Preparation of Sodium Alginate/Poly(vinyl alcohol) Blend Microspheres for Controlled Release Applications

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ABSTRACT: Sodium alginate (NaAlg)/poly (vinyl alcohol) (PVA) blend microspheres (MS) were prepared by water-in-oil (w/o) emulsion method. These polymer microspheres were crosslinked with glutaraldehyde and loaded with metformin hydrochloride (MHC). The microspheres were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), scanning electron microscopy (SEM), and X-ray diffraction (XRD) analysis to confirm the molecular dispersion of the drug, thermal stability, morphological properties, and crystallinity of the polymer matrix before and after blending. SEM of the microspheres suggested the formation of microspheres in spherical structure. Drug release data were analyzed using an empirical equation to understand the nature of drug transport through polymeric matrices. The controlled release (CR) characteristics of the polymer matrices was investigated in pH 7.4 media and from the results it was obtained that the drug was released in controlled manner up to 10 h. The physicochemical properties of the microspheres were studied by calculating drug entrapment efficiency and drug release kinetics. Percent of encapsulation efficiency (% EE) decreased with increase in crosslinking agent (GA) and PVA content in the microspheres. The optimum % EE (80%) was observed in case of MS containing 40% of PVA with 15% MHC. The release profiles indicate that the release of MHC decreases with increasing the PVA/NaAlg (w/w) and drug/polymer ratio. At the end of 10 h, the highest release of MHC was found to be 96% for MS containing PVA/NaAlg (40 : 60) and 15 wt % drug loaded.
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Key words: microspheres; metformin hydrochloride; drug delivery; sodium alginate

INTRODUCTION

Polymeric microspheres here after referred to as MS are important class of devices in controlled release (CR) applications. MS have received a greater attention in recent years as effective drug delivery devices in biomedical engineering.[1–3] Amongst various polymers, natural polymers are widely used in drug release systems due to their biocompatibility, biodegradation, and nontoxicity *in vivo* administration.[4]

The widely used natural polymers for CR of drugs are chitosan (CS), sodium alginate (NaAlg), cellulose derivatives, guar gum[3–5] etc. Among these, NaAlg, a biodegradable polymer used extensively in drug delivery applications.[6–9] It is a natural polysaccharide, composed of D-mannuronic acid and D-guluronic acid which is derived from the brown seaweeds; it has wide range of application viz., agriculture.[10–12] Alginate salts are known to form a reticulated structure when in contact with calcium ions or glutaraldehyde; this characteristic has been used to prepare the sustained release particulate systems for a variety of drugs, proteins, and cells.[13–15]

Poly (vinyl alcohol) (PVA) has been used widely in variety of fields since its discovery in 1924[16] for its desirable properties such as nontoxicity and noncarcinogenicity.[17] It finds extensive applications as biomaterials[17–19] such as contact lenses, artificial blood vessels, artificial intestines,[16] and kidneys.[18] Drug release (DR) studies have also been carried on PVA-based hydrogels, a biocompatible, chemically stable, and desirable for bioseparations and cell encapsulations.[17,19,20] However, PVA is a highly hydrophilic polymer and has poor stability in water, thus its solubility is prevented for use in aqueous systems. To overcome this problem, PVA should be insolubilized by blending,[21] copolymerization,[22] grafting,[23,24] and cross-linking.[25] Polymer blending technique can be considered as a useful tool for the preparation of new polymer blends of NaAlg/PVA. NaAlg can be cross-linked using glutaraldehyde (GA), due to the chemical reaction between —OH groups of NaAlg and aldehydic groups of GA.[12]

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In earlier studies, Sanli and Isiklan[26] reported release characteristics of Diclofenac sodium from PVA/NaAlg and PVA-*g*-poly (acrylamide)/NaAlg blend beads. Kulkarni et al.[27] prepared interpenetrating polymer network (IPN) beads of NaAlg for the release of Cefadroxil. Kulkarni et al.[28] and Hua et al.[29] studied the CR of prozosin hydrochloride and diclofenac sodium respectively through NaAlg/PVA blend microspheres. In their recent studies Reddy et al.[30] reported CR of chlorpheniraminemaleate through IPN beads of NaAlg-*g*-methylmethacrylate.

From a perusal of the literature it was found that no reports are available on NaAlg/PVA blend MS for CR of antidiabetic metformin hydrochloride (MHC) drug. This prompted us to undertake a detailed study on CR of water soluble MHC drug. The drug has anti diabetic properties and is used in treatment of diabetes. The authors successfully studied the release profiles for different formulations by varying PVA content in NaAlg/PVA blend, cross-linking agent and drug concentration.

EXPERIMENTAL

Materials

Poly (vinyl alcohol) (PVA) (mol.wt ~ 1,25,000), sodium alginate (NaAlg) (medium molecular weight), light paraffin oil, glutaraldehyde (25% aqueous solution) (GA) were purchased from sd.fine chemicals (Mumbai, India). Tween-80 was purchased from Aldrich chemicals; a gift sample of metformin hydrochloride (MHC) was obtained from Walkman salesman pharmaceuticals, Anantapur, India. Double distilled water collected in the laboratory was used throughout the study.

Preparation of NaAlg/PVA blend microspheres

NaAlg and PVA were dissolved separately in water at different concentration by stirring overnight. The two polymer solutions were mixed and stirred well for proper mixing to form homogeneous blend solution. A known amount of MHC was dissolved in 1 mL of water under sonication and added to the above polymer blend solution. The drug-loaded polymer blend solution was emulsified in liquid paraffin (100 mL) to form water-in-oil (w/o) emulsion using high-speed stirrer (Eurostar, IKA Labortechnik, Germany) at a speed of 400 rpm for 30 min. To this a known amount of Tween 80 (2%w/v), 1 mL of HCl (0.1 *M*) and required amount of GA[31] was added and stirring was continued for 30 min to form MS with uniform size. The MS thus formed were filtered, washed with *n*-hexane and water repeatedly to remove oil, excess amount of surfactant and unreacted GA and dried under vacuum to a constant weight and stored in a desiccator for further characterization and *in vitro* release studies.

Estimation of drug loading and encapsulation efficiency

Specific amount of microspheres was weighed and kept in a beaker containing phosphate buffer solution (PBS) (pH: 7.4) and kept at 37°C for 48 h to extract the drug by centrifuging at 10,000 rpm. The aqueous solution was assayed using UV spectrophotometer at fixed λ_{max} of 230 nm. The results of percentage of drug loading and encapsulation efficiency (EE) were calculated using eqs. (1) and (2)

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

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

In vitro release study

In vitro release studies have been carried out using a tablet dissolution tester (Lab India, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37°C at a rotating speed of 100 rpm.[32] Drug release from the MS was studied in an intestinal (pH: 7.4) fluid atmosphere (PBS). At regular intervals of time, sample of aliquots were withdrawn and absorbance values were analyzed by UV spectrophotometer (Lab India UV 3000^{+}) at a fixed λ_{max} of 230 nm.

FT-IR spectroscopy

FTIR spectral measurements was performed using (Perkin Elmer, USA) spectrophotometer. Polymeric microspheres were finely ground with KBr to prepare pellets under a hydraulic pressure of 400 kg N^{-1} and spectra were scanned between 4000 and 400 cm^{-1}.

X-ray diffraction (XRD) studies

XRD measurements of plain drug, drug-loaded microspheres, and plain microspheres were recorded with a Rigaku Geiger flex Diffractometry (Tokyo, Japan) equipped with Ni-filtered Cu Kα radiation (λ = 1.548 Å). The dried microspheres of uniform thickness were mounted on sample holder, and the

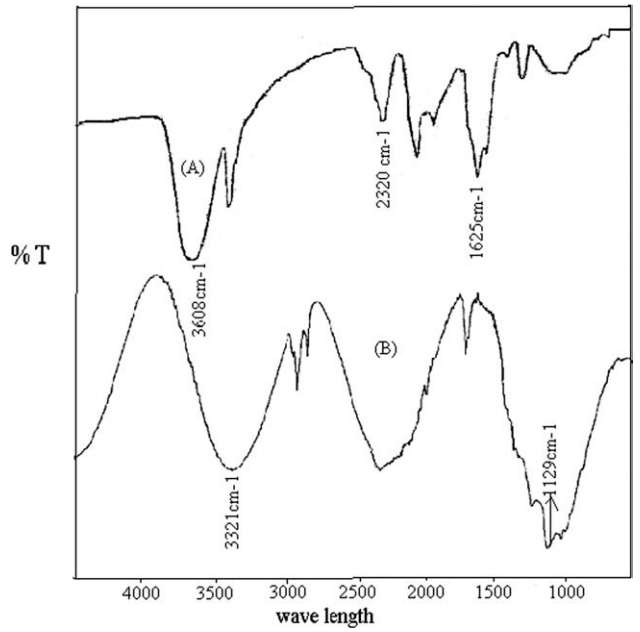

Figure 1 NaAlg/PVA blend uncrosslinked (A) and NaAlg/PVA blend crosslinked microspheres (B).

patterns were recorded in the range of $2\theta = 0$–80° at a speed of 10° min^{-1}.

Morphological (SEM) studies

SEM micrographs of microspheres were obtained under high resolution (Mag 150× 20 kv) using ZEISS scanning electron microscope.

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of uncrosslinked NaAlg/PVA (A), crosslinked NaAlg/PVA blend microspheres (B) are shown in Figure 1. The spectrum of crosslinked NaAlg/PVA microspheres showed peaks of both NaAlg and PVA. However, recognizable peak is found in the spectrum around 2320 and 1625 cm^{-1} attributed to C—H stretching of PVA and associated carboxylic acid salt of NaAlg, respectively, suggesting that NaAlg/PVA blend compatibility to lead to significant changes in molecular dynamics for constituted components of the blend. A peak at 1129 cm^{-1} might be due to the formation of ether linkages formed during the crosslinking reaction between >C—HO of GA and —OH groups of NaAlg and PVA [Fig. 1(B)]. This is also supported by a sharp intensity peak at 1129 cm^{-1} attributed to —CH group of alkyl chain due to crosslinking of two —OH groups of the blend microspheres forming acetyl ring.

X-ray diffraction studies (XRD)

XRD studies helps to determine the crystallinity of the drug in crosslinked microspheres. The most

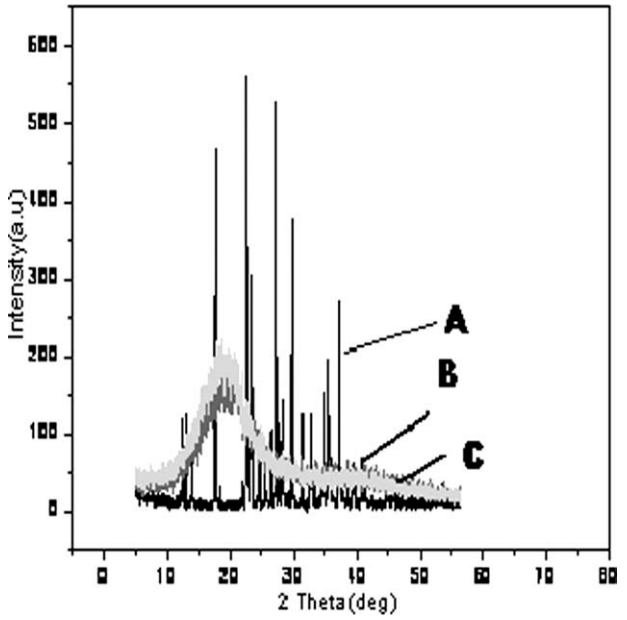

Figure 2 X-RD spectra of plain MHC (A), Unloaded NaAlg/PVA blend microspheres (B), MHC-loaded NaAlg/PVA blend microspheres (C).

intensive peaks of MHC are observed at $2\theta = 22$ and 27° [Fig. 2(A)], suggesting its crystalline nature. But, these peaks are absent in case of MHC loaded MS [Fig. 2(C)], indicating that the dispersion of drug in the polymer matrix is in the order of molecular level

Deferential scanning calorimetry

DSC thermograms of plain NaAlg/PVA (A), MHC loaded NaAlg/PVA microspheres (B) and plain MHC (C) is displayed in Figure 3. The pure MHC

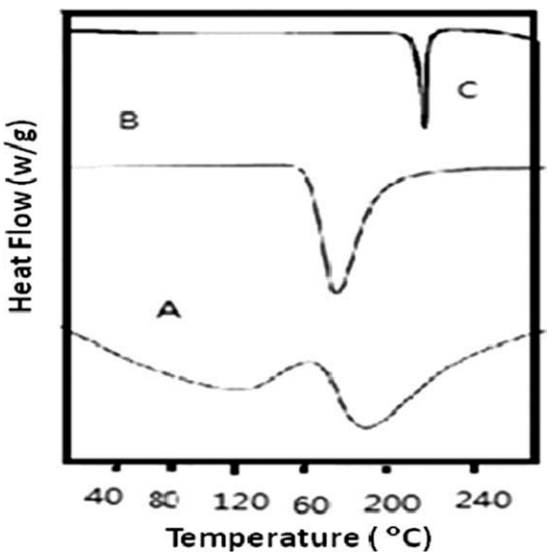

Figure 3 DSC thermo grams of (A) plain NaAlg/PVA, (B) MHC loaded NaAlg/PVA microspheres and (C) plain MHC.

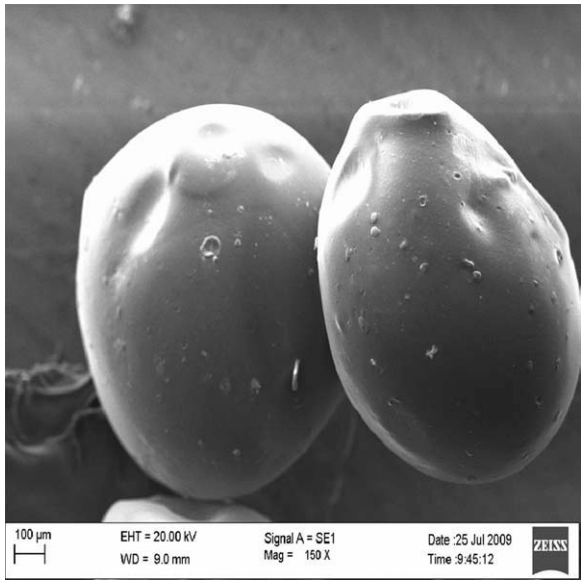

Figure 4 Scanning electron micrographs of NaAlg/PVA blend microspheres.

(C) exhibits a sharp endothermic peak at 220°C. However, in case of MHC loaded microspheres this peak was not observed, suggesting the drug is molecularly dispersed in the polymer matrix.

Morphological (SEM) studies

SEM images of single microspheres taken at 150× magnifications are shown in Figure 4. Microspheres prepared in the present study are spherical without any 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 different ratios of NaAlg/PVA (not shown in figure) did not show any effect on the surface properties.

Estimation of drug loading and encapsulation efficiency

Three different concentrations of MHC (5, 10, and 15 wt %) was loaded during the preparation of microspheres. Results of % encapsulation efficiency are included in Table I. The percentage of entrapment efficiency and microspheres yield may change depending on the preparation condition and the type of the matrix material used to prepare the microspheres. Table I shows that % EE increased with increasing amount of drug loading (60, 72, and 80%) and with increase in PVA content (20–60 wt %) the EEs are in the range of 56–74%.

Encapsulation efficiency decreased with increase in crosslinker concentration, this decrease might be due to the increase in crosslinking density of the polymer matrix (Table I). The increase in crosslinking density leads to the formation of rigid structure as a result, reduction in free volume within the polymer matrix, thereby reducing their EEs. The % EE of microspheres prepared with NaAlg/PVA (60 : 40) crosslinked with different amounts of GA (5, 7.5, 10 mL) are 72, 68, and 62%, respectively.

Drug release kinetics

The phenomenon of solvent sorption by polymeric microspheres depends mechanistically on the diffusion of water molecules into the polymer MS and subsequent relaxation of macro molecular chains of the microspheres.[33] The release data of all the formulations have been further substantiated by fitting the fraction release data M_t/M_∞ to empirical equation proposed by Peppas.[34]

$$(M_t/M_\infty) = kt^n \tag{3}$$

where M_t is the amount of MHC released at time "t" and M_∞ is the drug released at infinite time, "k" is a constant characteristic of the drug-polymer system; and "n" is the diffusion exponent which suggests the nature of release mechanism. Fickian release is defined by an initial $t^{1/2}$ time dependence of the fractional release for slabs, cylinders, and spheres. Analogously, Case II transport is depended by an initial linear time dependence of the fractional release for all geometries.[35] A value of $n = 0.5$ indicates the Fickian transport mechanism; while $n = 1$ is of Case II or non-Fickian transport (swelling controlled). The intermediary values ranging between 0.5 and 1.0 are indicative of the anomalous transport.[8,26]. The least square estimations of the fractional release data along with the estimated correlation coefficient values ("r") are presented in Table II, "n" values for various formulations are in the range of 1.1334–1.9523, indicating that MHC drug release from the microspheres following

TABLE I
Estimation of Drug Loading and Encapsulation Efficiency

Formulation code	% of PVA	% of MHC	Amount of GA (mL)	% of encapsulation efficiency
NaAlg/PVA 1	40	5.0	5.0	60
NaAlg/PVA 2	40	10	5.0	72
NaAlg/PVA 3	40	15	5.0	80
NaAlg/PVA 4	40	10	7.5	68
NaAlg/PVA 5	40	10	10	62
NaAlg/PVA 6	60	10	5.0	74
NaAlg/PVA 7	20	10	5.0	56

TABLE II
Release Kinetics Parameters of Different Formulations

Formulation code	*n*	*k*	Correlation coefficient *r*
NaAlg/PVA1	0.4013	1.6403	0.9492
NaAlg/PVA2	0.4266	1.7079	0.9429
NaAlg/PVA3	0.5464	1.1334	0.9000
NaAlg/PVA4	0.8059	1.9523	0.9012
NaAlg/PVA5	0.7183	1.9003	0.9561
NaAlg/PVA6	0.4255	1.7002	0.9400
NaAlg/PVA7	0.3970	1.7057	0.9590

non-Fickian trend. Correlation coefficients, "*r*" values are in the range of 0.900–0.974, suggesting a good fit of experimental release data.

In vitro release studies

The percent of cumulative release data vs. time plots for MS with varying amounts of GA (5, 7.5, and 10 mL) at a fixed amount of the drug (5%) are displayed in Figure 5. The % CR is quite fast and large (85%), at lower amount of GA (5 mL) whereas the release is quite lower (70%) at higher amount of GA (10 mL). Probably, at higher concentration of GA, polymeric chains become rigid due to the contraction of micro voids, thus decreasing % cumulative release of MHC through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA. Similar observations were also reported by Kulkarni et al.[27,28] in case of NaAlg/PVA IPN network hydrogel membrane.

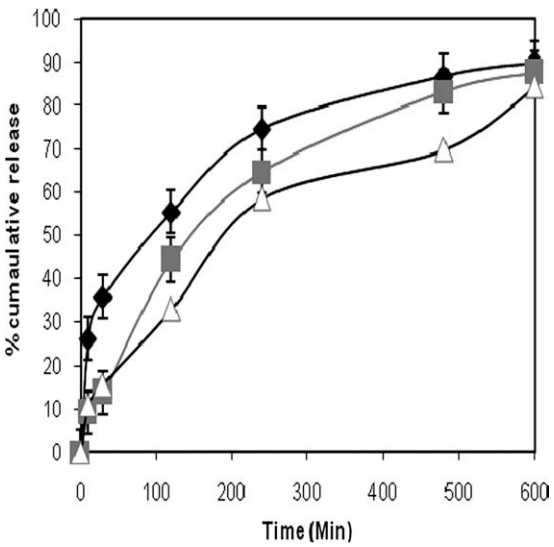

Figure 5 % Cumulative release of MHC through NaAlg/PVA Microspheres containing different amount of cross-linking agent 5 mL (◆), 7.5 mL (■), 10 mL (▲) with 10% of metformin hydrochloride and 60 : 40 NaAlg/PVA.

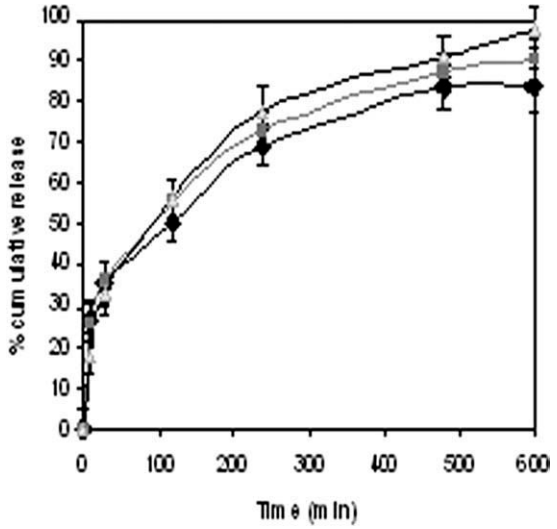

Figure 6 % Cumulative release of MHC through NaAlg/PVA microspheres containing different amounts of metformin hydrochloride 5% (◆), 10% (■), and 15% (▲) with NaAlg/PVA 60 : 40 and 5 mL GA.

Effect of drug content

Figure 6 displays the release profiles of NaAlg/PVA microspheres loaded with different amounts of drug (5, 10, and 15 w/w%). Release data showed that formulations containing highest amount of drug (15 w/w %) displayed fast and higher release rates (96%) than those formulations containing a small amount of MHC (75% cumulative release). A prolonged release was observed for the formulation containing lower amount of MHC (5w/w%). In other words, with decreasing the amount of drug in the matrix, it is noticed that the release rate becomes quite slower; this is due to the availability of more free void spaces through which lesser number of drug molecules will transport. Because drug release from the MS is sustained by diffusion mechanism, the release rates are slow at lower amount of MHC. Similar release profiles were also reported by various researchers.[8,28] In case of all the formulations under study complete MHC release was obtained in about 10 h.

Effect of PVA content

Effect of PVA content on encapsulation efficiency and *in vitro* release of MHC was also investigated. *In vitro* release profiles of MHC for various formulations prepared with different amounts of PVA (10% of MHC and 5 mL of GA) are shown in Figure 7. Faster release rates were observed from the formulations prepared with 20 w/w% of PVA than those formulations prepared with 60 w/w% of PVA. About 95% of the drug was released within the 10 h

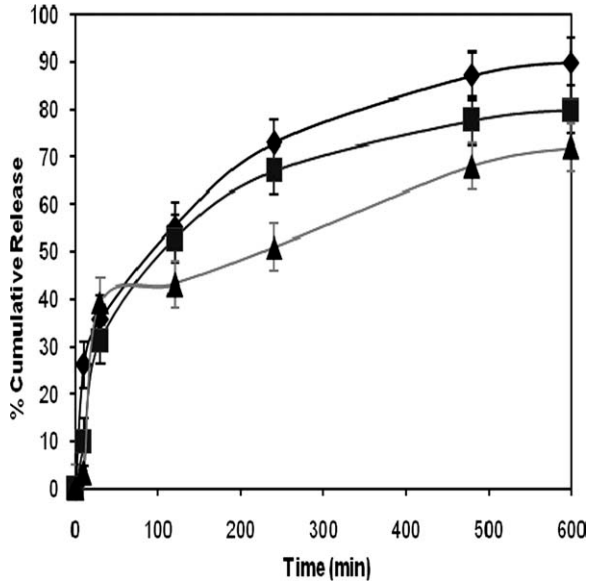

Figure 7 % Cumulative release of MHC through NaAlg/PVA microspheres containing different amounts PVA 20% PVA (◆), 40% PVA (■), 60% PVA (▲) and with 5% of metformin hydrochloride and 5 mL GA.

from the formulations prepared with 20% of PVA; whereas only 77% of MHC release was observed in case of formulation prepared with 60% of PVA. Similar reports were also reported by Sanli et al.[26] from their drug release studies through sodium alginate and poly(vinyl alcohol) blend microspheres. Kulkarni et al.[28] reported that drug release decreased with increase in PVA content in case of Prazosin hydrochloride release through NaAlg/PVA IPN hydrogel membrane. Sanli et al.[36] studied CR of Naproxen from NaAlg/PVA blend beads crosslinked with Naproxen and reported the similar results. Bajpai and Giri[37] reported the graft copolymerization of crosslinked poly(acrylamide) chains onto carboxymethylcellulose and PVA and reported that swelling degree and KNO_3 release decreased with the PVA content.

Future potential

In the present study NaAlg/PVA blend microspheres was prepared using MHC as a model drug and achieved controlled drug release profiles suitable for oral administration. MHC, a potential anti diabetic drug with pronounced diabetics properties were successfully studies by varying the different parameters. Because of short biological half-life time (1–2.5 h) and associated adverse effects, the authors made an attempt to overcome these drawbacks using NaAlg/PVA microspheres in which the drug release was observed for over an extended period of 10 h. Hence the present polymer blend system can be used as an ideal candidate for controlled drug release applications delivery in diabetes treatment.

CONCLUSIONS

Blend microspheres of sodium alginate/poly (vinyl alcohol) were prepared using MHC as a model drug. XRD analysis of the drug-loaded microspheres confirmed the molecular level dispersion of the drug in blend microspheres. SEM analysis showed the formation of spherical microspheres with rough surfaces. Drug release studies indicated controlled release of MHC extended up to about 10 h from the blend microspheres.

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References

1. Moerkerke, R.; Meeussen, F.; Koningsveld, R.; Berghmans, H. Macromolecule 1998, 31, 2223.
2. Ramkissoon, G. C.; Liv, F.; Baudys, M.; Kin, S. W. J Control Release 1999, 59, 287.
3. Agnihotri, S. A.; Mallikarjuna, N. N.; Aminabhavi, T. M. J Control Release, 2004, 100, 5.
4. Peppas, N. A.; Bures, P.; Leobandung, W.; Ichikawa, H. Eur J Pharm Biopharm 2000, 50, 27.
5. Reddy, K. M.; Ramesh Babu, V.; Sairam, M.; Subha, M. C. S.; Mallikarjuna, N. N.; Kulkarni, P. V.; Aminabhavi, T. M. Design Monomers Polym 2006, 9, 491.
6. Aminabhavi, T. M.; Kulkarni, A. R.; Soppimath, K. S.; Dave, A. M.; Mehta, M. H. Polym News 1999, 24, 285.
7. Lin, S. Y.; Ayres, J. W. Pharma Res 1992, 9, 1128.
8. Ramesh Babu, V.; Krishna Rao, K. S. V.; Sairam, M.; Naidu, B. V. K.; Hosamani, K. M.; Aminabhavi, T. M. J Appl Polym Sci 2006, 99, 2671.
9. Downs, E. C.; Robertson, N. E.; Riss, T. L.; Plunkett, M. I. J. J Cell Physiol 1992, 152, 422.
10. Cai, Z.; Shi, Z.; Sherman, M.; Sun, A. M. Hepathology 1985, 10, 855.
11. Kumbar, S. G.; Aminabhavi, T. M. J Appl Polym Sci 2002, 84, 552.
12. Kulkarni, A. R.; Soppimath, K. S.; Aminabhavi, T. M.; Dave, A. M.; Mehta, M. H. J Control Release 2000, 63, 97.
13. Ferreia, A. P.; Almeida, A. J. J Control Release 2004, 97, 431.
14. Draget, K. I.; Braek, G. S.; Smidsrod, O. Int J Biolog Macromol 1997, 21, 47.
15. Gombotz, W. R.; Wee, S. F.; Adv Drug Deliv Rev 1998, 31, 267.
16. Horiike, S.; Matsuzawa, S.; Yamaura, K. J Appl Polym Sci 2002, 84, 1178.
17. Sreenivasan, K. J Appl Polym Sci 1997, 64, 1811.
18. Orienti, I.; Trere, R.; Luppi, B.; Bigucci, F.; Cerchiara, T.; Uccari, G.; Zecchi, V. Arch Pharm 1999, 335, 89.
19. Kweon, D. K.; Kang, D. W. J Appl Polym Sci 1999, 74, 458.
20. Feng, X.; Huang, R. Y. M. J Membr Sci 1996, 109, 165.
21. Lee, K. H.; Kim, H. K.; Rhim, J. W. J Appl Polym Sci 1995, 58, 1707.

22. Huang, R. Y. M.; Yeom, C. K. J Membr Sci 1991, 62, 59.
23. Isiklan, N.; Sanli, O. J Appl Polym Sci 2004, 93, 2322.
24. Isiklan, N.; Sanli, O. Chem Eng Sci 2005, 44, 1019.
25. Sanli, O.; Asman, G. J Appl Polym Sci 2004, 91, 72.
26. Sanli, O.; Isiklan, N. A. Eur J Pharm Bio Pharm 2007, 65, 204.
27. Kulkarni, A. R.; Soppimath, K. S.; Aminabhavi, T. M. Pharma Acta Helv 1999, 74, 29.
28. Kulkarni, R. V.; Sreedhar, V.; Mutalik, S.; Mallikarjuna Setty, C. M.; Sa, B. Int J Biol Macromol 2010, 47, 520.
29. Hua, S.; Ma, H.; Li, X.; Yang, H.; Wang, A. Int J Biol Macromol 2010, 46, 517.
30. Lakshmi Narayana Reddy, C.; Yerri Swamy, B.; Venkata Prasad, C.; Subha, M. C. S.; Chowdoji Rao, K. J Appl Polym Sci 2010, 118, 2342.
31. Kumbar, S. G.; Soppimath, K. S.; Aminabhvi, T. M. J Appl Polym Sci 2003, 87, 1525.
32. Kukuri, M. D.; Aminabhavi, T. M. J Control Release 2004, 96, 9.
33. Bajpai, A. K.; Sharma, M. J Macro Sci Pure Appl Chem 2005, 42, 663.
34. Peppas, N. A. Pharm Acta Helv 1985, 60, 110.
35. Ritger, P. L.; Peppas, N. A. J Control Release 1987, 5, 37.
36. Sanli, O.; Solak E. K. J Appl Polym Sci 2009, 112, 2057.
37. Bajpai, A. K.; Giri, A. React Funct Polym 2002, 53, 125.