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Preparation of sodium alginate–methylcellulose blend microspheres for controlled release of nifedipine ☆

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Abstract

Carbohydrate polymeric blend microspheres, consisting of sodium alginate (NaAlg) and methylcellulose (MC) were prepared by water-in-oil (W/O) emulsion method. These microspheres were cross-linked with glutaraldehyde and loaded with nifedipine (NFD), an anti-inflammatory drug. The microspheres were characterized by differential scanning calorimetry (DSC), scanning electron microscopy (SEM) and laser particle size analyzer. DSC thermograms of NFD-loaded NaAlg–MC microspheres confirmed the molecular level distribution of NFD in the polymer matrix. SEM picture of the microspheres suggested the formation of spherical particles. Swelling experiments on the microspheres provided important information on drug diffusion properties. Release data have been analyzed using an empirical equation to understand the nature of transport of drug containing solution through the polymeric matrices. The controlled release characteristics of the matrices for NFD were investigated in pH 7.4 media. Particle size and size distribution of the microspheres was studied by laser light diffraction particle size analyzer. Drug was released in a controlled manner up to 12 h.

Keywords: Carbohydrate polymers; Blend microspheres; Nifedipine; Controlled release

1. Introduction

Polysaccharides, a class of naturally available carbohydrate polymers, have been used extensively in food industry as gelling agents and for encapsulation of living cells (Cai, Shi, Sherman, & Sun, 1989; Hertzberg, Moen, Vogelsang, & Oestgaard, 1995; Lim & Moss, 1981). Sodium alginate (NaAlg), a natural polysaccharide, composed of D-mannuronic acid and D-guluronic acid, is derived from the brown seaweeds. NaAlg is a biodegradable polymer used extensively in drug delivery applications (Aminabhavi, Kulkarni, Soppimath, Dave, & Mehta, 1999; Downs, Robertson, Riss, & Plunkett, 1992; Lin & Ayres, 1992; Ramesh Babu, Krishna Rao, & Sairam, 2006). Earlier literature cites many applications of NaAlg in agricultural applications (Cai et al., 1989; Kulkarni, Soppimath, Aminabhavi, Dave, & Mehta, 2000; Kumbar & Aminabhavi, 2002) after cross-linking with glutaraldehyde. Alginate salts are known to form a reticulated structure in contact with calcium ions or glutaraldehyde, and this characteristic has been used to prepare the sustained release particulate systems for a variety of drugs, proteins, and cells (Almeida & Almeida, 2004; Draget, Braek, & Smidsrod, 1997; Gombotz & Wee, 1998).

Methylcellulose (MC) is also a carbohydrate polymer, is soluble in water. It forms aqueous solutions and demonstrates a unique property to form reversible physical gels due to hydrophobic interactions when heated above a particular temperature (Haque & Morris, 1993). MC finds applications as a binder or thickener in pharmaceutical, food and ceramic processing industries and can undergo thermo-reversible gelation in aqueous solution upon heating (Hirrien, Chevillard, Desbrieres, Axelos, & Rinaudo, 1998; Hirrien, Desbrieres, & Rinaudo, 1996; Ibbett, Phillip, & Price, 1992; Sarkar, 1995). Cellulose, the raw material of

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MC, is hydrophilic, but cellulose fibers contain the crystalline ordered regions formed by the intra and intermolecular hydrogen bonds; consequently, cellulose does not dissolve in water. However, the crystalline fraction depends on the source of cellulose, but when methoxyl groups substitute a certain number of hydroxyl groups, some hydrogen bonds are broken and MC becomes water-soluble. Commercial MC is produced by a reaction in which cellulose is exposed to aqueous sodium hydroxide and methyl chloride under mechanical mixing, with methylation occurring more rapidly in NaOH-rich and/or higher temperature regions. Consequently, it is assumed that distribution of methyl groups is in homogeneity along each chain and from chain to chain. However, the MC prepared in a more homogeneous manner, i.e., the reaction carried out in solution, was reported not to undergo gelation for the same average degree of substitution (DS) (Ibbett et al., 1992). It has been suggested that crystallites of trimethylglucose units, the most hydrophobic repeat units, act as ''cross-linking loci'' upon heating. Being a polyhydroxy polymer, MC can be chemically cross-linked with a dialdehyde in the presence of a strong acid to generate a hydrogel (Gimenez, Reina, Mantecon, & Cadiz, 1999; Horkay & Zrinyi, 1982; Tomita & Ikeda, 1997).

Controlled drug delivery technology represents the more rapidly advancing area in recent years due to the involvement of multidisciplinary scientists, who are contributing to the human health care related problems. The drug delivery systems offer numerous advantages as compared to conventional dosage, forms including improved efficiency, reduced toxicity, and improved patient compliance and convenience (Uhrich, Cannizaro, Langer, & Shakesheff, 1999). Over the past decades, blends have been investigated to satisfy the need of specific sectors of polymer industry. Such polymeric blends show superior performances over the conventional individual polymers and consequently, the range of applications have grown rapidly for such class of materials. In the recent past, carbohydrate and biodegradable polymers have been extensively used to develop the controlled release (CR) formulations (Isiklan, 2006; Vaithiyalingam, Nutan, Reddy, & Khan, 2002) to decrease the release rates of drugs having short plasma life. Among the various polymers employed, hydrophilic biopolymers are quite suitable in oral applications (Liu Xing, Dawei, Liping, & Rongqing, 2003) due to their inherent advantages over the synthetic polymers.

Nifedipine is a prototype 1,4-dihydropyridine calcium channel blocker. By allosteric interference with the gating mechanism of L-type voltage activated calcium channels in smooth muscle, these drugs prevent the influx of extracellular calcium required activating the contractile machinery of the cell (Godfraind, 1994; McDonald, Pelzer, Trautwein, & Pelzer, 1994). Nifedipine exerts its clinical effects due to vascodilation of arterial smooth muscle, leading to reduced peripheral resistance and improved coronary flow. It has little effect on cardiac tissue. Nifedipine is indicated for the prophylaxis of angina pectoris and in peripheral circulatory disorders such as Raynaud's syndrome (Godfraind, 1994).

In continuation of our work, presently we are aiming to prepare carbohydrate blend microspheres, consisting of sodium alginate and methylcellulose loaded with nifedipine. In order to investigate the release of NFD from NaAlg–MC microspheres, NFD-loaded blend microspheres were prepared by varying blend ratio, NFD content and amount of cross-linking agent. These microspheres were characterized by SEM, X-RD and DSC to investigate the shape and distribution of drug in the blend microspheres. Swelling experiments were carried out on the blend microspheres to evaluate the diffusion properties of drug through the microspheres.

2. Experimental

2.1. Materials

Sodium alginate (low viscosity grade sample), methylcellulose, light paraffin oil and glutaraldehyde (25% aqueous solution) (GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Tween 80 was purchased from Sigma Chemical Co., Milwaukee, USA. Nifedipine was purchased from HiMedia Laboratories Pvt. Ltd, Mumbai, India.

2.2. Preparation of sodium alginate/methylcellulose blend microspheres

NaAlg and MC were dissolved separately in water at different concentration by stirring overnight. The two polymer solutions were mixed and stirred well for proper mixing, which led to a miscible polymer solution. A known amount of nifedipine was dissolved in 1 mL of methanol and was added to the blend polymer solution. The drug-loaded blend polymer solution was emulsified into liquid paraffin to form a water-in-oil (W/O) emulsion at 400 rpm speed using a Eurostar (IKA Labortechnik, Germany) high-speed stirrer for 30 min in a separate 500 mL beaker containing 100 mL of light liquid paraffin oil, 2% (w/v) of Tween 80, 1 mL of 0.1 M HCl and the required amount of GA. The microspheres formed were filtered, washed repeatedly with *n*-hexane and water to remove the oil as well as excess amount of surfactant and the unreacted GA. These microspheres were dried under vacuum at 40 °C and stored in a desiccator before further analysis.

First, the microspheres were prepared with different amounts of cross-linking agent, i.e., 2.5, 5, and 7.5 mL of GA with 10% of MC and 5% of NFD are designated as NaAlg–MC-1, NaAlg–MC-2, and NaAlg–MC-3, respectively. Second, the microspheres were prepared by varying the amount of methylcellulose, i.e., 10%, 20%, and 30% with 5 mL GA and 5% NFD are designated as NaAlg–MC-2, NaAlg–MC-4, and NaAlg–MC-5, respectively. Lastly, microspheres prepared by varying the NFD content in the microspheres, i.e., 5%, 10%, and 20% with 10% MC and 5 mL GA are designated as NaAlg–MC-2,

NaAlg–MC-6, and NaAlg–MC-7, respectively. The plain NaAlg microspheres with 5% NFD and cross-linked with 5 mL of GA were prepared are designated as NaAlg–MC-8. The blend matrix is cross-linked with GA as shown in Scheme 1.

2.3. Fourier transform infrared spectroscopy (FTIR)

FTIR spectral measurements were performed using Perkin-Elmer FTIR Spectrometer (Model: Spectrum GX, USA) to confirm the presence of cross-linking in NaAlg–MC and blend formation. The blend particles were finely ground with KBr to prepare the pellets under a hydraulic pressure of 392.2 dynes/m^2 and spectra were scanned between 400 and 4000 cm^{-1}.

2.4. Differential scanning calorimetry (DSC)

DSC curves of the plain NFD, NaAlg–MC microspheres and NFD-loaded NaAlg–MC microspheres were recorded using Rheometric Scientific differential scanning calorimeter (Model-DSC SP, UK). The analysis was performed by heating the samples at the rate of 10 °C/min under an inert nitrogen atmosphere.

2.5. X-RD

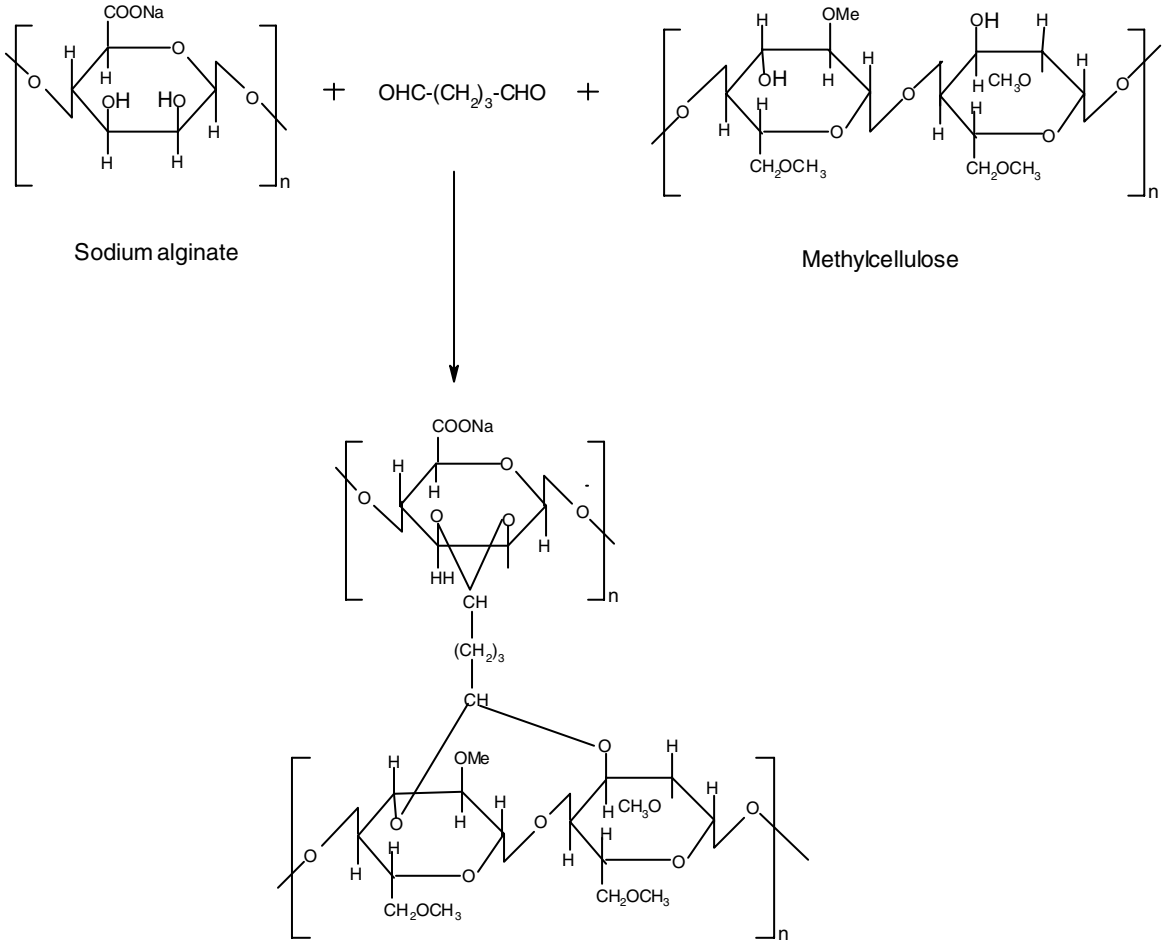
The X-ray diffraction (XRD) patterns of placebo microspheres, plain NFD, plain NaAlg–MC microspheres and NFD-loaded NaAlg–MC microspheres were recorded using a Rigaku Geigerflex diffractometer equipped with Ni-filtered CuKα radiation ($\lambda = 1.5418$ Å). Dried MGs of uniform size were mounted on a sample holder and the patterns were recorded in the range 10°–50° at the speed of 5°/min to know the crystallinity.

2.6. Scanning electron microscopy (SEM)

SEM images of the microspheres were recorded using a Hitachi S520 scanning electron microscope (Japan) at the required magnification. A working distance of 33.5 mm was maintained and the acceleration voltage used was 10 kV with the secondary electron image (SEI) as a detector.

2.7. Particle size analysis

Size of the microspheres was measured by using a particle size analyzer (Mastersizer 2000, Malvern Instruments, UK). About 500 mg of microspheres were transferred to



Scheme 1. Formation of NaAlg–MC blend microspheres cross-linked with glutaraldehyde.

the dry sample holder and stirred vigorously to avoid the agglomeration of particles during measurements. For measurement of sizes of different formulations/batches, the sample holder was cleaned by vacuum. The particle size was also measured using an optical microscopy.

2.8. Estimation of drug loading and encapsulation efficiency

Specific amount (100 mg) of dry microspheres was vigorously stirred in a beaker containing 10 mL of dichloromethane to extract the drug from the microspheres. A 10 mL of 7.4-pH phosphate buffer containing 0.02% Tween 80 was added to the above solution to make the drug soluble and dichloromethane was evaporated with a gentle heating and continuous shaking. The aqueous solution was then filtered and assayed by UV spectrophotometer (model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 238 nm. It was possible that 100% NFD was extracted from the microspheres using dichloromethane. A sintered glass filter was used for this filtration and there was no trace amount of NFD retained by the filter because the porosity of the filter was larger than the size of the NFD particles that were dissolved in dichloromethane. The results of % NFD loading and encapsulation efficiency were calculated using Eqs. (1) and (2). These results are compiled in Table 1.

$$\%\ \text{Drug loading} = \left(\frac{\text{Wt. of drug in microspheres}}{\text{Wt. of microspheres}}\right) \times 100 \quad (1)$$

$$\%\ \text{Encapsulation efficiency} = \left(\frac{\text{Actual loading}}{\text{Theoretical loading}}\right) \times 100 \quad (2)$$

2.9. Swelling studies

Dynamic swelling of NaAlg–MC microspheres prepared by using three different cross-link densities as well as three different drug loadings, different MC content and NFD loaded pure NaAlg microspheres were studied in water by weight uptake measurements with time. Swelling experiments performed in 7.4 pH buffer solutions produced no significant changes and hence, we studied the swelling of microspheres in water (Korsmeyer & Peppas, 1981). To perform the swelling experiments, microspheres were soaked in water; several of them were removed from the swelling bottles at different time intervals and blotted carefully (without pressing hard) to remove the surface-adhered water. The microspheres were then weighed (w_1) on an electronic microbalance (Mettler, AT 120, Switzerland) accurate to ±0.00001 g. The microspheres were dried to a constant weight (w_2) in an oven maintained at 60 °C for 5 h. Swelling experiments were repeated thrice for each sample and average values were used in data analysis. The standard deviations (*SD*) in all cases were <3%. The weight % water uptake was calculated as

$$\%\ \text{Water uptake} = \left(\frac{\text{Weight of swollen } MGs(w_1) - \text{Weight of dry } MGs(w_2)}{\text{Weight of dry } MGs(w_2)}\right) \times 100 \quad (3)$$

2.10. In vitro release

In vitro release studies have been carried out by performing the dissolution experiments using a tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37 °C under 100 rpm rotor speed. Drug release from the microspheres was studied in an intestinal (7.4 pH phosphate buffer) fluid. At regular intervals of time, sample aliquots were withdrawn and analyzed by UV spectrophotometer (Model Anthelie, Secomam, Dumont, France) at the fixed λ_{max} value of 238 nm.

3. Results and discussion

3.1. Fourier transform infrared spectroscopy (FTIR)

Results of FT-IR spectra for methylcellulose, alginate and alginate/methylcellulose showed that the characteristic peak observed at 2826 cm^{-1} was the CH stretch in methyl ether (O–CH_3) on methylcellulose shown in Fig. 1. Additionally, the spectrum of alginate showed a characteristic

Table 1
Results of % of encapsulation efficiency, mean size, and water uptake of different formulations

Formulation codes	% MC in microspheres	% NFD loaded	Amount of GA added (mL)	% Encapsulation efficiency ± *SD*	Mean particle size (μm) ± *SD*	% Water uptake
NaAlg–MC-1	10	5	2.5	68.2 ± 0.8	368 ± 5	397
NaAlg–MC-2	10	5	5	66.4 ± 1.1	356 ± 6	356
NaAlg–MC-3	10	5	7.5	61.5 ± 0.9	312 ± 8	337
NaAlg–MC-4	20	5	5	72.6 ± 0.8	360 ± 7	294
NaAlg–MC-5	30	5	5	79.8 ± 1.2	375 ± 9	251
NaAlg–MC-6	10	10	5	68.5 ± 1.1	398 ± 5	378
NaAlg–MC-7	10	15	5	70.9 ± 1.5	405 ± 6	398
NaAlg–MC-8	00	5	5	61.8 ± 0.6	418 ± 5	435

SD, standard deviation.

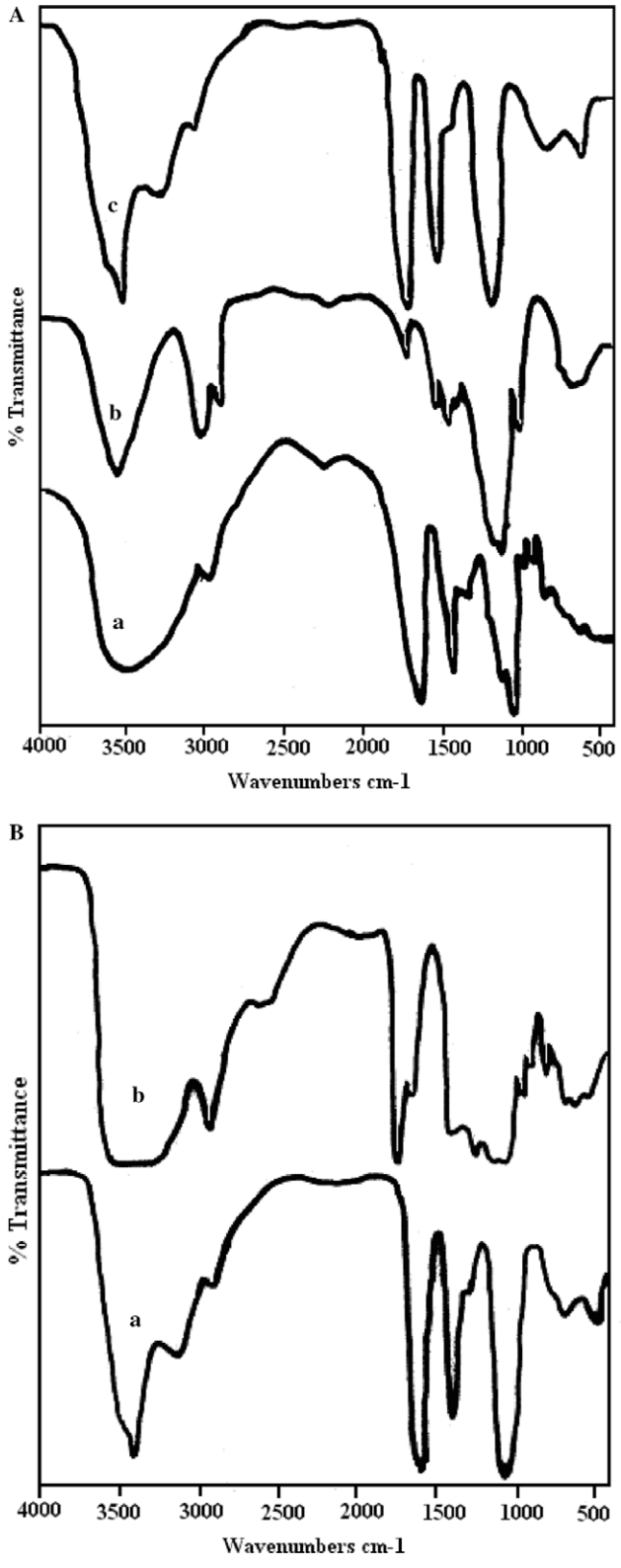


Fig. 1. FTIR spectra of (A): plain NaAlg (a), plain methylcellulose, NaAlg–MC blend (c), (B): NaAlg–MC blend uncross linked (a) and NaAlg–MC blend cross-linked (b).

peak at 1615 cm^{-1} for the associated carboxylic acid salt (–COO– antisymmetric stretch, 1500–1650 cm^{-1}). In contrast, the spectrum of the methylcellulose/alginate showed

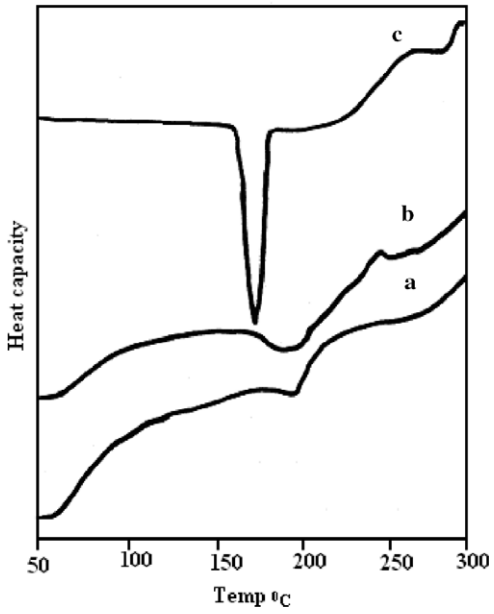


Fig. 2. DSC thermograms of (a) pristine NaAlg–MC microspheres, (b) NFD loaded NaAlg–MC microspheres, and (c) pristine NFD.

both the aforementioned characteristic peaks for methylcellulose and alginate. However, recognizable peak shifts were found in the spectrum: 2826–2834 cm^{-1} for the CH stretch in methyl ether on methylcellulose and 1615–1630 cm^{-1} for the associated carboxylic acid salt on alginate. This suggested that methylcellulose/alginate was well mixed to lead to significant changes on molecular dynamics for the constituted components. During cross-linking, GA might have reacted with –OH groups of blend through the formation of ether linkages (Fig. 1B). Hence, the appearance of a peak at 1263 cm^{-1} in the spectra of cross-linked microspheres confirms the formation of more ether linkages. This is further supported by the presence of a sharp high intensity peak due to $–CH_2$ group of alkyl chain as a result of cross-linking. The acetal ring formation is a further test of cross-linking of hydroxyl groups of the polymer with aldehydes of GA, which is shown by the peak observed at 1263 cm^{-1}.

3.2. Differential scanning calorimetry (DSC)

DSC thermograms of pure NFD, NFD-loaded NaAlg–MC microspheres and plain NaAlg–MC microspheres are displayed in Fig. 2. Nifedipine shows a sharp peak at 177 °C due to polymorphism and melting, but in case of NFD-loaded microspheres, no characteristic peak was observed at 177 °C (Fig. 2C), suggesting that NFD is molecularly dispersed in the matrix.

3.3. X-ray diffraction (X-RD)

X-RD analyses can provide a clue about crystallinity of the drugs in cross-linked microspheres. XRD patterns recorded for plain NFD (a), NFD-loaded microspheres

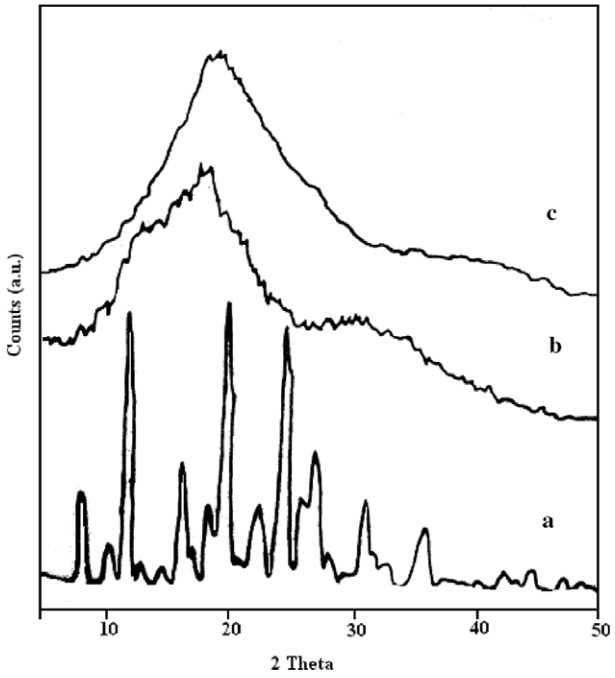


Fig. 3. X-RD spectra of plain NFD (a), NFD-loaded NaAlg–MC blend microspheres (b), and plain NaAlg–MC blend microspheres (c).

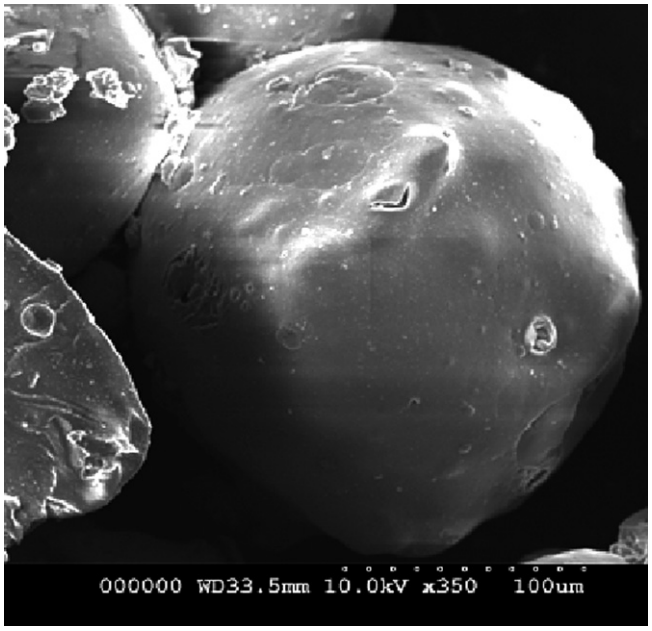


Fig. 4. Scanning electron micrograph of NaAlg–MC blend microspheres.

(b), and pristine microspheres (c) are presented in Fig. 3. Here, NFD peaks observed at 2θ of 6°, 12°, 16°, 20°, 25°, and 27° are due the to crystalline nature of NFD. These peaks are not found in the NFD-loaded microsphres and in pristine microspheres. This indicates that drug particles are dispersed at molecular level in the polymer matrices since no indication about the crystalline nature of the drugs was observed in the drug-loaded microspheres.

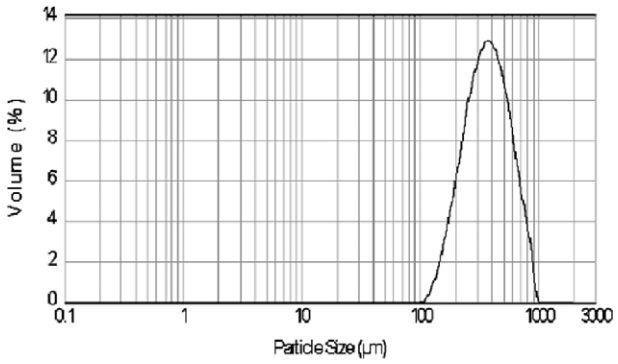


Fig. 5. Particle size distribution curve for NaAlg–MC blend microspheres.

3.4. Scanning electron microscopy

SEM images of single microspheres taken at 350× magnifications are shown in Fig. 4. Microspheres are spherical without forming agglomeration and their surfaces are slightly rough. However, polymeric debris seen around some particles could be due to the method of particle production (i.e., simultaneous particle production and formation of the blend matrix). Microspheres produced by blending of different polymers did not show any effect on the surface properties.

3.5. Laser particle size analyzer

Results of mean particle size with standard errors are presented in Table 1, while the size distribution curve for a typical formulation containing 10% MC, 10% NFD, and 5 mL of NaAlg–MC-6 is displayed in Fig. 5. It is obvious that size distribution is narrow and volume mean diameter of the microspheres is found to be 398 μm. Particle size of different formulations containing different amount of drug, GA and different amount of MC are presented in Table 1.

3.6. Microscopic study

Particle size was also measured alternatively by optical microscopy. These results along with % encapsulation efficiency, % drug-loading and mean particle size for different formulations is presented in Table 1. The size of particles depends on the amount of drug present, % MC content and extent of GA employed. Particles are generally spherical in shape with sizes ranging from 312 to 418 μm. Particle size of the pristine NaAlg is higher than those of NaAlg–MC microspheres. By increasing the MC content of the microspheres, size of the microspheres increased from 356 to 375 μm for 5% NFD-loaded microspheres. This can be explained on the basis of hydrodynamic viscosity concept, i.e., as the amount of MC in microspheres increases, interfacial viscosity of the polymer droplets in the emulsion also increases. On the other hand, with increasing amount of MC, the number of free sites avail-

able for cross-linking is less so that size of the microspheres will also increase with increasing MC content of the microspheres. For instance, as the amount of MC increases from 10% to 30%, the particle size has increased from 356 to 375 μm.

For all the formulations, with increasing amount of drug in the microspheres, particle size also increased. For formulations containing 10% MC and microspheres loaded with different amounts of drug, particle size has increased from 356 to 405 μm; a similar trend was also observed for all other formulations (see Table 1). This is attributed to the fact that drug molecules might have occupied the free volume spaces within the matrix, thereby hindering the inward shrinkage of the polymer matrix (Soppimath, Kulkarni, & Aminabhavi, 2002). However, the extent of cross-linking has shown an effect on particle size (see data in Table 1). For microspheres containing 10 wt% MC and 5 wt% NFD with increasing amount of GA from 2.5 to 7.5 mL, the particle size has decreased from 368 to 312 μm. This is attributed to the fact that with increasing amount of GA in the semi-IPN matrix, the shrinkage of particles has taken place, thereby reducing their size (Korsmeyer & Peppas, 1981; Soppimath et al., 2002).

3.7. Encapsulation efficiency

Three different concentrations of NFD, i.e., 5, 10, and 15 wt% were loaded during cross-linking of the microspheres. Results of % encapsulation efficiency included in Table 1 show increasing trends with increasing drug loading. Encapsulation efficiency of 61.8% was observed for pristine NaAlg microspheres, but for the remaining formulations, it ranged from 66.4% to 70.9%. Such smaller values are due to a lesser soluble drug in the polymer solution, thus incorporating a lesser amount of NFD into microspheres. Notice that % encapsulation efficiency increased with increasing amount of MC in the blend microspheres. For microspheres containing 10, 20, and 30 wt% MC and 5 wt% NFD with 5 mL GA, encapsulation efficiencies were 66.4%, 72.6%, and 79.8%, respectively. For 10% MC in the matrix, the results of extent of cross-linking on size and encapsulation efficiency increased, but the % encapsulation efficiency decreased (see Table 1). For microspheres cross-linked with 2.5, 5, and 7.5 mL of GA, encapsulation efficiencies are, respectively, 68.2%, 66.4%, and 61.1%. Such a decreasing trend is due to an increase in cross-link density, because the microspheres will become rigid, thereby reducing the free volume spaces within the polymer matrix and hence, a reduction in encapsulation efficiency is observed.

3.8. Swelling studies

In microspheres, extent of cross-linking depends upon the amount of cross-linking agent used. In the present study, different amounts of GA were added as the cross-linking agent to the blend microspheres of NaAlg–MC containing 5 wt% of NFD and these data are also included in Table 1. Extent of cross-linking is dependent upon equilibrium swelling. For instance, % equilibrium swelling decreased from 393 to 337 with increasing amount of GA from 2.5 to 7.5 mL. This is due to increased cross-link density and decreased pore volume of the blend matrix (Patel, Patel, & Kansara, 1994) with increasing amount of GA in the matrix. Since MC is a water-soluble polymer, it is readily miscible with NaAlg in all proportions and hence, blending of MC with NaAlg will increase the matrix swelling due to their higher water uptake. By increasing the drug loading of the blends, % water uptake also increased. For instance, for NaAlg–MC-2, NaAlg–MC-6, and NaAlg–MC-7, % equilibrium swelling values are 356, 378, and 398, respectively. Such an increase in swelling of the blends is due to the incorporation of hydrophilic NaAlg along with MC chains into the blend matrix. The % water uptake or % dynamic swelling of the formulated blend matrix has decreased with increasing amount of MC in the blend matrix. However, the % water uptake or % dynamic swelling of the blend matrix containing 10%, 20%, and 30% of MC are 356, 294, and 251, respectively. The % water uptake has decreased with increasing amount of MC in the blend matrix. This is due to the fact that as the amount of MC increases in the blend matrix, hydrophobicity of the blend decreases because of the presence of methyl groups in MC as well as a lesser number of residual –OH groups, which increases the hydrophobic character of the blend.

3.9. Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data vs time by fitting these data to exponential equation of the type (Ritger & Peppas, 1987).

$$\left(\frac{M_t}{M_\infty}\right) = kt^n. \tag{4}$$

Here, M_t/M_∞ represents the fractional drug release at time t, k is a constant characteristic of the drug-polymer system and n is an empirical parameter characterizing the release mechanism. Using the least squares procedure, we have estimated the values of n and k for all the nine formulations and these values are given in Table 2. If $n = 0.5$, the drug diffuses and releases out of the polymer matrix following a Fickian diffusion. For $n > 0.5$, an anomalous or non-Fickian type drug diffusion occurs. If $n = 1$, a completely non-Fickian or Case II release kinetics is operative. The intermediary values ranging between 0.5 and 1.0 are attributed to anomalous type diffusive transport (Aminabhavi & Naik, 1998; Ritger & Peppas, 1987).

The values of k and n have shown a dependence on the extent of cross-linking, % drug loading and MC content of the matrix. Values of n for beads prepared by varying the amount of MC in the blend microspheres of 10, 20, and 30 wt% and keeping NFD (5%) and GA (5 mL) constant,

Table 2
Release kinetics parameters of different formulations

Formulation code	k	n	$D \times 10^6$ ($cm^2 s^{-1}$)	Correlation coefficient, r
NaAlg–MC-1	0.102	0.34	2.93	0.861
NaAlg–MC-2	0.050	0.48	2.15	0.979
NaAlg–MC-3	0.012	0.66	2.49	0.993
NaAlg–MC-4	0.027	0.58	3.54	0.990
NaAlg–MC-5	0.014	0.63	3.40	0.983
NaAlg–MC-6	0.062	0.43	3.99	0.988
NaAlg–MC-7	0.017	0.66	5.63	0.928
NaAlg–MC-8	0.113	0.33	3.56	0.965

ranged from 0.478 to 0.625 leading to a shift of transport from Fickian to the anomalous type. The NFD-loaded particles exhibited n values ranging from 0.48 to 0.66 (see Table 2), indicating the shift from erosion type release to a swelling-controlled, non-Fickian type mechanism. This may be due to the reduction in the regions of low microviscosity and closure of microcavities in the swollen state of the polymer. Similar findings have been observed elsewhere, wherein the effect of different polymer ratios on dissolution kinetics was studied (Lyu, Sparer, Hobot, & Dang, 2005). On the other hand, the values of k are quite smaller for drug-loaded microspheres, suggesting their lesser interactions compared to microspheres containing varying amounts of MC.

The diffusion coefficient, D of water in the microspheres was calculated (Kulkarni et al., 2000) using the equation

$$D = \left(\frac{r\theta}{6M_\infty}\right)^2 \pi, \tag{5}$$

where θ is slope of the linear portion of the plot of M_t/M_∞ vs $t^{1/2}$, r is radius of the spherical particles and M_∞ is the maximum sorption value. Diffusion coefficients were estimated by assuming the Fickian diffusion transport. The D (see Table 2) values calculated are in the range of (2.15–5.63) $\times 10^{-6}$ cm^2/s and these are found to depend upon the extent of cross-linking. For instance, D values show a systematic decrease with increasing cross-linking of the matrix in all the formulations. This is obvious because of the increased rigidity of the chain due to increased cross-linking, thereby prohibiting the transport of more water molecules.

3.10. Effect of methylcellulose content

The effect of MC content was studied at a constant loading of 5 wt% NFD. It was found that NaAlg produced almost 100% cumulative drug release in about 10 h, whereas NaAlg–MC blend microspheres produced up to 90% cumulative release in 12 h. Release of NaAlg–MC microspheres prepared with different amounts of MC are displayed in Fig. 6. Notice that during the dissolution experiments, microspheres have systematically swollen with the decreasing amount of MC, due to the formation of loosely cross-linked network chains of MC. As the amount of MC increases, the cumulative release has decreased due to lesser swelling of the MC chains than NaAlg. This is due to the fact that as the amount of MC increases in the blend matrix the hydrophobicity of the blend decreases because of the presence of methyl groups in MC as well as lesser number of the residual –OH groups, which make the blend to increase the hydrophobicity to decrease the release rates. Thus, a regaining-type response of the polymeric chains is possible due to the stresses induced by the surrounding solvent media during dissolution, resulting in a decrease of chain dimension (radius of gyration) of the polymer; this will further decrease molecular volume of the hydrated polymer due to decreased swelling of MC component of the blend matrix, thereby reducing the free volume space of the blend matrix. Notice that the nature of release profiles remains almost identical in all the formulations containing different amounts of GA, indicating a linear relationship with the drug release profiles.

3.11. Effect of cross-linking agent

The % cumulative release vs time curves for varying amounts of GA, i.e., 2.5, 5.0, and 7.5 mL at a fixed amount of the drug (5 wt%) are displayed in Fig. 7. The % cumulative release is quite fast and large at lower amount of GA (i.e., 2.5 mL), whereas the release is quite slower at higher amount of GA (i.e., 7.5 mL). The cumulative release is somewhat smaller when lower amount of GA was used probably because at higher concentration of GA, the polymeric chains would become rigid due to the contraction of microvoids, thus decreasing the % cumulative release of NFD through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA.

3.12. Effect of drug loading

Fig. 8 shows the release profiles of NFD-loaded NaAlg–MC blend microspheres at different amount of drug loadings. Release data showed that formulations containing

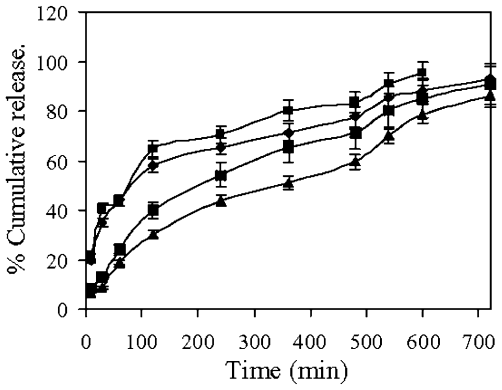


Fig. 6. Percentage of cumulative release of NFD through NaAlg–MC blend microspheres containing different of amount of MC. Symbols: (■) Pure NaAlg, (◆) 10 wt% MC, (■) 20 wt% MC, and (▲) 30 wt% of MC.

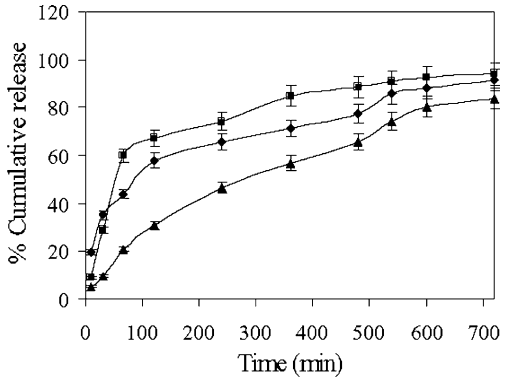


Fig. 7. Percentage of cumulative release of NFD through NaAlg–MC blend microspheres containing different of amounts of cross-linking agent. Symbols: (■) 2.5 mL, (◆) 5 mL, and (▲) 7.5 mL.

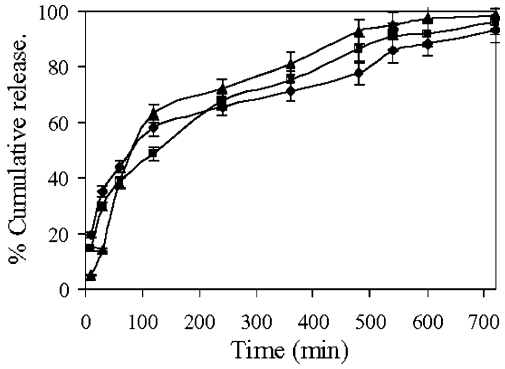


Fig. 8. Percentage of cumulative release of NFD through NaAlg–MC blend microspheres containing different amount of NFD. Symbols: (◆) 5 wt%, (■) 10 wt%, and (▲) 15 wt%.

the highest amount of drug (15 wt%) displayed the fast and higher release rates than those formulations containing small amount of NFD. A prolonged release was observed for the formulation containing a lower amount of NFD. In other words, with decreasing amount of drug in the matrix, a shift from anomalous type release to Case II is observed. Notice that the release rate becomes quite slower at the lower amount of drug in the matrix, due to the availability of more free void spaces through which a lesser number of drug molecules will transport. For all the NFD-loaded formulations, a 90% of NFD release occurred around 600 min, but a complete drug release was observed at 700 min.

4. Conclusions

Carbohydrate polymeric blend microspheres of sodium alginate and methylcellulose were prepared and characterized by differential scanning calorimetry, scanning electron microscopy, and particle size distribution. DSC thermograms have confirmed the uniform molecular distribution of the drug molecules in the microspheres. SEM micrographs exhibited a spherical morphology of the prepared microspheres. The drug was released in a controlled manner. The swelling studies of microspheres have shown that with an increasing amount of MC in the microspheres, water uptake has decreased. This effect is correlated with the release rates of the drug though the microspheres containing different amount of MC. The microspheres have shown lower densities and hence, these could be retained in the gastric environment for more than 12 h, which would help to improve the bioavailability of nifedipine.

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