Research Article

Available Online at: www.ijphr.com

International Journal of Pharmaceuticals and Health care Research

ISSN: - 2306 – 6091

CHITOSAN COATED ALGINATE -CARRAGEENAN PARTICULATE SYSTEMS FOR SUSTAINED RELEASE OF NAPROXEN

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Abstract

The purpose of this work was to develop sustained release particulate systems of naproxen, an anti-inflammatory agent by using natural polysaccharides polymers, such as sodium alginate, chitosan and carrageenan. Naproxen -loaded chitosan coated alginate microspheres were prepared by ionotropic gelation methods using various combinations of chitosan and Ca^{2+} as cations and alginate & carrageenan as anion. In-vitro drug release & pattern of the microspheres were studied at pH 1.2 and 7.4. Fourier transform infra-red (FTIR) spectrometry, scanning electron microscopy (SEM), differential scanning calorimetry (DSC), x-ray diffraction (XRD) were also applied to investigate the physicochemical characteristics of the drug in formulations. The surface morphology, size, and drug loading of the microspheres varied with increment in the concentration of chitosan, alginate and calcium chloride in the gelation medium and curing time was observed. The microspheres prepared with chitosan coated alginate shows 77% of the drug release within 6 h, whereas microspheres prepared with carrageenan slowed the drug release to 60 %. The release data from all the formulation was found to fit in first-order kinetics model. Data's from characterisation studies indicate that there was no change in the physical state of the drug in the formulations. It is concluded that the release of the naproxen could be prolonged by using mixture with carrageenan in chitosan coated alginate microspheres.

Keywords: Sustained release, Naproxen, Sodium alginate, Chitosan, Carrageenan, Microparticles.

Introduction

Natural polymers, such as polysaccharides, are widely used in pharmaceutical applications due to their good biocompatibility and biodegradability. Alginate and Chitosan are the most extensively studied polysaccharides and has shown great potential as a drug carrier. The simple, mild, aqueous-based gel formation of sodium alginate in the presence of divalent cations is extremely suitable for encapsulating various drugs with different properties[1]. In recent years much attention has been given to the use of chitosan alginate polyelectrolyte complex in controlled drug delivery[2]. The use of chitosan has been reported in the literature for coating alginate microspheres in order to alter the diffusion rate of the encapsulated substances[3], also adding carrageenan as an additive for the bulk modification of the microspheres structure because of its gelling, viscosity enhancing, and proven safety properties[4] carrageenan can be used as a sustained-release composition[5].

Naproxen, (S)-2-(6-methoxynaphth-2-yl) propionic acid, is a non-steroidal anti-inflammatory drug

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(NSAID) commonly used for the reduction of mild to moderate pain, fever, inflammation and stiffness caused by conditions such as osteoarthritis, rheumatoid arthritis, psoriatic arthritis, gout, ankylosing spondylitis, injury, menstrual cramps[6], It works by inhibiting cyclooxygenase and consequent decrease in prostaglandin concentrations that cause inflammation and pain in the body. With many drugs, the basic goal of therapy is to achieve a steady state blood or tissue level which will be therapeutically effective and non-toxic for extended periods of time[7].Naproxen is extensively bound to plasma albumin, so it may be more efficient to deliver this drug in its sustained-release dosage form.

Materials & Methods

Naproxen was received as a gift sample from Dr.Reddys Lab, Hyderabad; Chitosan powder was gifted from India Sea Foods, Cochin, Kerala; Sodium alginate procured from Fluka Chem, Buchs and Carrageenan from Sigma, USA; Lactic acid from Merck Limited, Mumbai; and all other chemicals and solvents were of analytical grade satisfying pharmacopoeial specifications.

Formulation of chitosan Microspheres

Chitosan coated alginate microspheres

Sodium alginate was dissolved in double distilled water at a various concentrations of 1 to 4% (w/v) as shown in Table 1. Naproxen was slowly dispersed in the sodium alginate solution with constant stirring. The gelation medium was prepared by mixing equal proportion of $CaCl_2$ solution (0.5-2%w/v) with different concentrations of chitosan solution (0.5-2%) already prepared with 2.4% lactic acid and the pH of the medium was adjusted to 4.5 ± 0.1. The homogenous mixture of sodium alginate drug solution was added drop wise into the gelation medium using a 5 ml hypodermic syringe through a needle # 21 under constant stirring at room temperature. The microspheres thus formed were cured in the gelation medium for 4 hr, followed by washing with double distilled water and then allowed to dry at room temperature (25°C) in a dust free chamber till they attained constant weight.

Chitosan coated alginate/ carrageenan microspheres

Sodium alginate was dissolved in double distilled water at different concentrations of 1 to 4% (w/v). This was mixed with carrageenan, dissolved separately in various ratios as shown in Table 2. Naproxen was dispersed slowly in the sodium alginate and carrageenan solution with constant stirring. Then it was sonicated for 30min to remove any air bubbles that may have been formed during mixing. The gelation medium was prepared by mixing equal proportions of $CaCl_2$ solution (0.5-2%w/v) with different concentration of chitosan solution (0.5-2%) previously prepared with 2.4 % lactic acid and the pH of the medium was adjusted to 4.5 ± 0.1. The medium was mixed for 2h before use. The homogenous mixture of sodium alginate, carrageenan and drug was added drop wise into the gelation medium using a 5 ml hypodermic syringe through a needle # 21 under constant stirring at room temperature. The microspheres thus formed were cured in the gelation medium for 4 hr, followed by washing with double distilled water and then allowed to dry at room temperature (25°C) to attained constant weight. The prepared microspheres by both the methods were then stored in air tight container at room temperature.

Determination of drug loading and Entrapment efficiency

Accurately weighed samples (50 mg) of drug-loaded microspheres from each batch were incubated in 100ml of phosphate buffer solution (pH 7.4) for 24hrs accompanied by occasional shaking. The solution was filtered through Whatmann filter paper. An aliquot following suitable dilution was assayed spectrophoto--metrically[8] (UV-Visible spectrophotometer, Shimadzu 1800, Japan) at 230nm.

Drug Loading was calculated using the formula in Equation 1.

$$\text{Drug Loading in \%} = W/W_t \times 100 \quad \text{- (Equation 1)}$$

Where,
W = Drug content of the microspheres
W_t = Weight of the microspheres

Theoretical drug loading was determined by calculation assuming that the entire drug present in the polymer solution gets entrapped in microspheres and no loss occurs at any stage of preparation of the microspheres. The unloaded microspheres did not interfere with the spectrophotometric determination of drug, which

was checked before performing the drug loading studies. The results of the drug loading studies and those for the entrapment efficiency are given in Table 3 & 4.

Fourier Transform- Infrared Spectroscopy

Drug polymer interactions were studied by FT-IR spectroscopy (Shimadzu, Japan) for pure drug, polymer(s), physical mixture of drug and polymer(s), blank microspheres and drug loaded microspheres. Samples were weighed and mixed properly with potassium bromide to obtain a uniform mixture. A small quantity of the powder was compressed into a thin semitransparent pellet by applying pressure. The IR- spectra of the pellets were recorded from 400 – 4000 cm^{-1} taking air as the reference.

Scanning Calorimetry (DSC)

Differential Scanning Calorimeter model Pyris Diamond TG/DTA, PerkinElmer, Singapore in a nitrogen atmosphere (150ml/min). Platinum crucible was used with alpha alumina powder as reference to study the thermal behaviours of pure drug, polymer(s), physical mixture of drug & polymer(s) and drug loaded microspheres. Thermograms were recorded at scanning speed of 10º C/ min over a temperature range of 30 º -300º C.

X-Ray Powder Diffraction

The X-ray diffraction patterns of pure naproxen, polymer(s), physical mixture of drug & polymer(s), blank microspheres and drug loaded microspheres were recorded using Miniflex goniometer to investigate the physical state of the drug in the formulations. The instrument was operated at a scanning speed of 1º/ min, over a 2^{θ} angle range of 10-70.

***In-Vitro* Drug Release Studies**

Each sample (100mg) for release studies consisted of drug loaded microspheres filled into a hard gelatin capsule. Drug release studies were carried out using a USP XXI dissolution rate test apparatus, in 900 ml of 0.1N Hydrochloric acid for 2 h and followed in Phosphate buffer (pH 7.4) for 7 h at 37± 0.5°C. The apparatus was operated at a stirring speed of 75 rpm. 3 ml of the dissolution medium was sampled at predetermined time intervals and replenished with the same quantity of fresh dissolution medium in each occasion to keep the volume constant. The withdrawn samples were filtered through Whatmann No. 1 qualitative filter paper and analyzed for drug content at 230 nm using Shimadzu 1800 UV spectrophotometer (Japan).

Drug release kinetics[9]

To study the release kinetics, data obtained from in vitro drug release studies were fitted into various kinetic models: zero order (cumulative amount of drug released vs time), first order (log cumulative percentage of drug remaining vs time) and Higuchi's model (cumulative percentage of drug released vs square root of time).

Drug release obeying Zero order can be described as represented in equation 2:

$$C = K_0 t \qquad \text{- (Equation 2)}$$

Where K_0 is the zero-order rate constant expressed in units of concentration/time and t is the time in hours. A graph of concentration vs time would yield a straight line with a slope equal to K_0 and intercept the origin of the axes.

Drug release obeying First order can be described as represented in equation 3:

$$\text{Log } C = \text{Log } C_0 - kt/2.303 \quad \text{- (Equation 3)}$$

Where C_0 is the initial concentration of drug, k is the first order constant, and t is the time.

Drug release obeying Higuchi model can be described as represented in equation 4:

$$Q = Kt_{1/2} \qquad \text{- (Equation 4)}$$

Where K is the constant reflecting the design variables of the system and t is the time in hours. Hence, drug release rate is proportional to the reciprocal of the square root of time.

The kinetic data obtained from the in vitro dissolution studies were analyzed to obtain correlation coefficients for the different kinetic equations.

Table No. 01: Formulation design for the preparation of naproxen loaded chitosan coated alginate microspheres

Formulation code	Sodium alginate	$CaCl_2$	Chitosan	Drug : Alginate ratio	Curing time
NPA1	3	2	1	1:4	4
NPA2	3	2	1	1:3	4
NPA3	3	2	1	1:2	4
NPA4	3	2	1	1:4	2
NPA5	2	2	1	1:4	4
NPA6	3	1	1	1:4	4
NPA7	3	2	2	1:4	4
NPA8	3	2	1	1:4	8

Table No. 02: Formulation design for the preparation of naproxen loaded chitosan coated alginate and carrageenan microspheres

Formulation code	Sodium alginate	Sodium alginate :carrageenan ratio	CaC_{l2}	Chitosan	Drug: alginate ratio	Curing time
NPAC1	3	3:1	2	1	1:3	4
NPAC2	3	3:1	2	1	1:2	4
NPAC3	3	3:1	2	1	1:4	2
NPAC4	2	2:1	2	1	1:4	4
NPAC5	3	3:1	1	1	1:4	4
NPAC6	3	3:1	2	2	1:4	8
NPAC7	3	3:2	2	2	1:4	4
NPAC8	3	1:1	2	2	1:4	4

Table No. 03: Mean particle size, Percentage drug loading and Percentage entrapment efficiency of naproxen loaded chitosan coated alginate microspheres (Mean ± SD, n=3)

Formulation code	Particle size (µm)	Drug loading (in %)	Entrapment efficiency (in %)
NPA1	856.85 ± 2.01	18.87 ± 4.00	91.55 ± 2.00
NPA2	886.48 ± 6.13	21.81 ± 2.96	96.21 ± 3.37
NPA3	875.00 ± 13.0	23.41 ± 3.63	99.16 ± 0.95
NPA4	881.84 ± 12.5	20.85 ± 5.33	82.95 ± 3.66
NPA5	825.08 ± 5.00	21.66 ± 0.28	98.21 ± 1.83
NPA6	851.04 ± 0.93	22.88 ± 3.59	95.01 ± 4.61
NPA7	891.47 ± 1.75	19.66 ± 1.75	90.58 ± 2.11
NPA8	841.94 ± 3.00	17.73 ± 2.46	86.71 ± 5.38

Table No. 04: Mean particle size, Percentage drug loading and Percentage entrapment efficiency of naproxen loaded chitosan coated alginate and carrageenan microspheres (Mean ± SD, n=3)

Formulation code	Particle size (µm)	Drug loading (in %)	Entrapment efficiency (in %)
NPAC1	968.96 ± 34.96	19.16 ± 3.88	95.70 ± 3.28
NPAC2	999.64 ± 9.21	20.19 ± 6.78	92.26 ± 6.95
NPAC3	1007.01 ± 17.16	21.06 ± 1.11	99.11 ± 1.10
NPAC4	1003.05 ± 7.65	21.56 ± 2.63	96.58 ± 2.50
NPAC5	986.48 ± 82.91	20.61 ± 2.09	94.28 ± 3.02
NPAC6	1014.45 ± 6.21	16.86 ± 2.32	89.83 ± 2.05
NPAC7	1096.30 ± 9.00	15.40 ± 3.11	92.62 ± 3.31
NPAC8	1110.59 ± 21.50	14.16 ± 1.48	94.04 ± 1.54

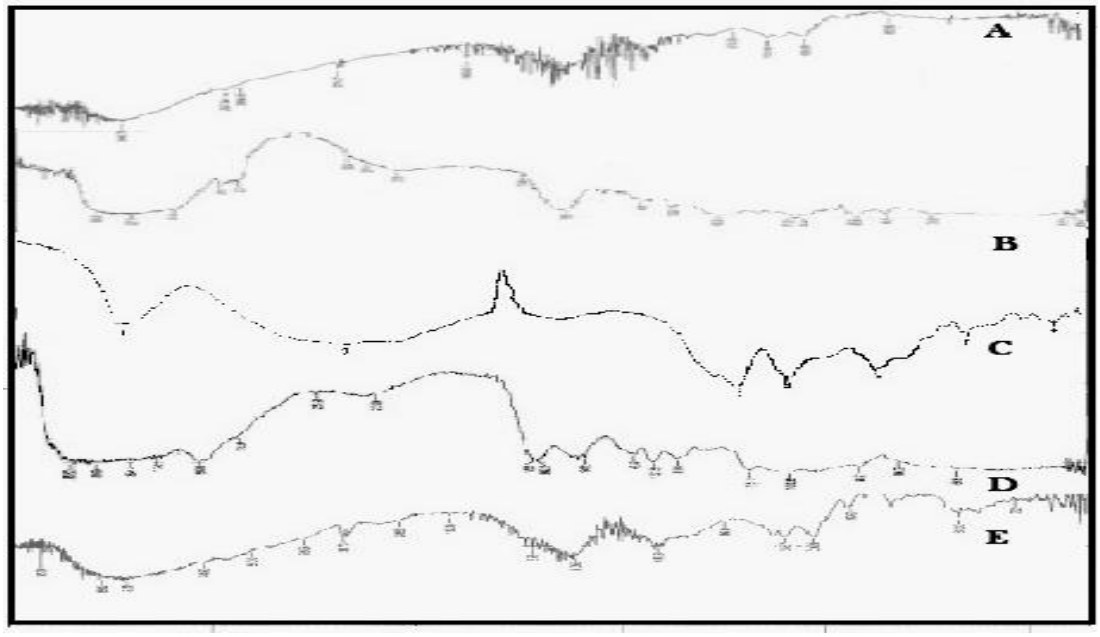


Fig. No. 01: FTIR spectra of (a) Chitosan coated alginate/carrageenan blank microspheres; (b) Carrageenan; (c) Chitosan coated alginate carrageenan blank microspheres; (d) Chitosan, (e) Sodium alginate

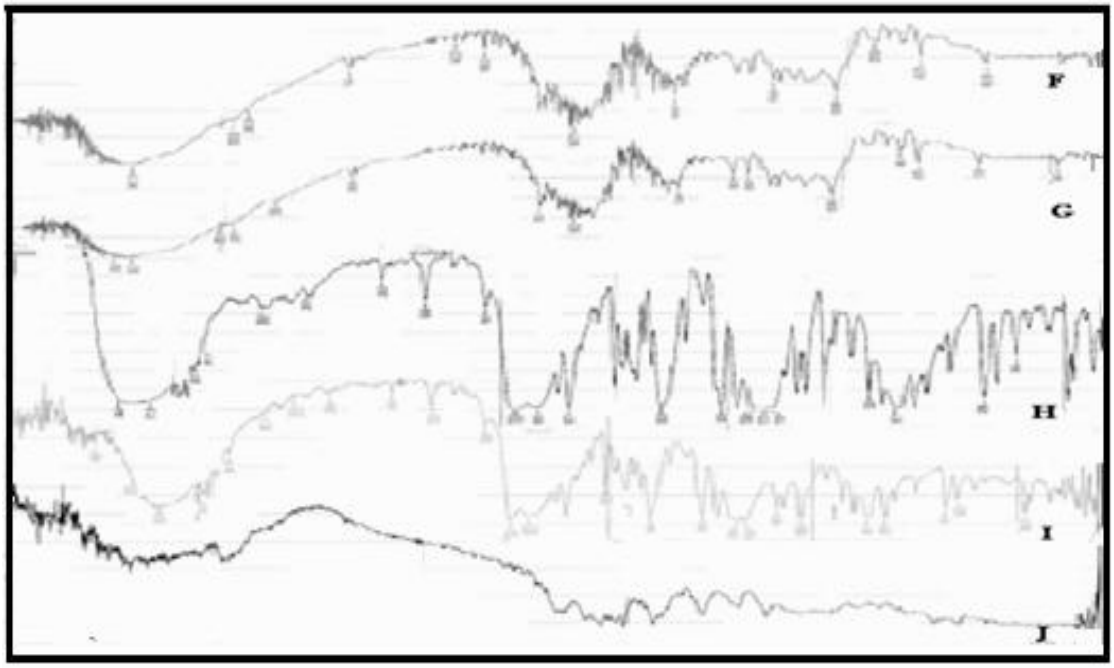


Fig. No. 02: FTIR spectra of (f) naproxen loaded chitosan coated alginate & carrageenan microspheres; (g) naproxen chitosan coated alginate microspheres; (h) pure naproxen; (i) physical mixture of naproxen, alginate, chitosan and carrageenan; (j) physical mixture of naproxen, chitosan and alginate

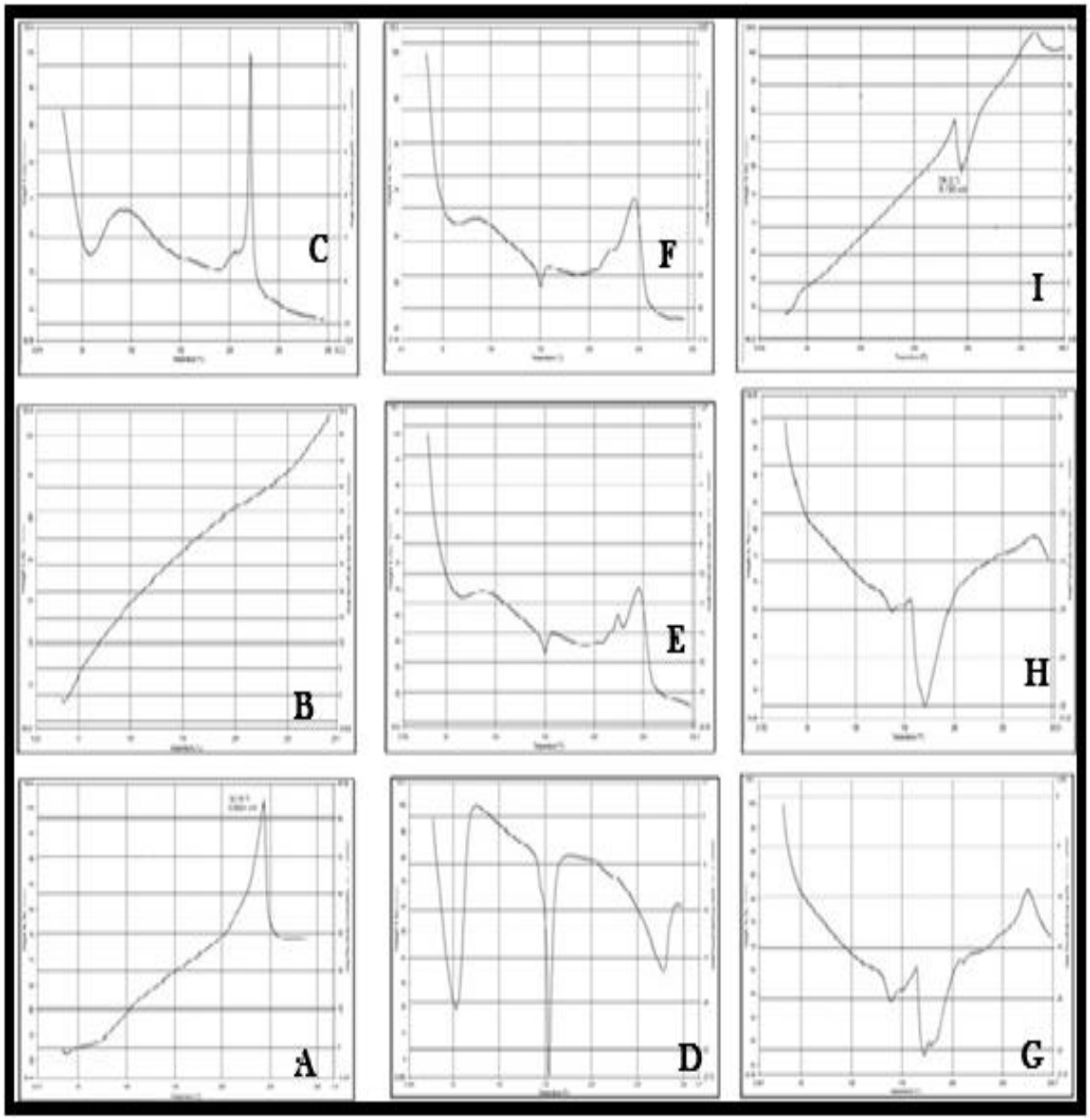


Fig. No. 03: DSC thermograms of a) sodium alginate; b) chitosan; c) carrageenan; d) pure naproxen e) physical of naproxen, sodium alginate chitosan and carrageenan; f) physical of naproxen, sodium alginate and chitosan; g) naproxen loaded chitosan coated alginate microspheres ; h) naproxen loaded chitosan coated alginate and carrageenan microspheres; i) unloaded (blank) chitosan coated alginate microspheres.

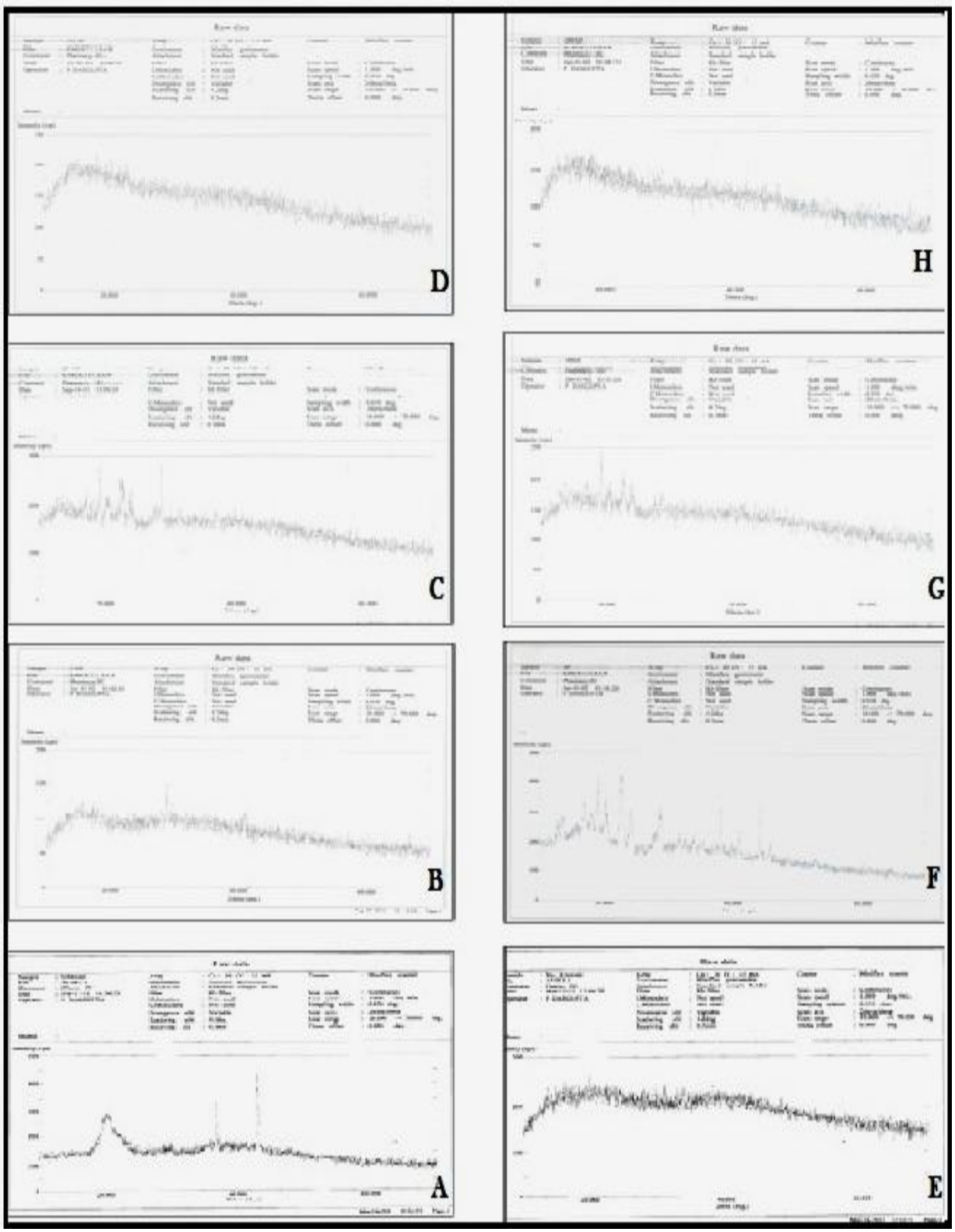


Fig. No. 04: X-ray diffractograms of (a) sodium alginate; (b) carrageenan; (c) physical of naproxen, sodium alginate, chitosan polymers; (d) naproxen loaded chitosan coated alginate microspheres; (e) chitosan; (f) pure naproxen; (g) physical of naproxen, sodium alginate, chitosan & carrageenan polymers; (h) naproxen loaded chitosan coated alginate& carrageenan microspheres

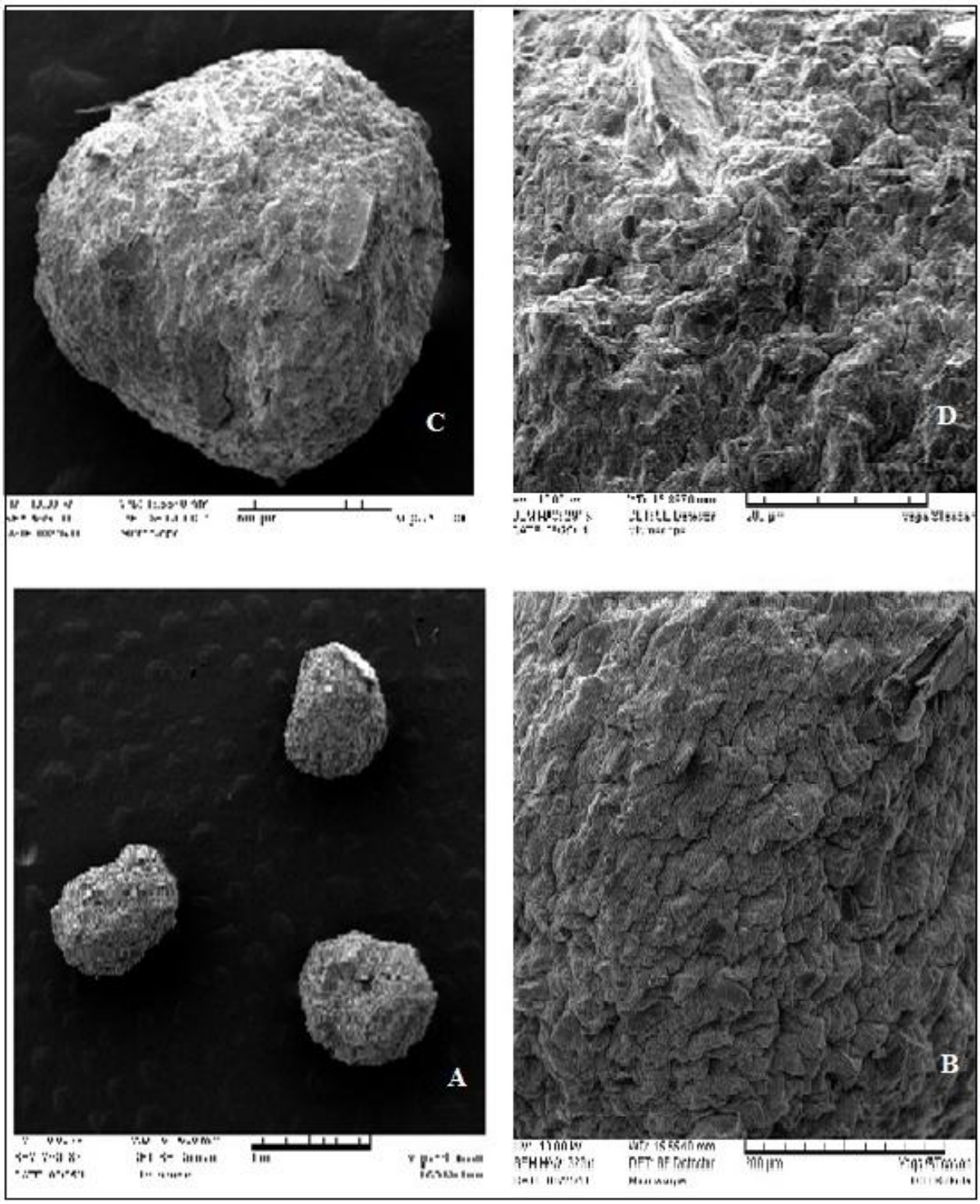
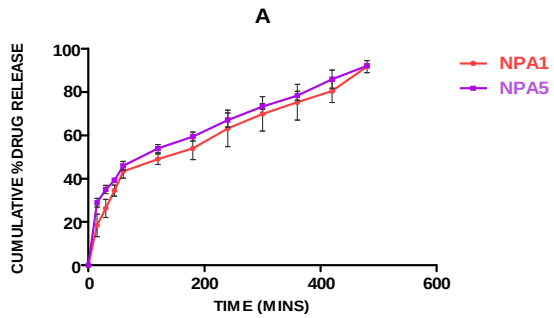
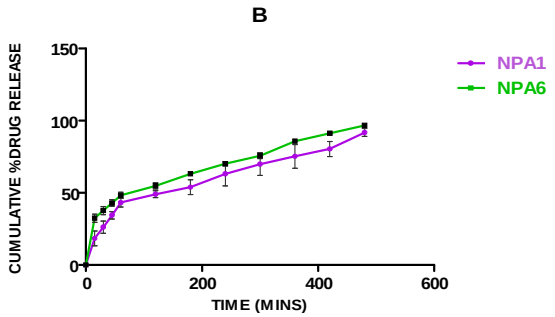


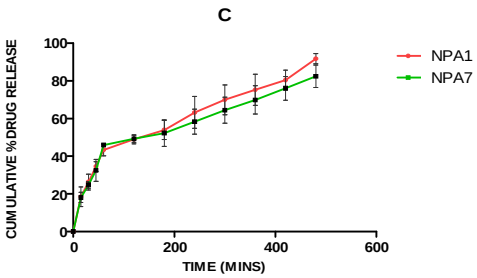
Fig. No. 05: (a) & (b) Scanning electron micrographs of naproxen loaded chitosan coated alginate/carrageenan microspheres (c) & (d) naproxen loaded chitosan coated alginate microspheres.



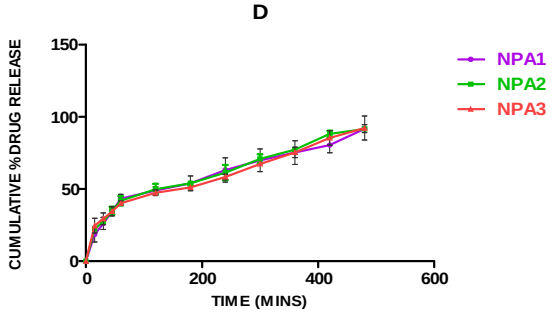
Effect of alginate concentration on the cumulative percent release of drug from naproxen loaded chitosan coated alginate microspheres



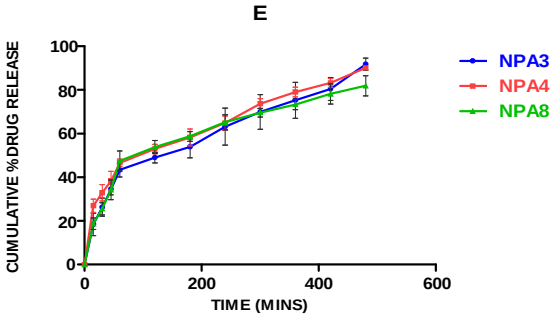
Effect of $CaCl_2$ concentration on the cumulative percent release of drug from naproxen loaded chitosan coated alginate microspheres



Effect of chitosan concentration on the cumulative percent release of drug from naproxen loaded chitosan coated alginate microspheres



Effect of alginate drug ratio on the cumulative percent release of drug from naproxen loaded chitosan coated alginate microspheres



Effect of gelation time on the cumulative percent release of drug from naproxen loaded chitosan coated alginate microspheres

Fig. No. 06: Naproxen release profiles from chitosan coated alginate microspheres with different concentration and variable of (a) Alginate, (b) $CaCl_2$, (c) Chitosan, (d) Alginate drug ratio and (e) Curing time.

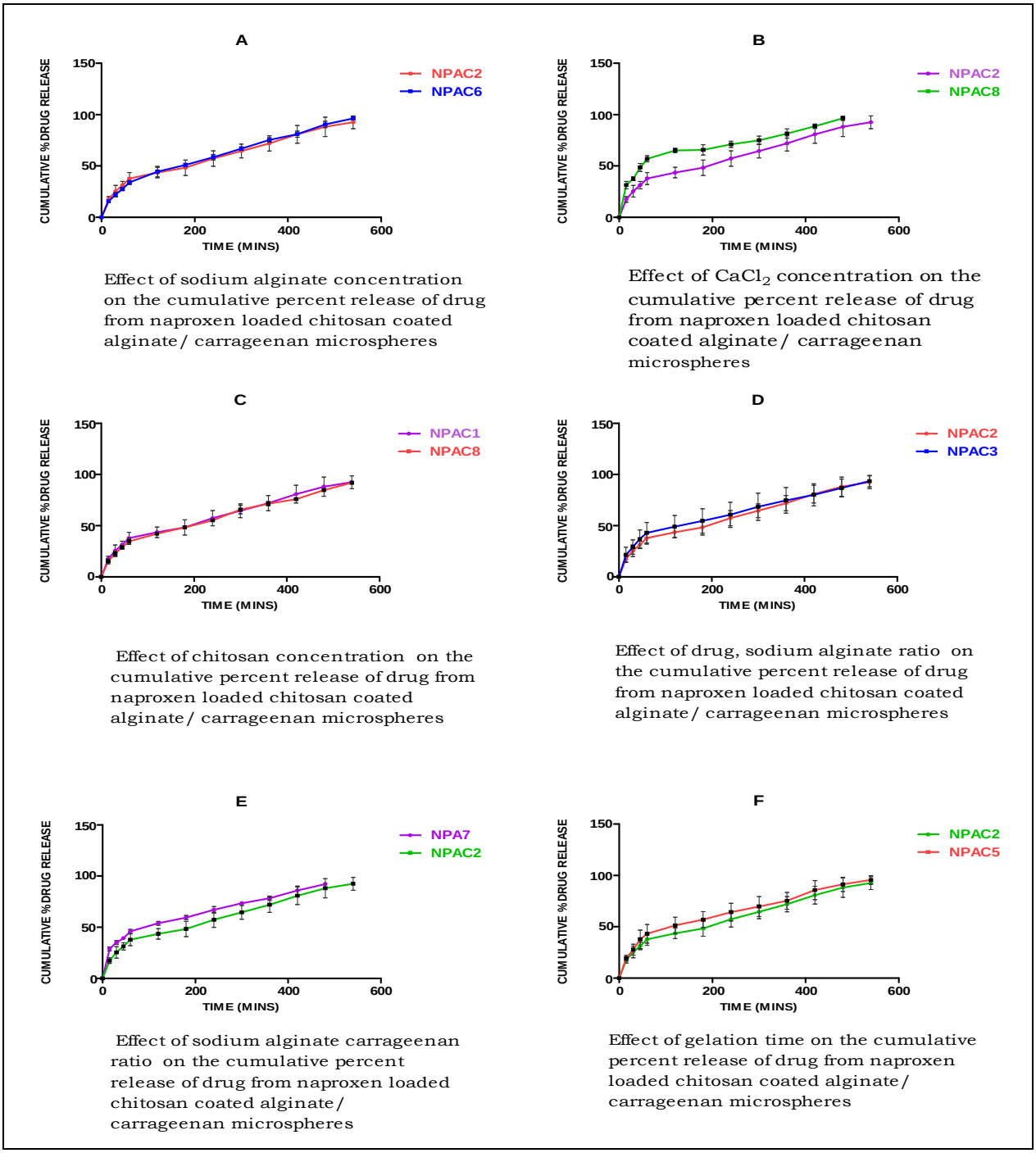


Fig. No. 07: Naproxen release profiles from chitosan coated alginate & carrageenan microspheres with different concentration and variable of (a) Alginate, (b) $CaCl_2$, (c) Chitosan, (d) Alginate-Drug ratio and (e) Alginate-Carrageenan ratio, (f)Curing time.

Results and discussion

Loading efficiency and Entrapment efficiency

The percentage of loading efficiency (%LE) in each microspheres formulation is given in Table 1. The results indicated that % LE of the different experimental variables, namely, calcium chloride concentration, sodium alginate concentration, chitosan concentration, drug-alginate ratio and gelation time affected the drug loading of prepared chitosan coated alginate microspheres, in case of naproxen loaded chitosan coated alginate & carrageenan microspheres including the effect of sodium alginate & carrageenan ratio was studied (Table 1 & 2). From the data reported in Table 3, it can be seen that highest drug loading was observed in batch NPA3 (23.41%). On the other hand,

formulation NPA8 showed the lowest drug loading of 17. 7%. From batches, NPA5 it can be observed that, increase in the sodium alginate (polymer) concentration from 2-3% w/v resulted in an increase in the percentage drug loading. Further increase in the concentration to 4% w/v of the same resulted in lower drug loading (NPA8). Increase in concentration of calcium chloride upto 1% w/v increased the drug loading; further increase in its concentration shows decrease in drug loading (NPA1). The addition of chitosan resulted in decreased drug loading when compared with microspheres prepared without the use of chitosan. This is due to the formation of a polyelectrolyte complex, which reduces the porosity at the surface of the microspheres, which may result in the lower drug loading. The batch NPA3 shows highest drug loading at a drug to polymer ratio of 1:2. From the results obtained it can be inferred that when drug to polymer ratio decreases, drug loading increases (NPA1, NPA2, NPA3). Higher drug loading in batch NPA1 prepared with a gelation time of 2h, however at gelation time of 4 and 8 hours, decrease in drug loading occurs, which may be possibly due to tight matrix junctions formed during this gelation time squeezing out the drug. Entrapment efficiency was observed to be in the range of 82.95 to 99.49% for naproxen loaded chitosan alginate microspheres.

In case of naproxen loaded chitosan coated alginate and carrageenan microspheres (Table 4), the highest drug loading was observed in the batch NPAC4 (21.56%) and lowest in NPAC8 (14.16%). Increase in the sodium alginate (polymer) concentration from 2-3% w/v resulted in an increase in the percentage drug loading (NPAC4). Increase in concentration of calcium chloride upto 1% w/v (NPAC9, NPAC5), further increase in its concentration show decrease in drug loading (NPAC2). Increase in the concentration of chitosan shows a decrease in drug loading (NPAC1, NPAC2, NPAC8) possibly due to formation outer coating microspheres and dense matrix of microspheres squeezed out the drug. From the results it can be observed that drug to polymer ratio at 1:2 shows higher drug loading (NPAC4) and it can be inferred that when drug to polymer ratio decreases drug loading increases (NPA3, NPA4, NPA5). Drug loading was affected with changes in the gelation time (NPAC2, NPAC5) increases in gelation time reduces the drug loading. Entrapment efficiency in the case of naproxen loaded chitosan coated alginate & carrageenan microspheres the same was in range of 85.34 % to 99.11 %.

Morphological characteristics and microspheres size

From the results of particle size determination of the prepared microspheres, it was observed that the mean particle size was in range of 825.08 µm to 891.47 µm for naproxen loaded chitosan alginate microspheres and 968.96 µm to 1110.59 µm for naproxen loaded chitosan alginate & carrageenan microspheres. SEM photographs show that the prepared naproxen loaded chitosan alginate microspheres and naproxen loaded chitosan alginate & carrageenan microspheres were spherical in shape and had a rough surface as shown in Figure 5 a&b. From this, it can be inferred that the drug is dispersed in the polymeric matrix without having any core or coat, confirming that the system is a polymeric matrix system.

FT-IR spectroscopy

The FTIR of naproxen (drug) shows intense bands at 1726cm^{-1}, 3111cm^{-1}, 1604cm^{-1} and 2895cm^{-1} corresponding to the functional groups C=O, OH, aromatic stretch, and aliphatic stretching as represented in Figure 2(h). In the FTIR spectrum of naproxen loaded chitosan coated alginate microspheres, prominent bands of C=O stretching 1734cm^{-1} and OH stretching was observed at 2939 cm^{-1} respectively for naproxen loaded prepared microspheres. This confirms the absence of any interaction between the drug and polymers during the preparation of the microspheres.

In case of naproxen loaded chitosan coated alginate & carrageenan microspheres, prominent bands of C=O stretching, a broad absorption band at 1373 cm^{-1} assigned to sulphonic acid ($SO3^{-}$) groups was observed for carrageenan (2b) and an intense and broad absorption band at 1647cm^{-1} assigned to –NH2 groups was observed for chitosan (figure 1d). The spectra of physical mixtures as well as pure drug and polymers appeared almost unchanged in the carbonyl stretching region, indicating the absence of any hydrogen bonding interaction between drug and polymers (2i). However, the spectra of the naproxen loaded chitosan coated alginate & carrageenan microspheres showed the disappearance of sharp carbonyl peak of naproxen in the chitosan coated alginate & carrageenan

microspheres indicates conversion of crystalline to amorphous form of drug and could be attributed to the in-situ complex formation between chitosan-naproxen.

Differential scanning calorimetric analysis

DSC tracing of pure naproxen shows an endothermic peak at 152°C which corresponds to its melting point [10] (Figure3d). Sodium alginate decomposes at about 240°C with an exotherm (3a). The thermograms of chitosan did not show any peaks. In the case of the blank microspheres, the DSC thermogram is different from that of the polymer (sodium alginate), which indicates the possibility of interaction between sodium alginate and calcium ions (3i). The peak of the drug did not appear in the thermograms of any type of prepared microspheres containing naproxen. It may indicate that the drug was uniformly dispersed at the molecular level in the polymeric matrix. One endothermic peak appeared in the range of 165-200°C, which may be due to the shifted peak of sodium alginate after interaction with calcium chloride. This also indicates that sodium alginate interact with other polymer (chitosan) and formed homogeneous dispersion. Therefore, absence of the exothermic peak of naproxen at around 152°C in the DSC of the drug loaded microspheres suggests that the drug existed in an amorphous state as a molecular dispersion in the polymeric matrix. The thermograms of the above samples are presented in Figure 3.

X-ray diffraction (XRD)

The X-ray diffraction patterns of naproxen loaded chitosan coated alginate microspheres and chitosan coated alginate & carrageenan microspheres are presented in figure 4. The X-ray diffraction pattern of naproxen shows many characteristic sharp peaks (Figure 4f), which did not appear in the X-ray diffraction pattern (Figure 4 d & h) of drug loaded microspheres. This indicates that the drug loaded inside the polymer matrix is not in the crystalline state for both chitosan coated alginate microspheres and chitosan coated alginate & carrageenan microspheres.

In vitro drug release of naproxen

The effect of different experiment variables on the release of naproxen from drug loaded chitosan coated alginate microspheres is represented in Figure 6.

Figure 6a shows the effect of sodium alginate concentration on drug release from naproxen loaded chitosan coated alginate microspheres. The microspheres prepared using a concentration of 4%w/v sodium alginate are able to prolong the drug release when compared to microspheres prepared with 2 and 3 % w/v sodium alginate. Increase in the concentration of calcium chloride resulted in a delay in the drug release as shown in Figure 6b. Increase in chitosan concentration increased the prolongation of the drug release (Figure 6c), possibly due to formation of a membrane with reduced permeability through ionic interaction between positively charged amino groups of chitosan with carboxylic residues of alginate, resulting from the addition of polycationic polymer (chitosan) to the gelation medium. A change in drug release profile was observed when the alginate: drug ratio was altered as depicted in Figure 6d. From the figure 6e, it can inferred that curing time had a pronounced on the rate of drug release from the prepared microspheres, the increase in the curing time from 4 to 8 hours resulted in a delayed release of the drug, and this increase may be due to the penetration of calcium ions to the interior of the microspheres resulting in increased cross linking. In case of drug release profile of naproxen loaded chitosan coated alginate & carrageenan microspheres is represented in Figure 7. With increase in alginate concentration, drug release is retarded from naproxen loaded chitosan coated alginate & carrageenan microspheres and also the drug release was delayed with increase in calcium chloride concentration. Increase in chitosan concentration up to 1% shows a prolongation in the release of drug (Figure 7c.). However, further increments did not result in enhancement in delay of the drug release. In case of microspheres prepared with a gelation time of 4 hours, the burst effect was reduced when compared with microspheres prepared with a gelation time of 2 hours (Figure 7f). No major difference in the drug release profile was observed when the alginate drug ratio was altered. The addition of carrageenan sustained the release of naproxen from the microspheres (Figure 7e).This evident when the drug release profiles of batches NPA7 & NPAC2 are compared. The sustained release profile obtained from naproxen loaded chitosan coated alginate & carrageenan microspheres is also advantageous from the view point of preparation. Addition of carrageenan does not create difficulty

with respect to the addition of the polymer solution into the gelation medium during preparation due to increase in viscosity of it with increase in concentration of sodium alginate.

Proposed drug release mechanism

In order to characterize the in-vitro release of naproxen from drug loaded microspheres of both the methods, different release models were applied, i.e., Zero-order, First order, Higuchi model. The model with the higher correlation coefficient was judged to be a more appropriate model for in vitro release data. As compared with zero order and higuchi's plot, linear regression analysis indicated a higher correlation coefficient for first order model where a linear relationship existed between the logarithm of the percent drug remaining to be released from the prepared microspheres and time. Hence, the release of naproxen from the naproxen loaded chitosan coated alginate microspheres and naproxen loaded chitosan coated alginate & carrageenan microspheres can be described by first-order kinetics model.

The data for all optimized batches kept under short term stability study showed that no appreciable change in drug loading and cumulative release profile occurred. Hence formulation was found to be stable under the conditions under which the stability studies were performed. This revealed that drug release in chitosan coated alginate microspheres, can be reduced extended over the period of time considerably by adding carrageenan into the formulations, which formed polyelectrolyte complex membrane with chitosan and bulk modification of the microspheres structure offering resistance to the release of the drug to different degree; thus, can be used as composition in a controlled release dosage form of naproxen.

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