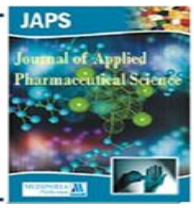
Journal of Applied Pharmaceutical Science
Available online at www.japsonline.com



ISSN: 2231-3354
Received on: 04-08-2011
Revised on: 10-08-2011
Accepted on: 23-08-2011

Interpenetrating polymer network of crosslinked blend microspheres for controlled release of Acebutolol HCl

P. Ramakrishna, B. Mallikarjuna, A. Chandra Babu, P. Sudhakar, K. Chowdoji Rao and M.C.S. Subha

P. Ramakrishna,
B. Mallikarjuna,
A. Chandra Babu,
P. Sudhakar,
and M.C.S. Subha
Department of Chemistry,
Sri Krishnadevaraya University,
Anantapur, India

K. Chowdoji Rao
Dept of Polymer Science & Tech.
Sri Krishnadevaraya University,
Anantapur. India.

For Correspondence:
M.C.S. Subha
Drug Delivery Laboratory,
Dept. of Chemistry,
Sri Krishana Devaraya University
Ph: 91-9441039629,
Fax: 08554255455.

ABSTRACT

Carbohydrate polymeric blend microspheres consisting of chitosan (CS) and poly (vinyl alcohol) (PVA) were prepared by water-in-oil (W/O) emulsion method. These microspheres were crosslinked with glutaraldehyde and loaded with Acebutolol HCl, an anti hypertensive drug. The microspheres were characterized by Fourier transform infrared spectroscopy (FTIR), Differential scanning calorimetry (DSC), X-Ray diffraction (X-RD) and Scanning electron microscopy (SEM).The FTIR spectroscopy explains the crosslinking between the CS-PVA. DSC& X-RD indicated the molecular level distribution of Acebutolol HCl drug in the polymer matrix. The SEM 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 characteristic of the matrices for Acebutolol HCl was investigated in pH 7.4 media. The results indicate that the drug was released in a controlled manner up to 10 h.

Key words: Chitosan (CS); Poly (Vinyl alcohol) (PVA); microspheres; Acebutolol HCl; drug delivery, blend, crosslinking.

INTRODUCTION

Polymer blending constitutes a most useful method for the improvement or modification of the physicochemical properties of polymeric materials. Some of the polymer blends exhibit unusual properties, which are different from the constituent homo polymers. An important property of a polymer blend is the miscibility of its components, because it affects the mechanical properties, the morphology, its permeability and degradation (Paul, 1978; Olabisi and Robinson, 1979). Numerous investigations regarding the miscibility in multi-component polymer systems have been reported in literature. Among them, the blends between biopolymers and synthetic polymers are of particular significance because they can be used as biomedical and biodegradable materials (Nishio and Manley, 1987; Nishio and Manley, 1988; Kondo et al., 1994; Hong et al., 1992; Miura et al., 1999). Poly (vinyl alcohol) (PVA) is a water soluble poly hydroxy polymer, employed in different practical applications, because of its easy preparation, excellent chemical resistance, physical properties, and biodegradable nature (Martien, 1986). Although PVA has good mechanical properties in the dry state, its high hydrophilicity limits its applications (Hodge et al., 1996; Muhlebach et al., 1997).

However, by crosslinking one can affect its hydrophilicity (Pines and Rins, 1973; Liu et al., 1995; Tomita and Ikeda, 1997; Gimenez et al., 1999; Wise and Weber,1995). PVA can generate a physical hydrogel by freeze- thaw cycles and a chemical hydrogel by the chemical reaction of its hydroxyls with a crosslinker (Horkay and Zrinyi, 1982;). It can also form hydrogels through its complexation with inorganic ions, such as the borate ions (Shihayama et al., 1992). PVA was chemically modified by using aldehydes, carboxylic acids, anhydrides, and thus its hydrophilicity, thermal and mechanical properties could be modified. The chemically crosslinked PVA hydrogels have received increasing attention in biomedical and biochemical applications, because of their permeability, biocompatibility and biodegradability (Yeom and Lee, 1996; Matsuyama et al., 1997).

Chitosan, obtained from deacetylation of chitin, is one of the most facile polymers that can be altered structurally to give useful hydrogel matrices (Park et al., 2001; Binder and Gruber, 2000). Chitosan has more uses in biomedical applications, since for an easy degradation in aqueous solutions; it is a preferred polymer due to hydroxyl and amino groups that can be easily modified (Kang et al., 1999).

However, the key properties of chitosan has biocompatibility, nonantigencity, nontoxicity (its degradation products are the well known natural metabolites) (Risbud et al., 2000; Mi et al., 2002), the ability to improve wound healing, blood clotting, ability to absorb liquids, form protective films and coatings, selective binding of liquids, all these have been used to lower the serum cholesterol levels. Chitosan is a copolymer of D-glucosamine and N-acetyl glucosamine derived from chitin. For drug delivery applications, chitosan needs to be crosslinked. Various crosslinking agents such as formaldehyde and glutaraldehyde have been used to crosslink chitosan (Ramesh Babu et al., 2007). The crosslinked chitosan can be used as a pH-sensitive hydrogel that swells in acidic solutions due to protonation of free amino groups. Therefore, chitosan hydrogels have been widely used in sustained drug delivery in stomach via oral route (Nakatsuka and Andrady, 1992). In the present study, Acebutolol HCl, an anti hypertensive drug which is widely used in pharmaceuticals. Because of their in numerable applications these two polymers are blended to prepare polymeric microspheres and loaded with anti hypertensive drug and used for drug delivery application and the results are presented here.

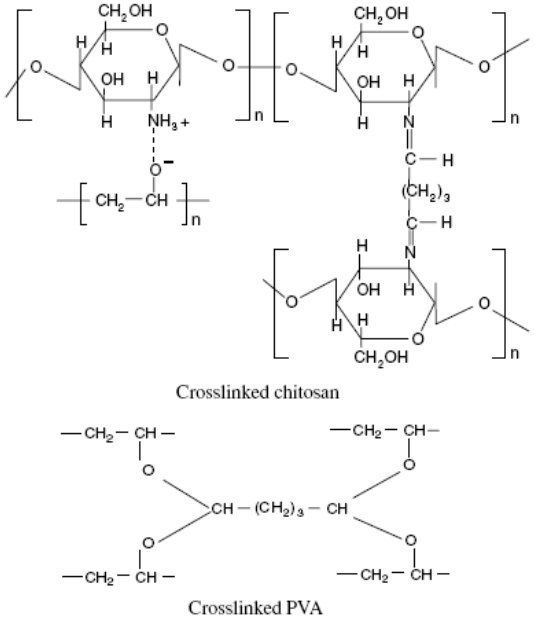
EXPERIMENTAL

Materials and methods

Chitosan (CS), Poly (Vinyl alcohol), light paraffin oil, Glutaraldehyde (25 % aqueous solution) (GA) were purchased from s.d. Fine Chemicals, Mumbai, India. Tween-80 was purchased from Sigma Chemical Co. Acebutolol HCl was obtained as gift sample (Waksman Saleman Pvt. Ltd. Anantapur, India.)

Preparation of chitosan (CS) and poly (vinyl alcohol) (PVA) blend microspheres for controlled release of Acebutolol HCl

Different weight ratios of chitosan (CS) and poly (vinyl alcohol) (PVA) were dissolved in water with certain concentration overnight. The two polymer solutions were mixed and stirred well for proper mixing, which lead to a miscible polymer solution. A known amount of drug dissolved in 1mL of water 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 REMI Motor (Vasai, India) 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 unreacted GA. These microspheres were dried under vacuum at 40^{o}C and stored in a desicator for further analysis. These microspheres were characterized by Differential scanning calorimetry (DSC), Scanning electron microscopy (SEM) and X- ray diffractometry (X-RD). The controlled release characteristic of the matrices for Acebutolol HCl was investigated in pH 7.4 media. Drug was released in a controlled manner up to 10 h.



Scheme-1: of Chitosan –PVA blend microspheres crosslinked with glutaraldehyde.

CHARACTERIZATION

Fourier Transform Infrared (FTIR) Studies

FTIR spectral measurements were performed with a Perkin Elmer (model Impact 410, Wisconsin, MI, USA) spectrophotometer. Microspheres were finely ground with KBr pellets under a hydraulic pressure of 400 kg and spectra were scanned between 4000 and 400cm^{-1} as shown in Fig.1.

Differential Scanning Calorimetric (DSC) Studies

DSC thermograms of plain drug, drug loaded microspheres and plain microspheres were recorded using Rheometric Scientific, UK (model DSC SP) instrument. Thermograms were recorded between 25^{0}Cand 400^{0}C at the

heating rate of 10^0C/min under nitrogen atmosphere as shown in Fig. 2.

X-ray Diffraction (X-RD) Studies

The X-RD measurements of plain drug, drug-loaded microspheres and plain microspheres were recorded with a Rigaku Geigerflex diffractometer (Tokyo, Japan) equipped with Ni-filtered Cu Kα radiation (λ=1.5418 Å). The dried microspheres of uniform thickness were mounted on a sample holder, and the patterns were recorded in the range 0 to 50° at the speed of 5°/min as shown in Fig. 3.

Scanning Electron Microscopic (SEM) Studies

SEM micrographs of microspheres were obtained under high resolution (Mag. 4000) using FEI-QUANTA-200, IISC, Bangalore, India. At the required magnification as shown in Fig. 4.

Particle Size Analysis

Particle 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 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 as shown in Fig. 5.

Estimation of Drug Loading and Encapsulation Efficiency

Loading efficiency of Acebutolol HCL in the microspheres was determined spectrophotometrically. About 10 mg of the drug-loaded microspheres were placed in 10mL of buffer solution and stirred vigorously for 48 h to extract the drug from the microspheres. The solution was filtered and assayed by UV spectrophotometer (Lab India, Mumbai, India) at fixed λ_{max} value of 270 nm. The results of % drug loading and encapsulation efficiency were calculated, respectively using Eqs: 1 and .2.

$$\%\ Drug\ loading = \left(\frac{Weight\ of\ drug\ in\ microspheres}{Weight\ of\ microspheres}\right) x100 \quad (1)$$

$$\%\ Encapsulation\ efficiency = \left(\frac{Actual\ loading}{Theoretical\ loading}\right) x100 \quad (2)$$

In-vitro Release Study

Dissolution was carried out using Tablet dissolution tester (LabIndia, Mumbai, India) equipped with eight baskets. Dissolution rates were measured at 37^0C under 100 rpm speed. Drug release from the microspheres was studied in intestinal (7.4 pH phosphate buffer) fluid like atmosphere. At regular intervals of time, aliquot samples were at regular intervals of time withdrawn and analyzed by UV spectrophotometer as explained before.

Swelling Studies

Dynamic swelling of PVA blended with CS microspheres were prepared using three different concentrations of cross-linker as well as three different drug loadings were studied in water by mass uptake measurements with time. Swelling experiments were performed in 7.4 pH buffer solution. To perform swelling experiments, microspheres were soaked in buffer solution with 7.4 pH, several of them were removed from the swelling bottles at different time intervals and blotted carefully with tissue papers (without pressing hard) to remove the surface adhered buffer solution. The microspheres were then weighed (w_1) on an electronic microbalance (ADAM AFP-210L England accurate to ± 0.0001 g). The microspheres were then dried to a constant weight (w_2) in an oven maintained at 60^0C for 5 hours. Swelling experiments were repeated thrice for each sample and average values were used in data analysis. The standard deviations (S.D.) in all cases were < 5 %. The weight % water uptake was calculated using Eq: 3.

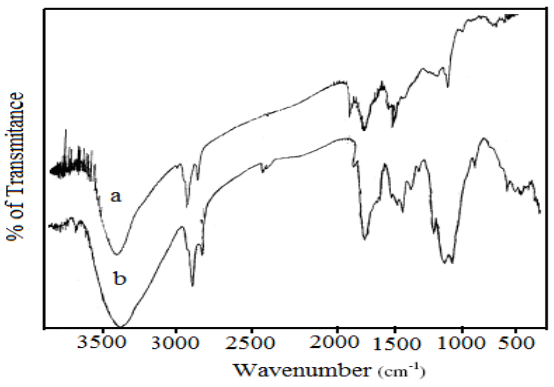
$$\%\ \text{Water uptake} = \left(\frac{\text{Wt of swollen } Microspheres\ (w_1) - \text{Wt of dry } Microspheres\ (w_2)}{\text{Wt of dry } Microspheres\ (w_2)}\right) \times 100$$

RESULTS AND DISCUSSION

Fourier transform infrared spectroscopy

Fig.1. shows the FTIR spectra of pure PVA, Pure Chitosan and Crosslinked CS-PVA blend microspheres. The Fig-1-a, shows the FTIR spectrum of Pure PVA, in this spectrum the peak at 3430 cm^{-1} shows the symmetric stretching frequency of –OH group in Poly (vinyl alcohol). The peaks 2928 & 1575, 1428 cm^{-1} indicated the symmetric stretching & bending vibrations of –C-H and the peak at 1020 cm^{-1} indicated the-C-O group in PVA. The Fig-1-b shows the pure FTIR spectrum of Chitosan, in this spectrum the 3408 cm^{-1} peak shows the –NH symmetric stretching frequency, the peaks 2897&1572,1475 cm^{-1} shows the symmetric and bending vibrations of –C-H whereas the peak at1087 cm^{-1} shows the –C-O stretching frequency.

The Fig-1-c, shows the FITR spectra of glutaraldehyde crosslinked CS-PVA blend microspheres, in this spectra the sharp & broad intense peak at-3437 cm^{-1} shows the –NH & - OH symmetric stretching frequency, The more intense peaks -1610&1010 cm^{-1} shows the –C=N & -C-O stretching frequencies, the formation of imine group, it clearly explains the crosslinking between chitosan and PVA with glutaraldehyde.



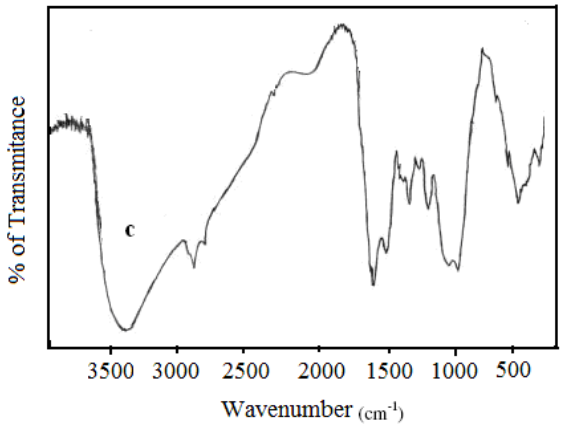


Fig.1. FTIR Spectra of (a) Pure PVA (b) Pure Chitosan (c) Crosslinked CS-PVA blend microspheres.

Differential Scanning Calorimetry (DSC)

DSC thermograms of pure Acebutolol HCl (a), plain CS-PVA blended microspheres (b) and Acebutolol HCl -loaded CS-PVA microspheres (c) are displayed in Fig. 2. Acebutolol HCl shows a sharp peak at 177^0C due to polymorphism and melting, but in case of Acebutolol HCl loaded microspheres, no characteristic peak was observed at 177^0C (Fig.2-c) suggesting that Acebutolol HCl is molecularly dispersed in the polymer matrix.

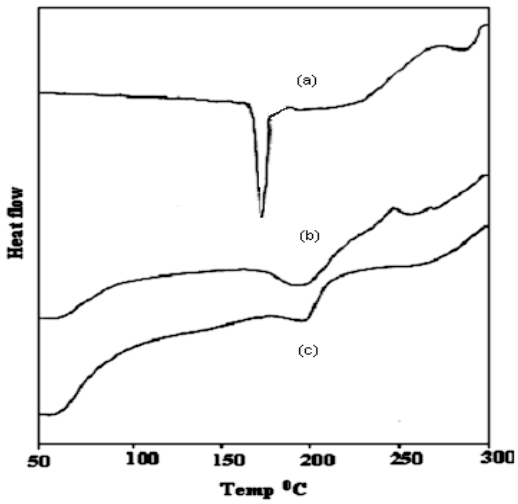


Fig.2. DSC thermograms of (a) plain Acebutolol HCl (b) plain CS-PVA microspheres and (c) Acebutolol HCl loaded CS-PVA microspheres.

X-Ray Diffraction (X-RD)

X-RD analysis can provide a clue about crystallinity of the drug in crosslinked microspheres. X-RD patterns recorded for (a) plain Acebutolol HCl, (b) plain microspheres and (c) Acebutolol HCl -loaded microspheres are presented in Fig 3. Here, Acebutolol HCl peaks observed at 2θ of 6, 12, 16, 20, 25, 24 and 27^0 are due to the crystalline nature of Acebutolol HCl. These peaks are not found in the plain microspheres and in Acebutolol HCl -loaded 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.

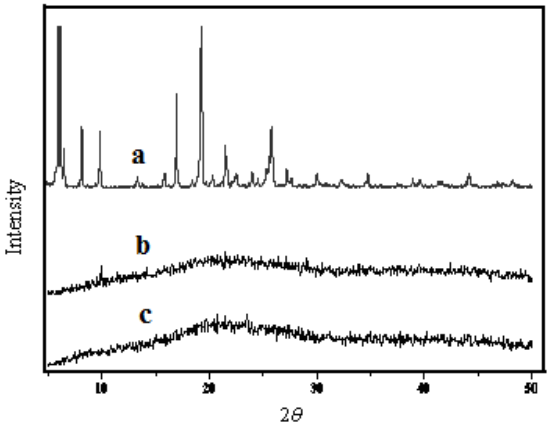


Fig.3. X-RD spectra of (a) plain Acebutolol HCl, (b) plain CS-PVA blend microspheres and (c) Acebutolol HCl-loaded CS-PVA blend microspheres.

Scanning Electron Microscopy

SEM images of single microspheres taken at 350x magnifications are shown in Fig.4. From this SEM it is noticed that the 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.

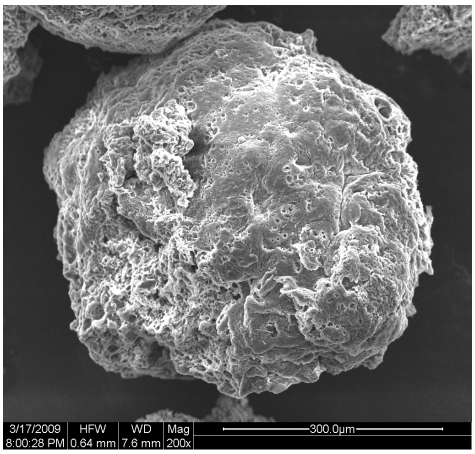


Fig: 4. Scanning electron micrograph of Drug loaded CS-PVA blend microspheres.

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 % PVA, 10 % Acebutolol HCl and 5 mL GA of CS-PVA-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 388 μm. Particle size of different formulations containing different amounts of drug, GA and different amounts of PVA are presented in Table. 1.

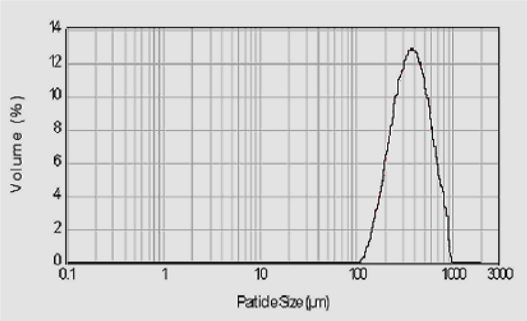


Fig.5. Particle size distribution curve for CS-PVA blend microspheres.

Encapsulation Efficiency

Three different concentrations of Acebutolol HCl i.e., 5, 10 and 15 wt. % were loaded during crosslinking of the microspheres. The % of encapsulation efficiency values were included in Table.1. It shows increasing trends with increasing drug loading. Encapsulation efficiency of 61.8 % was observed for plain CS microspheres, but for the remaining formulations, it ranged from 64.4 to 74.9 %. And the % of encapsulation efficiency increased with increasing amount of PVA in the blend microspheres. This can be attributed to the increasing hydrophilicity nature of PVA. The microspheres containing 10, 20 and 30 wt. % PVA and 5 wt. % Acebutolol HCl with 5 mL GA, encapsulation efficiencies were 57.5, 70.6, and 77.9 % respectively. The % of encapsulation efficiency decreased as the concentration of crosslinker increases with 10 % PVA and 5 wt % drug constant in the matrices, Microspheres crosslinked with 2.5, 5 and 7.5 mL of GA, the encapsulation efficiencies values are decreased (65.2, 64.4 and 57.5 %). respectively. Such a decreasing trend is due to an increase in crosslink 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.

Table. 1. Results of % of encapsulation efficiency, mean particle size and equilibrium swelling of different formulations.

Formulation codes	% PVA in microspheres	% Acebutolol HCl added	Amount of GA added (mL)	% Encapsulation efficiency ± S.D.	Mean particle size (µm) ± S.D.	% Equilibrium swelling
CS-PVA1	10	5	2.5	65.2 ± 0.8	368 ± 5	383
CS-PVA 2	10	5	5	64.4 ± 1.1	356 ± 6	346
CS-PVA 3	10	5	7.5	57.5 ± 0.9	302 ± 8	337
CS-PVA 4	20	5	5	70.6 ± 0.8	360 ± 7	394
CS-PVA 5	30	5	5	77.9 ± 1.2	375 ± 9	421
CS-PVA 6	10	10	5	68.5 ± 1.1	388 ± 5	368
CS-PVA 7	10	15	5	74.9 ± 1.5	405 ± 6	388
CS-PVA 8	00	5	5	61.8 ± 0.6	318 ± 5	325

S.D: Standard deviation

Swelling Studies

In microspheres, extent of crosslinking depends upon the amount of crosslinking agent used. In the present study, different amounts of GA were added as the crosslinking agent to the blend microspheres of CS-PVA containing 5 wt. % of Acebutolol HCl and these data are also included in Table.1. Extent of crosslinking is dependent upon equilibrium swelling. For instance, % equilibrium swelling decreased from 383 to 337 with increasing amount of GA from 2.5 to 7.5 mL. This is due to increased crosslink density and decreased pore volume of the blend matrix (Patel et al., 1994) with increasing amount of GA in the matrix. Since PVA is a water-soluble polymer, it is readily miscible with CS in all proportions and hence, blending of PVA with CS will increase the matrix swelling due to their higher equilibrium swelling. By increasing PVA in the drug loading of blends, % equilibrium swelling also increased. CS-PVA-2, CS-PVA-4 and CS-PVA-5 % equilibrium swelling values are of 346, 394 and 421, respectively. Such an increase in swelling of the blends is due to the incorporation of hydrophilic PVA along with CS chains into the blend matrix. The % equilibrium swelling or % dynamic swelling of the formulated blend matrix has decreased with increasing amount of CS in the blend matrix. This is due to the fact that as the amount of PVA increases in the blend matrix, hydrophobicity of the blend decreases because of the presence of residual -OH groups, which increases the hydrophilic character of the blend.

Drug Release Kinetics

In the area of pharmaceutics, it has been the usual practice to understand the release kinetics of a drug through a polymer matrix using an empirical relationship proposed by Ritger & Peppas (Ritger and Peppas, 1987). Following this practice, in the present study, we have analyzed the cumulative release data using the following equation.

$$\left(\frac{M_t}{M_\infty}\right) = kt^n \qquad \text{------1}$$

Here, the ratio 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 eight formulations and these values are given in Table.2. In general if n = 0.5, the drug diffuses and releases out of the polymer matrix following a Fickian diffusion. For n > 0.5, 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 (Ritger and Peppas, 1987; Aminabhavi and Naik, 1998).

The values of k and n have shown a dependence on the extent of crosslinking, % drug loading and PVA content of the matrix. Values of n for microspheres prepared by varying the amount of PVA in the blend microspheres of 10, 20 and 30 wt. % and keeping Acebutolol HCl (5 %) and GA (5 mL) constant, ranged from 0.478 to 0.625 leading to a shift of transport from Fickian to the anomalous type. The Acebutolol HCl -loaded particles exhibited n values ranging from 0.48 to 0.59 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 et al., 2005). The decrease in n values for CS-PVA-6 and CS-PVA-8 from 0.41 to 0.53 may be attributed for increase in drug content in the CS all the polymer matrix. The reason for this can be explained like this, as the CS content increasing in the matrix the viscosity of the solution increases because the more the CS content, more ionization takes place due to excess ionization of amine groups of CS which in turn increase the solution viscosity as well as the hydrophobicity nature of CS. A similar observation was made by Chuen-Chang Lin (Chuen-Chang Lin and chun-Hsien, 2009). 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 PVA.

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

$$D = \left(\frac{r\theta}{6M_{\infty}} \right)^2 \pi \quad \text{-----2}$$

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* (Table.2) values calculated are in the range of (2.15 to 5.63) x10^{-6} cm^2/s and these are found to depend upon the extent of crosslinking. For instance, *D* values show a systematic decrease with increasing crosslinking of the matrix in for CS-PVA-1, CS-PVA-2 and CS-PVA-3 formulations. This is obvious because of the increased rigidity of the chain due to increased crosslinking, thereby prohibiting the transport of more water molecules.

Table.2. Release Kinetics Parameters of Different Formulations.

Formulation code	*k*	*n*	*D*.10^{-6} (cm^2s^{-1})	Correlation coefficient, *r*
CS-PVA1	0.96	0.32	2.73	0.851
CS-PVA 2	0.040	0.48	2.05	0.970
CS-PVA 3	0.012	0.60	2.49	0.988
CS-PVA 4	0.025	0.58	3.44	0.990
CS-PVA 5	0.014	0.59	3.30	0.973
CS-PVA 6	0.049	0.41	3.79	0.980
CS-PVA 7	0.017	0.62	5.60	0.928
CS-PVA 8	0.103	0.33	3.56	0.965

Effect of Chitosan percent

The effect of chitosan content was studied at constant loading of drug. The release trends of CS/PVA microspheres prepared with different amounts of CS are displayed in Fig.6. It explained that during dissolution experiments, the microspheres have shown systematic swollen trends with decreasing amount of CS, probably due to the formation of loosely crosslinked network chains of CS. As the amount of CS increases, cumulative release decreased due to lesser swelling of the CS chains than PVA. This could be because as the amount of CS increases in IPN matrix, the hydrophobicity of the overall matrix increases, thereby decreasing the release rates for drug. Thus, a regaining-type response of polymeric chains is possible due to the stresses induced by the surrounding solvent media during the dissolution step, resulting in a decrease of chain dimension (radius of gyration) of the IPN polymer; this will further decrease the molecular volume of the hydrated polymer due to decreased swelling of CS component of the IPN matrix, thereby reducing the free volume spaces of the matrix.

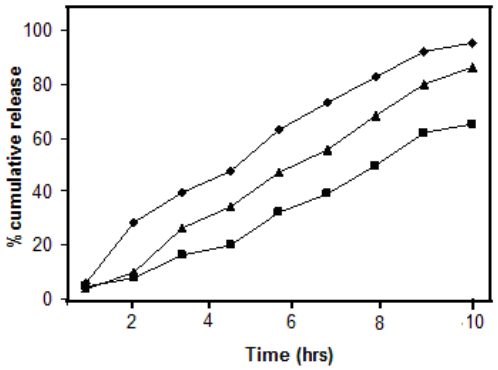


Fig.6. Cumulative % release of Acebutolol HCl through CS/PVA microspheres containing different amounts of CS. Symbols: (■) 30 wt. % CS (▲) 20 wt. % CS, (♦) 10 wt. % CS.

Effect of Crosslinking Agent

The % cumulative release vs time curves for varying amounts of GA i.e, 2.5, 5.0 and 7.5mL 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 higher amount of GA because, at higher concentration of GA, the polymeric chains would become rigid due to the contraction of microvoids, thus decreasing the % cumulative release of Acebutolol HCl through the polymeric matrices. As expected, the release becomes slower at higher amount of GA, but becomes faster at lower amount of GA.

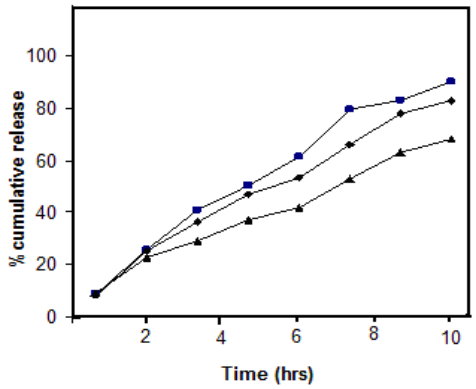


Fig.7. Cumulative % release of Acebutolol HCl through CS/PVA microspheres containing different amounts of Crosslinking agent. Symbols: (▲) 7.5mL, (♦) 5mL and (■) 2.5mL

Effect of Drug Loading

Figure 8 shows the release profiles of Acebutolol HCl-

loaded CS/PVA blend microspheres at different amounts of drug loading. Release data showed that formulations containing the highest amount of drug (30 wt. %) displayed fast and higher release rates than those formulations containing small amount of Acebutolol HCl. A prolonged release was observed for the formulation containing a lower amount of Acebutolol HCl. 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 Acebutolol HCl loaded formulations, the prolonged release of Acebutolol HCl was observed upto 600 min.

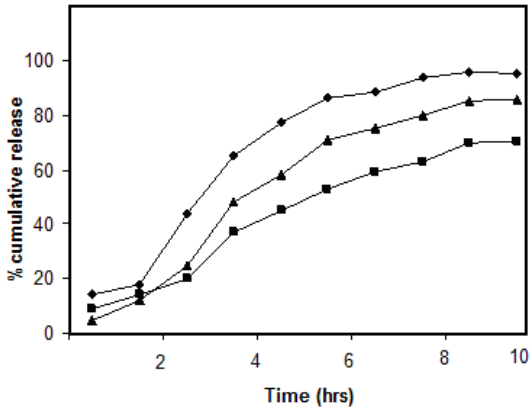


Fig.8. % of cumulative release of Acebutolol HCl through CS/PVA microspheres containing different amount of drug. Symbols: (■) 10 wt. % drug (▲)) 20 wt. % drug (♦) 30 wt. % drug.

CONCLUSIONS

Carbohydrate polymeric blend microspheres of chitosan and poly (vinyl alcohol) were prepared and characterized by Fourier transform infrared spectroscopy, Differential scanning calorimetry, X-Ray diffraction, 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 PVA in the microspheres, water uptake has increased. This effect is correlated with the release rates of the drug though the microspheres containing different amounts of PVA. The microspheres have lower densities and hence, these could be retained in the gastric environment for more than 10 h, which would help to improve the bioavailability of Acebutolol HCl.

REFERENCES

Aminabhavi TM., Naik H.G. Chemical compatibility study of geomembranes-sorption/desorption, diffusion and swelling phenomena J. Hazardous Mater. 1998; 60: 175-203.

Binder WH., Gruber H. Block copolymers derived from photoreactive 2-oxazolines, 1. Synthesis and micellization behavior . J. Macromole chem. Phys. 2000; 201: 949-957.

Chuen-Chang Lin, chun-Hsien Fu. Controlled release study of 5-fluorouracil-loaded chitosan/polyethylene glycol microparticles. Durg Delivery. 2009; 16: 274-279.

Gimenez V., Reina J A., Mantecon A., Cadiz V. Unsaturated modified poly (vinyl alcohol). Crosslinking through double bonds. Polymer. 1999; 40: 2759-2767.

Hodge RM., Edward GH., Simon GP. Water absorption and states of water in semi crystalline poly (vinyl alcohol) films. Polymer. 1996; 37: 1371-1376.

Horkay F., Zrinyi M. Studies on the mechanical and swelling behavior of polymer networks based on the scaling concept. 4. Extension of the scaling approach to gels swollen to euilibrium in a diluent of arbitrary activity. Macromolecules. 1982; 15: 1306-1310.

Hong JH., Kim JY., Lee YM., Kim KY. Properties and swelling characteristics of cross-linked poly(vinyl alcohol)/chitosan blend membrane. J. Appl Polym Sci. 1992; 45: 1711-1717.

Kang DW., Choi HR., Kweon DK. Stability constants of amidoximated chitosan-g-poly(acrylonitrile) copolymer for heavy metal ions J. Appl. Polym. Sci. 1999; 73: 469-476.

Kondo T., Sawatari C., Manley RSt., Gray DG. Characterization of hydrogen bonding in cellulose-synthetic polymer blend systems with regioselectively substituted methylcellulose J. Macromolecules. 1994; 27: 210-215.

Kulkarni AR., Soppimath KS., Aminabhavi TM., Dave AM., Mehta MH. Glutaraldehyde crosslinked sodium alginate beads containing liquid pesticide for soil application. J.Control. Rel. 2000; 63: 97-105.

Liu M., Cheng R., Quian R. Effect of solution concentration on the gelation of aqueous polyvinyl alcohol solution J Polym Sci, Polym Phys Ed. 1995; 33: 1731-1735.

Lyu SP., Sparer R., Hobot C., Dang K. Adjusting drug diffusivity using miscible polymer blends. J. Control. Rel. 2005; 102: 679-687.

Martien FL. Encyclopedia of polymer science and engineering, New York: Wiley. 1986; 17: 167.

Matsuyama H., Teramoto M., Urano H. Analysis of solute diffusion in poly (vinyl alcohol) hydrogel membrane. J Membr Sci. 1997; 126: 151-160.

Mi FL., Tan YC., Liang HF., Sung HW. In vivo biocompatibility and degradability of a novel injectable-chitosan-based implant. Biomaterials. 2002; 23: 181-191.

Miura K., Kimura N., Suzuki H., Miyashita Y., Nishio Y. Thermal and viscoelastic properties of alginate/poly(vinyl alcohol) blends cross-linked with calcium tetraborate. Carbohydr Polym. 1999; 39: 139-144.

Muhlebach A., Muller B., Pharisa C., Hofmann M., Seiferling B., Guerry D. New water-soluble photo crosslinkable polymers based on modified poly(vinyl alcohol) . J Polym Sci, Part A. 1997; 35: 3603-3611.

Nakatsuka S., Andrady AL. Permeability of vitamin B-12 in chitosan membranes. Effect of crosslinking and blending with poly (vinyl alcohol) on permeability J. Appl. Polym. Sci. 1992; 44: 17-28.

Nishio Y., Manley RSt. Blends of cellulose with polyacrylonitrile prepared from *N*,*N*-dimethylacetamide-lithium chloride solutions. J. Polymer. 1987; 28: 1385-1390.

Nishio Y., Manley RSt. Cellulose-poly(vinyl alcohol) blends prepared from solutions in N,N-dimethylacetamide-lithium chloride. J. Macromolecules. 1988; 21: 1270-1277.

Olabisi LM., Robinson MT. Polymer-polymer miscibility. New York: Academic, 1979.

Park SB., You JO., Park HY., Haam SJ., Kim WS. A novel pH-sensitive membrane from chitosan TEOS IPN; preparation and its drug permeation characteristics. Biomaterials. 2001; 22:323-330.

Patel GM., Patel NK., Kansara S. Dilute solution properties of poly (2-methoxycyanurate) of bisphenol F and bisphenol A. Polymer Inter. 1994; 35: 83-88.

Paul DR., Newman S. Polymer blends. New York, Academic, 1978.

Pines E., Rins W. Structure-Property Relations of Thermoreversible Macromolecular Hydrogels. Macromolecules. 1973; 6: 888-895.

Ramesh Babu V., Sairam M., Hosamani KM., Aminabhavi TM. Preparation and characterization of novel semi-interpenetrating 2-hydroxyethyl methacrylate-*g*-chitosan copolymeric microspheres for sustained release of indomethacin J. Appl. Polym. Sci. 2007; 106: 3778-3785.

Risbud MV., Hardikar AA., Bhat SV., Bhonde RR. PH-sensitive freeze-dried chitosan–polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. J. Control. Rel. 2000; 68: 23-30.

Ritger PL., Peppas NA. Simple equation for description of solute release.II. Fickian and anomalous release from swellable devices. J. Control. Release. 1987; 5: 37-42.

Shihayama M., Kurokawa H., Nomura S., Muthukumar M., Stein RS., Roy S. Small-angle neutron scattering from poly (vinyl alcohol)-borate gels.Polymer. 1992; 33: 2883-2890.

Tomita E., Ikeda Y. Crosslinking of hyaluronic acid with glutaraldehyde. J Polym Sci, Part A. 1997; 35: 3553-3559.

Wise ET., Weber SG. A Simple partitioning Model for reversibly crosslinked Polymers and Application to the poly (Vinyl alcohol)/Borate Systems (“Slime”). Macromolecules. 1995; 28: 8321-8327.

Yeom CK., Lee KH. Pervaporation separation of water-acetic acid mixtures through poly (vinyl alcohol) membranes crosslinked with glutaraldehyde. J Membr Sci. 1996; 109: 257-265.