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Poly (vinyl alcohol) and xanthan gum composite films for sustained release

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ABSTRACT

In the present work, films based on Poly(vinyl alcohol) (PVA) and composite films based on PVA and Xanthan Gum (XG) were synthesized in acidic, neutral and alkaline conditions using Epichlorohydrin as cross linker. The effect of pH during synthesis and the ratio of PVA: XG in the composite film on the equilibrium swelling ratio of the composite films were investigated. The *in vitro* release study on the synthesized films was carried out at 7.4 pH and 37°C (±1°C) using uric acid as model drug. The swelling capabilities of PVA/XG composite films were found to be lesser than PVA films and the equilibrium swelling ratio decreased with an increase in the XG content in the composite films. It was observed that the films synthesized at pH<4.0 have a higher equilibrium swelling ratio as compared to those synthesized at pH 7-7.5 and pH >9.0. The observed experimental data on uric acid were fitted to different kinetic models available in the literature and based on the minimum relative quadratic error it was found that the drug release data was well represented by first order kinetics.

KEYWORDS

Poly (vinyl alcohol);
Xanthan gum;
Composite films;
Equilibrium swelling ratio;
Release kinetics.

INTRODUCTION

Polymer matrix systems are widely used in oral controlled drug delivery systems because of their flexibility to obtain a desirable drug release profile, cost effectiveness and broad regulatory acceptance[1]. Drug release from such matrices is known to be a complex interaction between dissolution, diffusion and erosion mechanisms[2]. Various studies of drug release mechanism; effect of formulation variables on the release kinetics and swelling properties; to elucidate the water and drug transport processes and to predict the resulting drug release kinetics for such matrices have been reported[3-6].

PVA is a hydrophilic polymer and has been extensively used in controlled release applications[7,8] largely because of their permeability, biocompatibility and biodegradability. However, as this hydrogel is highly hydrophilic, it releases the drug with a relatively high rate. To prolong drug release from such a system, one needs to modify its macromolecular structure. This can be achieved by either cross-linking thus reducing the macromolecular mesh size available for drug diffusion or by combining with other polymers to constructively modify the structural and swelling properties of the resulting hydrogel.

Xanthan gum is another industrially important exocellular heteropolysaccharide natural gum used as

hydrophilic sustained release matrix material for different drugs[9,10]. It is known for its excellent solubility and stability under both acidic and alkaline conditions, its stability with salts and its resistance to common enzymes[11]. Because of its rigid structure incorporation of XG in PVA matrix should impart greater strength to the PVA/XG hydrogels as compared to PVA hydrogel.

The objective of this work is to evaluate PVA/XG composites for sustained release and to study the effect of PVA: XG ratio on the swelling and release profile of the composite membranes. Since the method of preparation and technological parameters can influence the release of drug from the polymer matrices[4], an effort is made to compare the swelling characteristics of PVA and PVA/XG composite films synthesized under acidic, neutral and alkaline conditions.

EXPERIMENTAL

Materials

Poly(vinyl alcohol) with $\overline{M_w} = 1,25,000$ and Hydrochloric acid were obtained from S.D.Fine Chemicals Limited. Xanthan Gum was procured from Sigma. Epichlorohydrin obtained from National Chemicals Limited was used as a cross linker for the synthesis of the composite films. The ratio of cross linker to polymer was kept constant at 1 for all the formulations. Sodium Hydroxide and n-Heptane were procured from Central Drug House Limited and used as such. Sulphuric acid, methanol and acetic acid (glacial) were obtained from Qualigens Fine Chemicals. Uric acid was gifted by Eaton Pharmaceuticals, Srinagar.

Synthesis of composite films

A 10% w/v aqueous solution of PVA was prepared by dissolving PVA in deionised water at 90°C for 6 hours in hot air oven. A homogeneous solution was obtained by stirring on a magnetic stirrer and then allowed to cool to room temperature. A 1% w/v aqueous solution of XG in deionised water was prepared using a magnetic stirrer. These two solutions were then mixed to yield PVA: XG weight ratios of 95:5, 90:10, 85:15 and 80:20 (TABLE 1). Cross linked pure PVA and PVA/XG blends were synthesised using Epichlorohydrin (EPC) as cross linker in the presence of sodium hydroxide. In all the blends the ratio of amount of cross linker to polymer was taken as 1. The presence of hydroxyl bonds in PVA and XG enables cross linking with EPC leading to the formation of ether bonds under alkaline conditions (pH >9.0). On the other hand, ester bonds are formed if the cross linking is carried out under acidic conditions with pH<4.0 and a mixture of ester and ether bonds are formed in the cross linked structure if the reaction is carried out under neutral conditions with pH between 7 and 7.5. In order to study the effect of type of cross linking in the composite films on the equilibrium swelling, the films were synthesized under acidic, neutral and alkaline conditions. 10% sulphuric acid, 10% acetic acid and 1.0N sodium hydroxide solutions were used to maintain the desired pH during synthesis. The formulations were then transferred to petri plates and the reaction was allowed to complete at room temperature leading to the formation of thin films. The samples were then removed from the petri plates and immersed in an excess of distilled water in order to remove the unreacted polymer or cross linking agent. The samples were then dried at room temperature and finally under vacuum at 40±1°C to constant mass and stored in desiccators till further use.

TABLE 1 : Composition and sample designation in the preparation of poly (vinyl alcohol) and xanthan gum composites

Sample Code	Ratio of PVA:XG (w/w)
A	100:0
B	95:5
C	90:10
D	85:15
E	80:20

Swelling measurements

To study the effect of pH on swelling behaviour of the synthesized composite films, samples were placed in buffer solution of pH 3.2, pH 7.4 and pH 9.2 at 37±1°C. The swelling studies were carried out using an electronic balance (Saritorius) with an accuracy of ±0.0001 g. Pre-weighed dry films of PVA and PVA/XG were immersed in 100 ml of the swelling medium at 37±1°C. After specific intervals of time the films were removed from the medium, the surface adhered liquid drops were wiped with blotting paper and the increase in weight was measured. The measurements were

continued until the weight of the swollen hydrogels attained a constant value. The equilibrium degree of swelling S_{eq}, after hydrogels has swollen to equilibrium in the swelling media was calculated using equation 1:

$$S_{eq}(\%) = \frac{w_{eq} - w_o}{w_o} \times 100 \quad (1)$$

Here w_o is the weight of initial dry sample and w_{eq} is the weight of the swollen sample at equilibrium. An average of three measurements was taken for the swelling studies.

Loading of uric acid

The sustained release properties of PVA, PVA/XG films were evaluated with Uric acid as model drug. A stock solution of the drug was prepared by dissolving known weight of the drug in distilled water. Calibration curves were prepared by measuring the absorbance (Hitachi 330 UV visible spectrophotometer) for known concentrations of uric acid solutions at 294 nm. The initial concentration of the drug in the stock solution was calculated from the calibration curve by measuring the absorbance of the stock solution. Synthesized films of PVA and PVA/XG were then soaked in the stock solution for 24 hours for swelling. The swelled films loaded with the drug were then dried and stored in desiccators till further use. The amount of drug loaded in the samples (M_o) was calculated as the difference in the concentration of the swelling medium before adding the films and after 24 hours of swelling of the film in the medium.

In Vitro release studies

The *in vitro* dissolution studies of the loaded PVA, PVA/XG films were carried in a buffer of pH 7.4 and at a temperature of 37±1°C. Samples were withdrawn from the buffer solution at pre determined time intervals and replaced with equal volumes of fresh dissolution medium maintained at the desired temperature. These aliquots were suitably diluted and the absorbance was measured at 294 nm. The amount of drug released was estimated from the calibration curve. The measurements were carried until nearly the entire amount of drug loaded on the film was released into the dissolution buffer. The percentage cumulative drug released was calculated using equation 2:

$$\%\ \text{cumulative drug released} = \left[\frac{\text{amount of drug released}}{\text{amount of drug loaded}}\right] \times 100 \quad (2)$$

The results obtained are an average of three readings.

RESULTS AND DISCUSSION

Swelling studies

The swelling behaviour of PVA and PVA/XG films synthesized under acidic, neutral and alkaline conditions was investigated by carrying out swelling measurements in an aqueous buffer of pH 3.2, pH 7.4 and pH 9.2 at 37±1°C. The equilibrium degree of swelling S_{eq} (%) calculated for samples A, B, C, D and E synthesized under varied pH is given in figure 1.

It is apparent that the equilibrium degree of swelling of these films can be controlled by varying the XG content in the PVA/XG film. Films containing XG had a lesser equilibrium degree of selling as compared to PVA hydrogels and this goes on decreasing with an increasing XG content in the composite. Crosslinking of XG may have led to a decrease in the macromolecular mesh size of the membranes resulting in lower equilibrium degree of swelling. XG having a double helical structure resists swelling and imparts stability to the membranes. The pH conditions during the synthesis of the composites also had a significant effect on the swelling profile of the samples. Samples synthesized under acidic conditions (pH <4) and in the pH range 7 to 7.5, having ester linkages and a mixture of ether and ester linkages were found to degrade after 48 hours confirming that ester bonds are degradable. The composites that were synthesized under alkaline conditions (pH >9) exhibited a higher strength and a steadily increasing swelling profile till S_{eq}. The stability is mainly attributed to the formation of ether bonds during crosslinking. The equilibrium degree of swelling also increased with increasing pH of the swelling buffer.

Drug release studies

Drug loaded films of PVA and PVA/XG synthesized under alkaline conditions were used to study the release profile. When the drug loaded films came in contact with a solvent, relaxation of the polymer chains takes place leading to swelling. The entrapped drug passes through the swollen polymeric matrix due to the

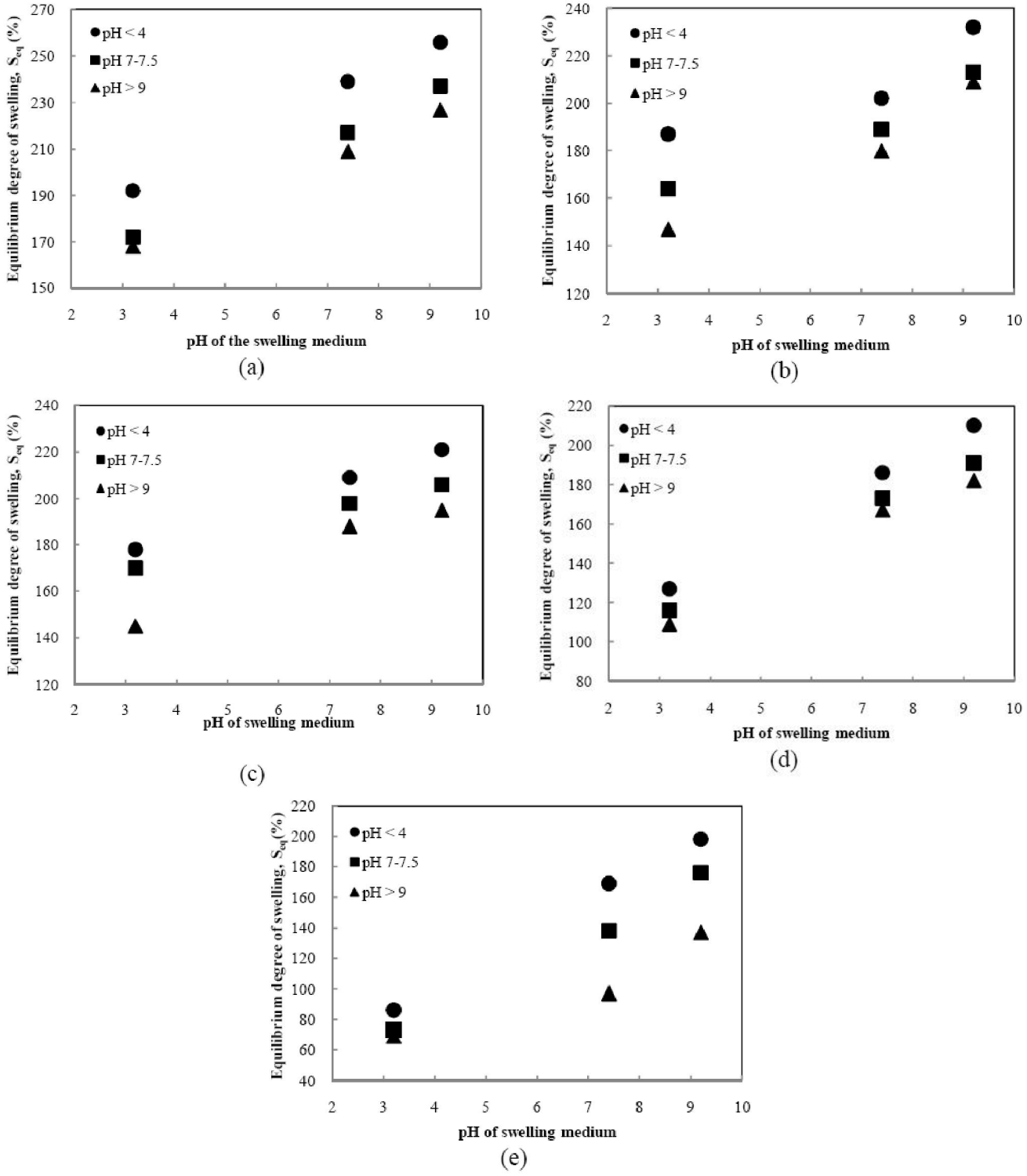

Figure 1 : Equilibrium degree of swelling for (a) Sample A (b) Sample B, (c) Sample C, (d) Sample D, (e)Sample E synthesized under varying pH conditions (pH<4, pH 7-7.5 and pH >9) as a function of pH of the swelling medium

concentration gradient into the swelling medium. The amount of drug released depends on the rate of swelling. In the present work, the release of Uric acid from the synthesized films at pH 7.4 and at a temperature of 37±1°C was studied. The percentage cumulative drug released was calculated using equation 2. A plot of drug release rate, defined as the ratio of amount of drug released at any time to the actual amount of drug loaded

on the film, as a function of time is shown in figure 2. From the graphs it is clear that with the addition of XG to PVA the drug release rate decreases. Variation in the amount of XG to PVA allows for a controlled release of the loaded drug from the films suggesting that PVA/XG blends can be used for sustained release. Higher amount of XG in the blend leads to a complex structure with high crosslinking density. The uric acid molecules get trapped into the cyclodextrin like structure of XG. Because of the presence of two phenolic groups in uric acid there is a possibility of hydrogen bonding with XG, hence the release of the molecule is retarded.

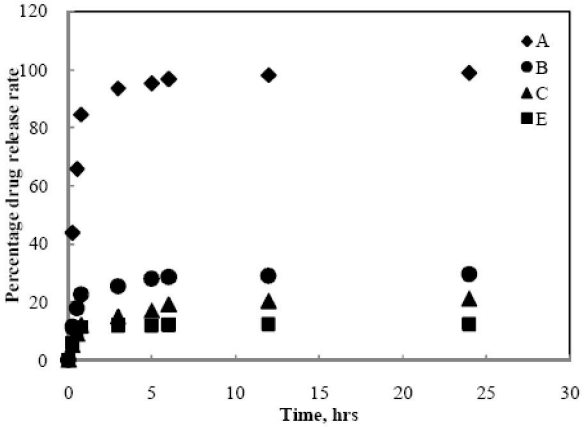

Figure 2 : Percentage drug release rate of uric acid at pH 7.4 as a function of time for the synthesized samples

In order to study the release kinetics, the data obtained from *in vitro* drug release studies were fitted to different kinetic models.

Higuchi's model[12] described the release of drugs from insoluble matrix as a square root of time, (equation 3)

$$\frac{M_t}{M_\infty} = kt^{1/2} \quad (3)$$

where M_t is the amount of drug released at time t, $M\infty$ is the amount of drug released at time when nearly the entire amount of drug loaded on the films has been released and k is kinetic constant. Korsmeyer et al.[5] derived a simple relationship which described drug release from the polymeric system expressed as:

$$\frac{M_t}{M_\infty} = kt^n \quad (4)$$

where k is the release rate constant and n is the release exponent. Peppas and Sahlin[13] considered the relaxation mechanism along with the diffusional release from the matrices and proposed equation 5 to explain the release kinetics from polymeric matrices.

$$\frac{M_t}{M_\infty} = k_1 t^n + k_2 t^{2n} \quad (5)$$

where k_1 and $k_2$represent the relative contributions of the fickian and relaxation mechanisms respectively and t is time. Hixson and Crowell[14] proposed equation 6 to describe the release rate of the drug from polymeric matrices as

$$\frac{M_t}{M_\infty} = [1-(1-kt)^3] \quad (6)$$

where k is kinetic constant and t is the time. Shah et al.[15] suggested a first order kinetics to characterize the release properties of hydrophilic matrices expressed as

$$\frac{M_t}{M_\infty} = (1-e^{-kt}) \quad (7)$$

where k is a kinetic constant and t is time. Catellani et al.[16] suggested equation 8 to predict the drug release from polymeric matrices.

$$\frac{M_t}{M_\infty} = k_1 t^{1/2} + k_2 t \quad (8)$$

where k_1 and k_2 represent the relative contributions of fickian and relaxation mechanisms and t is time.

The kinetic parameters, correlation coefficient (R^2) and the minimum relative quadratic error (MRQE) (equation 9) was calculated for each of these models (TABLE 2). Based on the MRQE value the drug release kinetics

TABLE 2 : Kinetic parameters, correlation coefficient and minimum relative quadratic error for the release of uric acid from synthesized composites of PVA/XG

Sample	Higuchi Model (Equation 3)			Korsmeyer Model (Equation 4)				Catellani Model (Equation 8)				Peppas and Sahlin Model (Equation 5)					Hixson-Crowell Model (Equation 6)			First Order Model (Equation 7)		
	k	R^2	MRQE	k	n	R^2	MRQE	k_1	k_2	R^2	MRQE	k_1	k_2	m	R^2	MRQE	k	R^2	MRQE	k	R^2	MRQE
A	0.401	0.21	0.534	0.742	0.148	0.932	0.173	0.899	-0.185	0.881	0.421	1.047	-0.271	0.338	0.965	0.147	0.131	0.116	3.844	2.333	0.993	0.032
B	0.385	0.404	0.513	0.677	0.179	0.946	0.175	0.813	-0.159	0.922	0.441	0.914	-0.212	0.359	0.924	0.137	0.128	0.339	3.450	1.865	0.970	0.069
C	0.344	0.765	0.3898	0.520	0.269	0.964	0.206	0.603	-0.096	0.965	2.069	0.631	-0.103	0.412	0.953	7.32	0.117	0.697	2.228	0.916	0.858	0.186
E	0.409	-0.035	0.5829	0.797	0.115	0.916	0.182	0.962	-0.206	0.798	0.499	1.176	-0.342	0.315	0.950	0.162	0.133	-0.172	4.000	2.949	0.993	0.042

of this formulation is well represented by the first order model (equation 7) suggested by Shah et al.[15].

$$MRQE = \sqrt{\frac{\left(\frac{M_{experimental} - M_{predicted}}{M_{experimental}}\right)^2}{N-1}} \quad (9)$$

Here N is the number of data points.

CONCLUSION

Analysis of the swelling and drug release behaviour of PVA and PVA/XG films suggests that combination of XG and PVA allows a retarded release of drug from the PVA/XG films. At the super molecular level, the macromolecules of Xanthan adopt a double helical structure stabilised by inter and intra molecular hydrogen bonds which allow for the slow release of the entrapped drug molecules in the present case uric acid. The swelling behaviour of PVA/XG films was found to be a function of pH during formulation, XG content and the pH of the swelling medium. Blends synthesized under alkaline conditions were found to be more stable that those synthesized under acidic or neutral conditions. An increase in the XG content lowers the equilibrium degree of swelling for PVA/XG films. PVA/XG blends can be used as pH-sensitive systems for targeted drug delivery. The drug release behaviour of PVA/XG films can be controlled by variation in the percentage of XG in the PVA/XG films. The release of uric acid from PVA/XG blends was found to follow first order kinetics.

REFERENCES

[1] G.N.Lordi; Sustained release dosage form, in L.Lachman, H.A.Liberman, J.L.Kanig, (Eds); The Theory and Practice of Industrial Pharmacy, Lea and Febiger, (U.S.), 430-456 **(1986)**.

[2] J.Siepmann, H.Kranz, R.Bodmeier, N.A.Peppas; Pharm.Res., **16**, 1748 **(1999)**.

[3] K.C.Sung, P.R.Nixon, J.W.Skoug, T.R.Ju, P.Gao, E.M.Topp, M.V.Patel; Int.J.Pharm., **142**, 53 **(1996)**.

[4] M.J.Vazquez, B.Perez-Marcos, J.L.Gomez-Amoza, R.iAnez-Pacheco, C.Souto, A.Concheiro; Drug Dev.Ind.Pharm., **18(11-12)**, 1355 **(1992)**.

[5] R.W.Korsmeyer, R.Gurny, E.Doelker, P.Buri, N.A.Peppas; Int.J.Pharm., **15(1)**, 25 **(1983)**.

[6] J.Siepman, N.A.Peppas; Pharmaceut.Res., **17**, 1290 **(2000)**.

[7] M.Hamidi, A.Azadi, P.Rafiei; Adv.Drug Deliv.Rev., **60(15)**, 1638 **(2008)**.

[8] I.Orienti, R.Trere, B.Luppi, F.Bigucci, T.Cerchiara, G.Zuccari, V.Zecchi; Arch.Pharm., (Weinheim), **335(2-3)**, 89 **(2002)**.

[9] M.M.Talukdar, R.Kinget; Int.J.Pharm., **120(1)**, 63 **(1995)**.

[10] P.G.Yeole, U.C.Galgatte, I.B.Babla, P.D.Nakhat; Indian J.Pharm.Sci., **68(2)**, 185 **(2006)**.

[11] B.R.Sharma, L.Naresh, N.C.Dhuldhoya, S.U. Merchant, U.C.Merchant; **1(15)**, 27 **(2006)**.

[12] T.Higuchi; J.Pharm.Sci., **52**, 1145 **(1963)**.

[13] N.A.Peppas, J.J.Sahlin; Int.H.Pharm., **57**, 169 **(1989)**.

[14] A.W.Hixson, J.H.Crowell; Ind.Eng.Chem., **23**, 923 **(1931)**.

[15] M.V.Shah, M.D.De Gennaro, H.Suryakasuma; J.Microencapsul., **4**, 223 **(1987)**.

[16] P.Colombo, R.Bettini, P.L.Catellani, P.Santi, N.A.Peppas; Eur.J.Pharm.Sci., **9**, 33 **(1999)**.