study for the estimation of ibuprofen in the formulation and *in vitro* studies.

***In vitro* drug release[33]**

The drug release study was carried out using USP XXIV paddle stirrer at 37±0.5^{o}C and at 50 rpm using 900 mL of phosphate buffer (pH 6.8) containing 1% sodium lauryl sulphate (SLS) as dissolution medium. Microspheres equivalent to 20 mg of Ibuprofen were used for the test. Five milliliters of sample solution was withdrawn at predetermined time intervals, filtered, diluted suitably, and analyzed spectrophotometrically (Model Cintra 6, Type GBC UV-Visible, GBC, Scientific Equipment Ltd., Victoria, Australia). An equal amount of fresh dissolution medium was replaced immediately after withdrawal of the test sample. Percentage drug released at different time intervals was tabulated and dissolution profile of the formulations were generated as plots of percent drug release vs time.[33]

Kinetics of drug release

To determine the mechanism of drug release from the microspheres, the results obtained from the *in vitro* drug release studies were analyzed by various kinetic models:

1. Zero order drug release: cumulative % drug release vs time.
2. First order drug release: log cumulative % drug retained vs time
3. Higuchi's classification diffusion equation: cumulative % drug release vs square root of time
4. Peppas-Korsemeyer exponential: log cumulative % drug release vs log time.[36,37]

Analysis of release data

The rate and mechanism of release of Ibuprofen from the prepared microcapsules were analyzed by fitting the release data into zero order equation, $Q = Q_o - K_o t$ (1), where Q is the amount of drug release at time t and K_o is the release rate; first order equation $Ln\ Q = Ln\ Qo - K_1 t$ (2), where K_1 is the release rate constant and Higuchi's equation, $Q = K_2 t^{1/2}$ (3), where Q is the amount of drug released at time t and K_2 is the diffusion rate constant. The release data were also analyzed as per Peppa's equation[3]. $Mt/M_\infty = Kt^n$ (4), where Mt/M_∞ is the fractional release of the drug, t is the release time, K is a constant incorporating structural and geometric characteristics of the release device, 'n' is the release exponent indicative of mechanism of release. For non-Fickian (anomalous/zero order) release, 'n' value is between 0.5 to 1.0; for Fickian diffusion, $n \leq 0.5$; for zero order release, $n = 1$; for super case transport II, $n > 1$; 'n' is estimated from linear regression of log (M_t / M) Vs log t.

RESULTS AND DISCUSSION

The ionic gelation method was used due to its simplicity and reproducibility.[37-41] The micrographs of the microspheres reveal that the ibuprofen microspheres containing the polymers were discrete, spherical in shape and free flowing. The microspheres prepared were in the size range of 736 ± 0.3 to 797 ± 0.4 µm and was in the rank order of F5>F2>F3>F4>F1 as shown in Table 3. Microspheres containing 75mg sodium alginate and 75 mg HPMC as polymer at ratio 1:1 were observed to have the smallest while microspheres containing 50mg sodium alginate, 50mg HPMC and 50mg chitosan as polymer at ratio 1:1:1 had the largest size. Particle size was observed to increase as polymer: drug ratio and total amount of polymer increased possibly due to increased viscosity of the polymer-drug dispersion which produced larger droplets that formed larger particles as shown in Table 1.

Carr's Index values suggest good flow of the microspheres at a rank order of F4>F2>F3>F5>F1as shown in Table 1.

Entrapment efficiency was in the range of 56 ± 0.4 to 70 ± 0.7% and observed to increase with increase in amount of polymer (Table 3). Ibuprofen microspheres containing 50mg each of sodium alginate, chitosan and HPMC at ratio 1:1:1 had significantly higher values ($p < 0.05$) than other formulations. Entrapment efficiency increased with increase in polymer: drug ratio.

From the dissolution profile, the time taken for 80% drug release (t_{80}) was determined. The ranking of t_{80} values were F5>F1>F2>F3>F4 as shown in Table 4. The quantity of drug released was observed to increase with increase in amount of polymer with polymer sodium alginate, HPMC and chitosan giving the fastest dissolution. The span of release of medicament from the microsphere formulations containing the starches was prolonged enough to justify the proposed polymer systems as drug release modulators for controlled delivery of ibuprofen.

Table 3: Particle size, percentage drug release, microencapsulation efficiency, % mucoadhesion of mucoadhesive microsphere.

Formulation	Particle size (μ)	% Drug content	Microencapsulation efficiency	% Mucoadhesion
F1	736±0.3	72.54	56±0.4	57±0.3
F2	774±0.4	73.81	58±0.3	67±0.6
F3	770±0.7	86.64	57±0.6	64±1.3
F4	756±0.5	84.21	63±0.4	75±0.7
F5	797±0.4	90.23	70±0.7	83±0.4

The FTIR spectra of pure ibuprofen and ibuprofen in combination with HPMC, chitosan, sodium alginate are presented in Figures 2, 3, 4, 5 respectively. It was observed that peaks were obtained as O-H, (stretching vibrations of O-H bonds of alginate appeared in the range 3000 – 3600 cm^{-1}) N-H stretch from chitosan, C=O stretch and carboxylic aromatic vibrations and a sharp peak of carbonyl group. The FTIR spectra obtained from pure drug and in combination with polymers showed no shift from the original peaks indicating that there was no interaction between pure drug and the polymers.

Figure 1: FTIR spectra of pure drug ibuprofen.

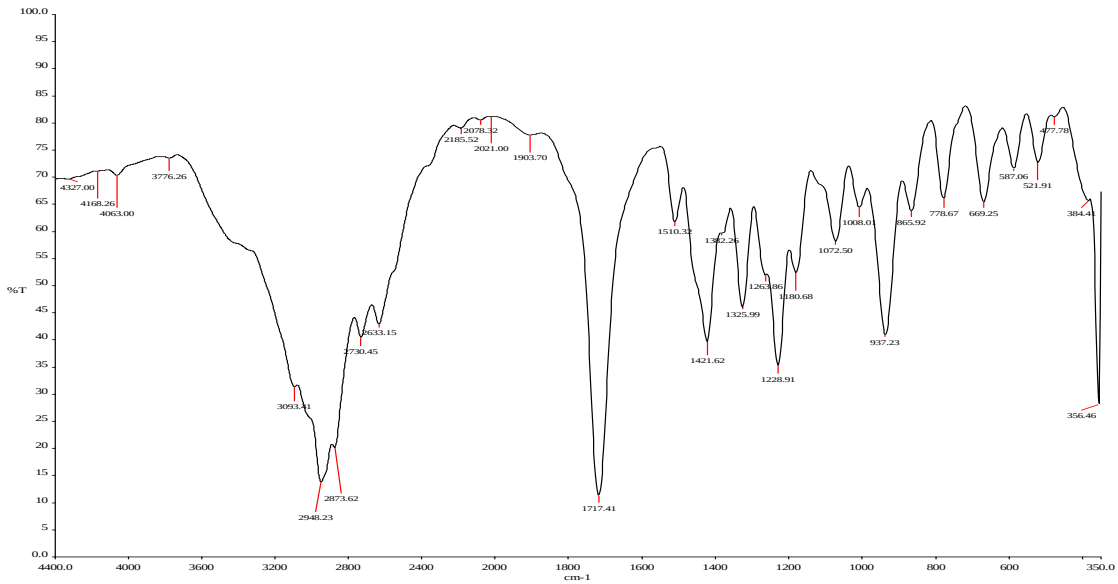

Figure 2: FTIR combination of drug and HPMC.

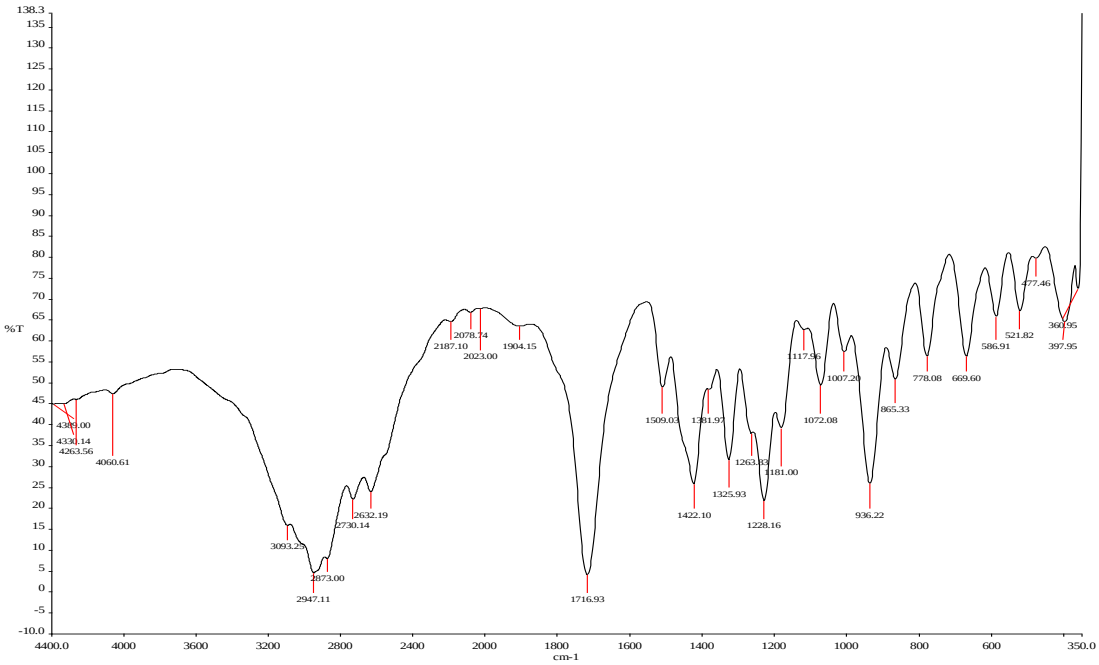

Fig. 3: FTIR spectra of drug and sodium alginate.

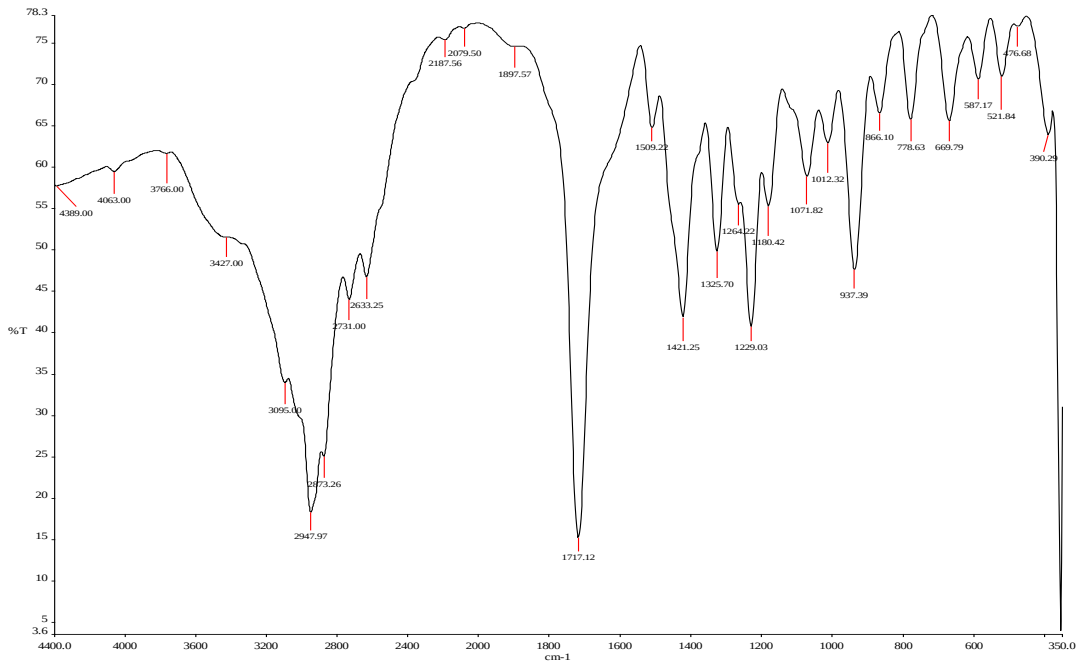

Figure 4: FTIR spectra of drug and chitosan.

Ibuprofen microspheres containing the polymers were discrete, spherical and free flowing. The size of the microspheres was determined by optical microscopy and the size analyses of different microspheres are presented in Table 4. Size analysis showed that they are almost uniform in size as they are made from same needle and the values range between 736 to 797µ. Percentage drug content of different microspheres are also presented in Table 4.

The results showed drug content was uniform and found to be within the limits. The microencapsulation efficiency presented in Table 4 showed values between 57 to 70%. The order of microencapsulation efficiency was found to be F5 > F4 > F2 > F3 > F1. *In vitro* wash off test was performed to assess the mucoadhesivity of the microspheres for 4 hours. F5 showed the highest mucoadhesivity of 83% due to the presence of combination of mucoadhesive polymers HPMC and chitosan. F1 containing HPMC only showed the lowest mucoadhesivity of 57%.

Drug release from microspheres was studied in phosphate buffer pH 6.8. The release data are given in Tables 4 and 5 while the release profile is graphically represented in Fig. 5. Ibuprofen release from all the

microspheres was slow and spread over a period of minimum of 8 hours and maximum of 10 hours and maximum of over 12 hours, dependent on nature of polymer and concentration of polymer. The correlation coefficient (r) values in the analysis of release data as per different kinetic models are given in Table 5.

Analysis of release data as per zero and first order kinetic models indicated that ibuprofen release from the microspheres followed first order kinetics. The correlation coefficient r values in the first order model were higher than those in the zero order model (Table 5). Correlation coefficient r values in Higuchi equation near to one show the release was controlled by diffusion mechanism. When the release data were analyzed using Peppas equation the release exponent n > 0.5 with all the formulation indicating non-fickian diffusion as the release mechanism. For Ritger-Peppas models, the release exponent n ≤ 0.5 for Fickian diffusion release from slab (non swellable matrix), 0.5 < n < 1.0 for non-Fickian release (anomalous), this means that drug release followed both diffusion and erosion controlled mechanisms and n = 1 for zero order release, where drug release is independent of time [30, 37-38]. [35, 42-44] Also, 0.45 < n < 1.0 for non-Fickian release (anomalous) from cylinders (non swellable matrix) and 0.43 < n < 1.0 for non-Fickian release (anomalous) from non swellable spherical samples. For Korsmeyer-Peppas models, the release exponent n ≤ 0.45 for Fickian diffusion release and 0.45 < n < 0.89 for non-Fickian release (anomalous).

Table 4: Release data of ibuprofen mucoadhesive microspheres.

	Time of release (hours)											
Formulation	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
F1	10	21	41	55	57	61	62	71	74	80	82	84
F2	10	22	40	56	58	59	62	63	70	74	74	-
F3	11	23	43	49	54	56	59	64	68	72	72	-
F4	12	21	49	48	50	54	58	60	62	68	-	-
F5	12	20	38	46	54	62	71	75	84	85	85	85

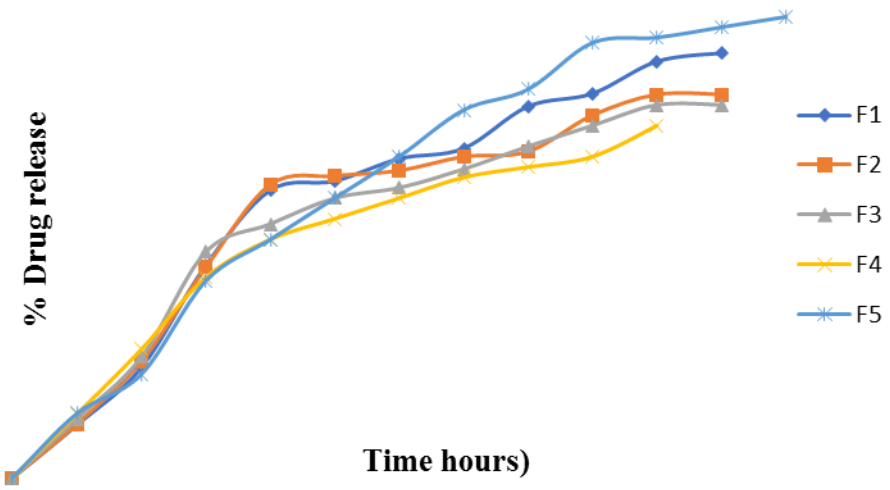

Figure 5: Drug release profile for microspheres.

Table 5: Correlation coefficient 'r' values in the analysis of release data of microspheres as per various kinetic models and 'n' value in Peppas.

Formulation	Zero order	First order	Higuchi	Peppas equation	n in Peppas equation
F1	0.9573	0.9374	0.9532	0.8473	0.9204
F2	0.9274	0.9322	0.9736	0.8956	0.7246
F3	0.9418	0.9647	0.9648	0.9321	0.7122
F4	0.9796	0.9847	0.9634	0.9644	0.7844
F5	0.9487	0.9658	0.9332	0.8967	0.8112

CONCLUSION

Mucoadhesive microspheres of ibuprofen showed good controlled release properties. The results of the present study demonstrated that ibuprofen can be considered for mucoadhesive drug delivery containing HPMC and Chitosan as mucoadhesive polymers for controlled release of the drug over a period of minimum of 10 hours to maximum of over 12 hours which is however dependent on the concentration and nature of polymers for the gradual reduction of pains and fever. Of all the formulations, F5 which contains combination of

polymers showed good entrapment efficiency, mucoadhesion and drug release profile and therefore it can be considered as best formulation.

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