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Preparation and evaluation of ibuprofen loaded sodium alginate/sodium CMC mucoadhesive drug delivery system for sustained release

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ABSTRACT

In the present study, ibuprofen was formulated as Mucoadhesive microspheres by ionic gelation technique by using varying concentrations of polymers sodium alginate and sodium carboxy methyl cellulose. The mucoadhesive microspheres of Ibuprofen was characterized by drug content, particle size distribution, production yield, *in vitro* drug release, and entrapment efficiency. The XRD study suggested that there is a change in the physical behavior of drug from crystalline to amorphous within the formulation. SEM of optimized batch showed that particles were found to be spherical having a rough outer surface and was porous. The EE of microspheres ranged from about 28.69-68.51 %. The cumulative amount of drug released was found to be in the range of 43.72-84.39 %. The data obtained from the *in-vitro* drug release profiles of Ibuprofen determined that all the batches of mucoadhesive microspheres showed prolonged drug release. It could be concluded that the mucoadhesive microspheres of Ibuprofen showed prolonged release of the drug.

Keywords: Solubility, drug release, ibuprofen, drug entrapment efficiency.

INTRODUCTION

Microspheres may be described as solid, nearly globular particles size range from 1-1000 μm. Substances could be included inside microspheres in the solid or liquid state by synthesizing or consequently by absorption. Microspheres

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or microparticles are common terms that include both microcapsule & micro matrix. In micro-capsules, the entrapped substance is entirely enclosed by an individual capsule is hedged and in micromatrices, the entrapped substance is distributed all through the microsphere model. Microspheres comprise an essential section of an innovative drug delivery system because of their mini size and productive transporter measurements[1]. Microspheres with mucoadhesive properties can be developed for both targeted and controlled release drug delivery systems. Microspheres are commonly used for drug delivery to the systemic circulation and constitute a significant part of such novel drug delivery systems[2]. The mucosal membranes of organs such as gastrointestinal tract (GIT), ocular, buccal, vaginal, rectal and nasal are the various sites of drug absorption[3].

Ibuprofen is an Non-Steroidal anti-inflammatory drug (NSAID) taken orally to relieve inflammation, fever, and pain initiated by various disorders such as toothache, headache, menstrual cramps, back pain, minor injury and arthritis[4,5]. Ibuprofen is very effective for treating arthritis of joints (Rheumatoid Arthritis) and for treating osteoarthritis, high doses are required approximately 1800-3200 mg daily (or 200-800 mg every 4-6 h as a single dose). Although it has a short plasma half-life of 1-5 h following oral dosing which makes it a standard candidate for modified release formulation[6], it works by decreasing hormones. Ibuprofen is a monocarboxylic acid that is propionic acid derivative. Ibuprofen is biopharmaceutical classification system (BCS) class II drug (High permeability, low water solubility) and well absorbed from the gastrointestinal tract. It has low water solubility and is the limiting step for absorption and bioavailability. Exposure of stomach to high level of Ibuprofen can cause gastric irritation (ulceration or bleeding). Due to the narrow therapeutic index, 95% of the administered dose gets excreted from the body after 4 h of administration[7]. To overcome the problem of solubility and for achieving sustained/controlled drug delivery, a mucoadhesive drug delivery system (MDDS) containing mucoadhesive microspheres of ibuprofen has been formulated which would lead to less frequent dosing and therefore lower level of gastric irritation. Thus, the development of controlled-release dosage forms would clearly be useful. Investigators have formulated oral controlled-release products of ibuprofen by numerous methods [8-13]. MDDS utilize the property of bioadhesion of certain water soluble polymers that become adhesive to mucous membranes on hydration[14] and hence can be used for targeting a drug to a particular mucus tissue (e.g. gastrointestinal, buccal, nasal, etc.) for an extended period of time[15].

Sodium alginate, the sodium salt of alginic acid, is a natural hydrophilic polysaccharide containing two types of monomers, beta-D-mannuronic acid (M) and alpha-L-guluronic acid (G). Alginate forms 3-dimensional ionotropic hydrogel matrices, generally by the preferential interaction of calcium ions with the G moieties resulting in the formation of an inhomogeneous gel[16]. Sodium CMC was combined in formulation to improve viscosity and for the additive effect of mucoadhesive property. Sodium CMC was selected as a polymer instead of other polymers due to its better mucoadhesive capacity in comparison to that of other mucoadhesive polymers like poly (acrylic acid) (PAA), polycarbophils.

The objective of the present work was to develop mucoadhesive microspheres of ibuprofen to enhance its dissolution, bioavailability and control of drug release. To prepare the mucoadhesive microspheres of Ibuprofen, use two biocompatible polymers (Sodium alginate and Sodium CMC) in combination. To control/sustain the release of drug, decrease the frequency of dosing. To establish the relationship between formulation variable, select responses and characterization of mucoadhesive microspheres for improving the bioavailability of Ibuprofen at the target site of the mucosa. The optimized mucoadhesive microspheres batch were extensively characterized by SEM, FTIR, DSC, XRD and further evaluated for *in-vitro* drug release profile, and stability studies.

METHODOLOGY

Materials

Ibuprofen was purchased from Alkem Pharmaceuticals (P) Ltd., Baddi (india), Sodium alginate and Sodium CMC were obtained from Sisco research laboratory, India. Methanol, Calcium chloride, Ethanol, Dipotassium hydrogen phosphate, Sodium dihydrogen phosphate and Hydrochloric acid were obtained from High Purity Laboratory Chemicals (P) Ltd., Mumbai. Sodium chloride was supplied by Sigma-Aldrich, Mumbai, India. Unless otherwise stated, all chemicals were used as received without further purification.

Methods

Preparation of mucoadhesive alginate microspheres of ibuprofen

Microspheres of Ibuprofen were prepared by ionic-gelation technique or ionic cross-linking technique (Figure 1) using various ratios of Sodium Alginate and Sodium (CMC). Calcium chloride act as cross-linking agents to form the microspheres[17, 18]. Sodium alginate and sodium CMC were weighed accurately. The drug solution and the polymeric solution were prepared in a beaker by adding a small amount of distilled water followed by the addition of ethanol. The total

drug and polymers mixture was kept on magnetic stirrer for 1 h at 700 rpm to obtain a homogenous mixture of desired viscosity to pass easily through the syringe dropper. The total mixture was filled into a 5 ml syringe with gauge 21. Calcium chloride solution (10% w/v) was prepared separately and the solution was poured into this cross-linking solution dropwise with continuous stirring to form alginate microspheres. For strengthening, the beads formed were allowed to stir for 2 h. After completion of stirring, the beads were finally collected by filtration and were dried for 24 hrs in the oven at 40 °C and prepared microsphere is shown in figure 2. The composition of the different Microsphere batches prepared is shown in Table 1.

Table 1. Formulation parameters of mucoadhesive microspheres of ibuprofen

Formulation code	Drug (mg)	Sodium Alginate (mg)	Sodium CMC (mg)
F1	100	200	100
F2	100	200	200
F3	100	200	700
F4	100	100	400
F5	100	100	800
F6	100	100	100
F7	100	500	500
F8	100	600	600
F9	100	700	700

Figure 1. Ionic-gelation technique for preparation of sodium alginate/sodium CMC microspheres

Figure 2. Ibuprofen loaded mucoadhesive microspheres

Entrapment efficiency and production yield

For determination of the drug content, accurately weighed amount of ibuprofen loaded microspheres (50mg) of each formulation batch was crushed in mortar and pestle, the crushed microspheres were suspended in 50ml of 6.8 pH phosphate buffer solution for complete swelling at 37° C for overnight. The solution was filtered using Whatman filter paper, grade 40, the solution was centrifuged to remove polymeric debris. The clear supernatant solution was analyzed for drug content using *UV-visible* spectrophotometer at 228nm of wavelength[19]. The drug entrapment efficiency was calculated using the following equation

$$\text{Drug entrapment efficiency (\%)} = \frac{\text{Actual drug content in microsphere}}{\text{Theoretical drug content in microspheres}} \text{X100}$$

The production yield of microspheres of different batches after drying was calculated by using the weight of the final product as compared with the initial total weight of drug and polymers used for preparation. The formula used is given below:

Percentage yield (%) = $(M_1/M_2)*100$

Where M_1 &M_2 represents Practical mass (microspheres) and Theoretical mass (drug + polymers) respectively.

Particle size determination

Particle size of formulated microspheres was determined by laser diffraction analyzer (Mastersizer 2000 Version 5.61, UK Malvern Instruments). A well-dispersion of samples was formed, 2mg of each dispersion was weighed and dispersed in 10ml of distilled water and sonicated for 15 minutes. After that, the samples were analyzed for particle size determination[20-22].

Mucoadhesive property of microspheres

The mucoadhesive property of the microspheres was studied by an *in-vitro* adhesion method, also known as the wash-off test. Mucoadhesive microspheres (100) were spread onto the wet, rat intestinal tissue specimen on a glass slide which was further hung onto the grooves of USP tablet disintegrating test apparatus with the help of thread. The disintegrating apparatus was operated such that the tissue specimen was subjected to regular up and down movement in a beaker containing 0.1N HCl up to 1hr. The number of microspheres left on the tissue was counted[23]. Percentage mucoadhesion was calculated by the following formula:

Mucoadhesion (%) = N_1/N_2*100

Where N_1 & N_2 represents the number of adhered microspheres on mucosa and the number of applied microspheres on mucosa respectively.

Swelling index

Accurately weighed microspheres (W_o) were kept separately in a beaker containing phosphate buffer of pH 6.8. After a specified time, the microspheres were filtered; excess of water was removed from the microspheres and blotted with filter paper, weighed immediately on weighing balance. After 1 hr, the microspheres were reweighed (W_t)[24]. The percentage swelling index was calculated using the formula

Swelling Index = $(W_t - W_o)/W_o$*100

Characterization

Differential Scanning Calorimetry (DSC)

DSC was performed to study the thermal behavior of pure drug and the optimized batch of mucoadhesive microspheres[25]. The DSC was obtained using, DSC (Mettler Toledo, Switzerland). To do this analysis 3-8 mg of sample was secured in the aluminum pan and the temperature was increased up to 10°C/min. from 40-400° C.

X-ray Diffraction (XRD)

The effect of polymerization on the crystallinity of the drug, polymer and optimized batch can be studied by using an X-ray diffractometer (Miniflex 2, Rigaku, Japan), at room temperature and at 30kV. The scanning diffraction angle (2θ) ranging from 0° to 80°. X-ray diffractograms of pure drug, physical mixture and optimized formulation were recorded[26].

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was done to determine particle size distribution, shape, texture and surface morphology of the optimized batch. Dried Ibuprofen loaded mucoadhesive microspheres were placed on electron microscope brass stub, images of mucoadhesive microspheres were taken by random scanning of the stub[27].

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

(A) *In vitro* drug dissolution and release from ibuprofen loaded mucoadhesive microspheres were evaluated using a six vessels USP type II dissolution apparatus (Labindia, Bangalore), at 37± 0.5°C with constant stirring rate

of 50 rpm for $Rel_{24h.}$ A 200 mg drug equivalent sample of microsphere was placed in 900 ml of phosphate buffer (pH 6.8) at 37±0.5°C with constant stirring speed of 50 rpm. The powder was dispersed over the dissolution medium. Aliquots of sample (5ml) were withdrawn at different time intervals for 1 h and restored with an equal volume of the dissolution medium to keep sink conditions in the course of the experiment[28, 29]. The 0.45µm milipore filters was used for the sample filtration and the drug concentration in the samples was determined by measuring the absorbance of the samples at a wavelength of 228 nm using the *uv–vis* spectrophotometer followed by determination of mechanism of release by fitting the release rate data in various release kinetic models[30].

(B) The drug release studies were also carried out for a marketed tablet of Ibuprofen (Advil 200). The procedure and parameters used in the study were the same as above in the study.

Drug release study of optimized formulation

Model dependent methods

The kinetic model-dependent generally describe the dissolution profile. After choosing the selected function, the dissolution profiles were evaluated depending on the derived model perimeters. Zero-order, first-order, Higuchi, Korsmeyer-Peppas models are some approaches of dependent models. The following four were utilized to study the dissolution behavior in the present investigation.

Drug Release Kinetics

To know the mechanism and kinetics of drug release of the formulations, the results obtained from the *in vitro* drug release studies were analyzed by best fitted kinetic models.

1. Zero-order drug release: cumulative % drug release versus time.

2. First-order drug release: log cumulative % drug retained versus time.

3. Higuchi's model: cumulative % drug release versus square root of time.

4. Korsmeyer-Peppas model: log cumulative versus log time.

In these plots, the best fit model was chosen by looking at the R^2 values acquired[31, 32].

Zero-Order Model

To study the zero-order release rate kinetics the release rate data were fitted to the following equation:

$Q_t = Q_o + K_o T$

Where Q_t = amount of drug dissolved in time t,

Q_o = initial amount of drug in the solution,

K_o = Zero-order release rate constant.

First-Order Model

To study the first-order release rate kinetics the release rate data were fitted to the following equation:

$\text{Log } Q_t = \log Q_o + K_1 t/2.303$

Where Q_t = amount of drug released in time

Q_o = initial amount of the drug in the solution

K_1 = first-order release rate constant

Higuchi Model

The dissolution from a planer system having a uniform matrix follows the release rate pattern as per the equation:

$Q_t = K_H . t^{1/2}$

Where Q_t = amount of drug released in time t,

K_H = Higuchi dissolution constant.

Korsmeyer-Peppas model

The exponential relation of time with the fractional release of drug is predicted by this model. N is the exponent for the diffusion release mechanism. The equation is given below:

$M_t/M_\infty = K.t^n$

Where M_t/M_∞ = fraction of drug release,

K = release constant,

t = release time,

n = Diffusional exponent for the drug release.

RESULTS and DISCUSSION

Drug entrapment efficiency and production yield

The percentage entrapment efficiency of drug into the microspheres ranged from 28.69-68.51 % shown in figure 3(a). The percentage production yield of the drug in the mucoadhesive microspheres ranged from 35.19-68.65 % shown in figure 3 (b) which indicated that an increase in the amount of sodium alginate and sodium CMC also enhanced the amount of production yield (Table 2). Increasing the concentration of the sodium CMC in the formulation increased the bonds forming groups, thus increasing the mucoadhesicve force of the formulations[33]. Mucoadhesion behavior of alginate was due to the low surface tension (31.5 mN/m) of the alginate.

The drug content of drug in the mucoadhesive microspheres ranged from 28.67-72.54 %. The percentage entrapment efficiency and percentage production yield of batch 3 (F3) is highest among the all other formulations. So this formulation is selected for the optimized formulation.

Swelling index (%)

From the swelling study[34], it was showed that all prepared formulation of microspheres quickly swelled in phosphate buffer pH 6.8. The swelling index of alginate microspheres after a specified time lies within the range of 71.25-82.37 % (table 2) shown in figure 3 (c).

Table 2. Responses result of all batches

Batch	In vitro Wash-off Test (% Mucoadhesion After 1 hr)	Entrapment Efficiency (%)	Production yield (%)	Swelling index (%)
F1	68	32.24	51.76	71.25
F2	71	37.19	48.24	74.29
F3	84	68.51	73.25	82.37
F4	63	32.58	39.67	73.18
F5	82	58.37	68.65	80.13
F6	67	45.14	53.17	77.82
F7	72	28.69	24.19	79.18
F8	70	34.45	37.45	76.51
F9	75	39.86	35.19	72.41

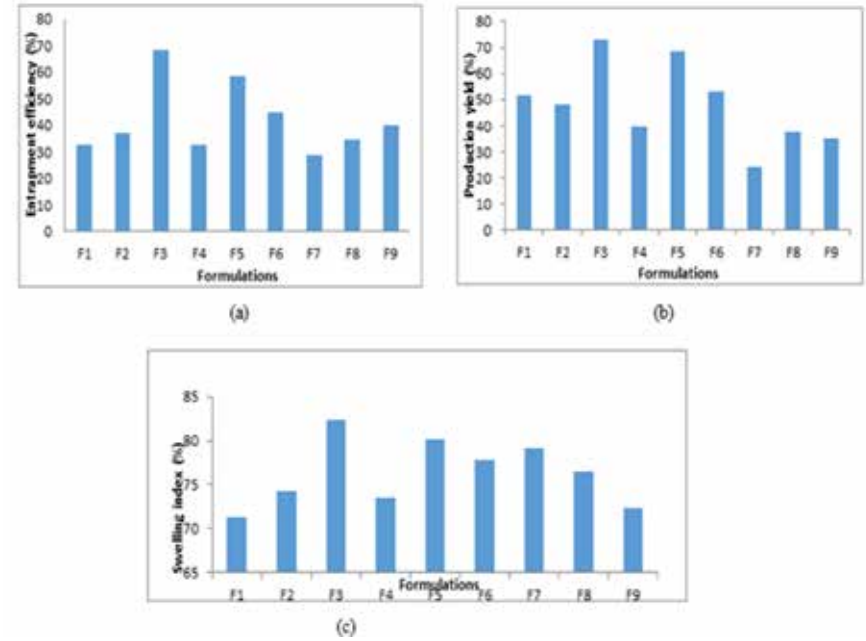

Figure 3. Drug entrapment efficiency (%) (a), production yield (%) (b) and Average swelling index (%) of microsphere

Mucoadhesive property of microspheres

The in vitro wash-off test for percentage mucoadhesion after 1 hour varied from 51 to 78%.

In-vitro drug release studies

The drug release studies were carried out on the prepared formulations as well as the marketed brand of Ibuprofen (Advil 200) for comparison of the drug release profile with optimized batch (F3). The cumulative amount of drug released from the marketed tablet was found to be about 74.45 % in 2 hours. The maximum amount of drug released from the microspheres formulations was 84.39. However, the drug release was found to be in the range of 35 to 77% approximately in 10 hours shown in figure 4. Moreover, it was observed that with an increase in the amount of polymers, the rate of drug release was retarded which was found to be in the range of about 43 % to 85 % at the end of the study period. The batch 3 (F3) was selected as the optimized batch due to highest entrapment efficiency and highest production yield.

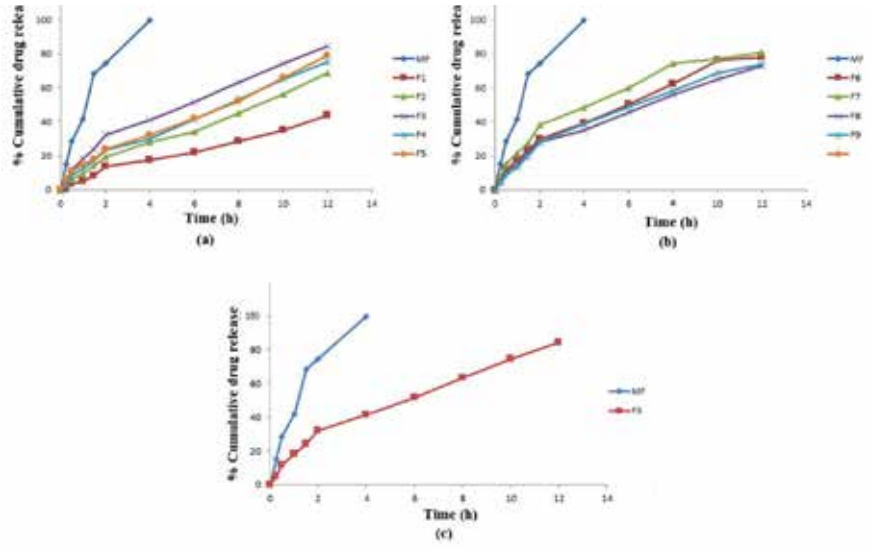

Figure 4. (a) Drug release profiles of batch F1-F5, (b) F6-F9 and (c) *In-vitro* drug release profile of optimized batch (F3) compared with marketed tablets (MF = Marketed Formulation).

Differential Scanning Calorimetry Analysis

DSC thermograms were recorded for pure ibuprofen and optimized batch (Figure 5). In both cases it was observed that the characteristic endotherm (corresponding to melt of the drug) did not shift appreciably, suggesting the lack of any interaction between the drug and excipients[35].

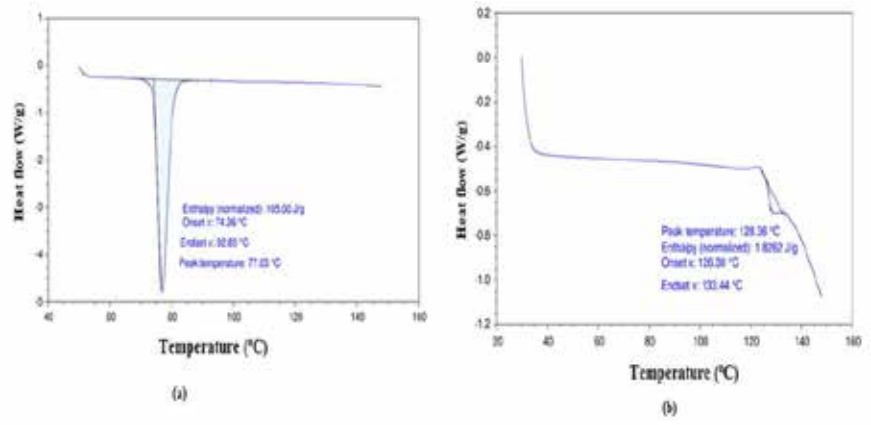

Figure 5. DSC thermogram of ibuprofen (a) and optimized batch (b). Scanning electron microscopy

The SEM study also revealed that there was no change in the morphology of drug loaded microspheres, and resulting microspheres were found to be discrete and spherical in shape and had nearly smooth surface as shown in the figure 6. During dissolution, the presence of drug particles on the surface of ibuprofen loaded microspheres may be responsible for an initial burst release of the drug[27].

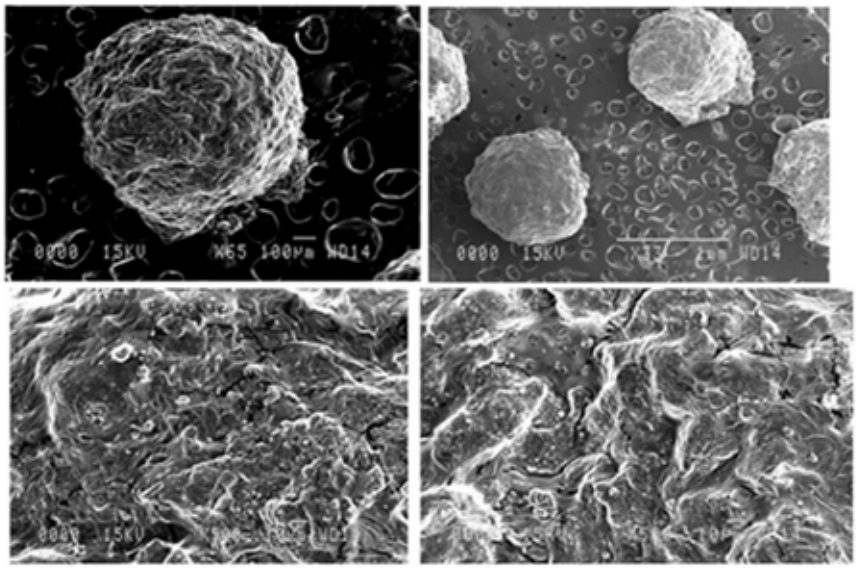

Figure 6. SEM images of mucoadhesive microspheres

X-Ray Powder Diffractometry (XRD)

The XRD patterns of drug, physical mixture (Sodium alginate, sodium CMC and drug) and Ibuprofen incorporated in mucoadhesive microspheres formulations are represented in Fig 7 (a-c). The presence of distinct characteristic peaks in the XRD pattern of Ibuprofen depicts its highly crystalline nature. Exploration of the XRD patterns of physical mixture shows a slight change in their intensity and optimized formulation shows less intense and wide diffraction peaks, which can be characterized by partial amorphous nature of Ibuprofen. XRD analysis does not exhibit any diffraction pattern of drug in optimized microspheres formulation, which reveals the significant reduction in the crystalline nature of the drug. XRD analysis of optimized formulation shows the presence of drugs as molecular dispersion in the optimized formulation of drug-loaded mucoadhesive microspheres.

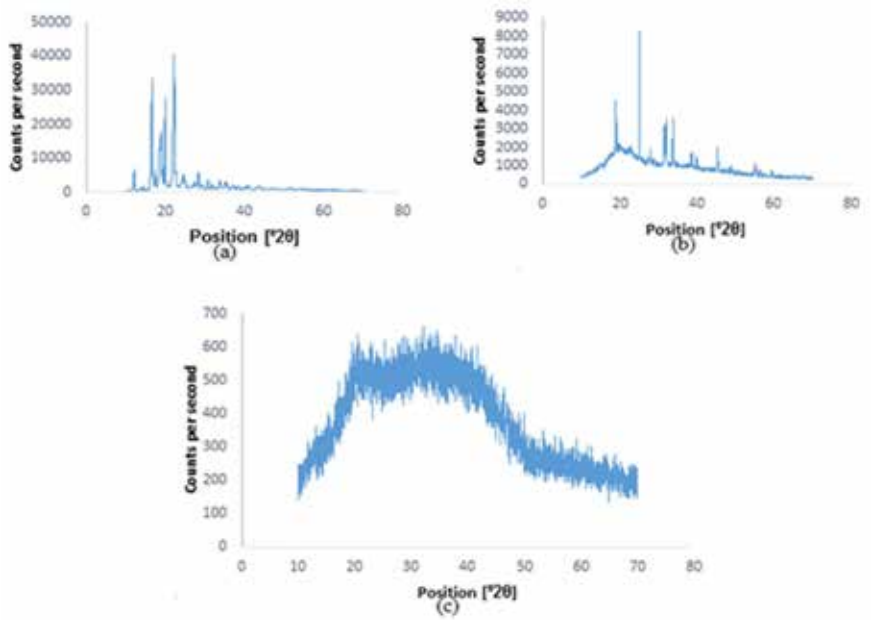

Figure 7. (a) XRD of pure drug (Ibuprofen), (b) physical mixture of polymers and (c) optimized batch of mucoadhesive microspheres

In-vitro drug release of mucoadhesive microspheres

The *in-Vitro* release data of drug were put into numerous models to determine the drug release kinetics. The batch 3 (F3) was found to fit in the Higuchi model as it showed the maximum value of the R^2. The Higuchi model showed that the drug discharge from the formulation by the Fickian diffusion mechanism. *In-vitro* drug release kinetics data of selected formulation (F3) is given in table 3.

Table 3. Various models with their R^2 values

Model	R^2 value
Zero-order	0.963
First-order	0.588
Higuchi	0.989
Korsmeyer-Peppas	0.603
Best Fit Model	**Higuchi model**

In the present study, ibuprofen was formulated as Mucoadhesive microspheres by ionic gelation technique (ionic cross-linking technique or drop extrusion method) by using varying concentrations of polymers sodium alginate and so-

dium CMC. The mucoadhesive microspheres of Ibuprofen were characterized by drug content, particle size distribution, production yield, *in-vitro* drug release, and entrapment efficiency. The optimized batch of microsphere (F3) was further evaluated by FT-IR, DSC, XRD, and SEM analysis. The data obtained from DSC studies confirmed no polymorphic change and chemical interaction with excipients in the drug-loaded microspheres. The XRD study suggested the change in the physical behavior of drug from crystalline to amorphous within the formulation. The SEM analysis shows that particles of all the formulated microspheres is spherical having a rough outer surface and is porous. The formulated batch F3 was chosen as optimized in terms of entrapment efficiency (68.51 %) and *in-Vitro* release of drug (84.39 %) in 12 hours. So from the result, it could be concluded that the concentration of polymers affected the various evaluation parameters. The Entrapment efficiency of the microspheres depends on variations in the concentration of polymers. The entrapment efficiency of microspheres ranged from about 28.69-68.51 %. The *in-vitro* drug release studies of each formulation was carried out for 12 hours in phosphate buffer pH 6.8. The cumulative amount of drug released was found to be in the range of 43.72-84.39 %. The data obtained from the *in-vitro* drug release profiles of Ibuprofen determined that all the batches of mucoadhesive microspheres showed prolonged drug release. The Higuchi model (R^2=0.9899) was found to be the best-fit model for the optimized batch (F3).

It could be concluded that the mucoadhesive microspheres of Ibuprofen showed prolonged release of the drug. The potential use of the formulations for a more effective management of inflammation and pain may be further explored with the help of long term pharmacokinetic and pharmacodynamic studies.

AUTHOR CONTRIBUTIONS

Kanika Sharma- Conceptualization, Writing – Original Draft Preparation; Sunita Devi- Conceptualization, Supervision.

DECLARATION OF INTEREST

The authors report no conflicts of interest.

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