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Crosslinked Alginate Films as Rate Controlling Membranes for Transdermal Drug Delivery Application

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The present investigation was undertaken to prepare and evaluate the crosslinked sodium alginate (SA) films as rate controlling membranes (RCM) for transdermal drug delivery application. The drug free films of SA were prepared by mercury substrate method and evaluated for thickness uniformity, tensile strength and water vapor permeation (WVP). The films were characterized by scanning electron microscopy (SEM) and differential scanning calorimetry (DSC). Drug diffusion characteristics of the films were studied using diclofenac diethylamine as a model drug. The prepared membranes were thin, flexible and smooth. Tensile strength measurement and DSC analysis suggested that as the crosslink density increases, the tougher membranes were formed. The WVP and drug diffusion were dependent upon the crosslink density and thickness of the films. The permeability was decreased with increasing crosslink density and thickness of the films. The molar mass between the crosslinks and crosslink density were calculated using empirical equations. The primary skin irritation study indicated that the prepared membranes were less irritant and safe for transdermal application.

Keywords: Rate controlling membranes, hydrogel, sodium alginate, transdermal drug delivery, diclofenac diethylamine

1 Introduction

Transdermal drug delivery systems (TDDS) offers many advantages such as reduced side effects, improved patient compliance, elimination of first-pass effect, sustained drug delivery and interruption or termination of treatment when necessary (1). In recent years, a great deal of research has been carried out to develop effective transdermal drug delivery systems for non-steroidal anti-inflammatory drugs (2–5). However, the barrier property of skin limits the effective systemic delivery of most of these agents. The transdermal entry of drugs into blood circulation at a desired rate can be achieved by using a suitable rate controlling membrane (RCM) (6).

Formulation of TDDS involves the optimization of several factors such as release rate, stability, safety, convenience of use etc. However, the key component in a TDDS, which monitors the release of drug, is the RCM. The polymer should possess good film forming properties, should be non-irritating, inert and stable. Hence, the selection of a polymer is quite difficult because of inherent diversity of structures, which requires thorough understanding of the surface and bulk properties of the polymer that can offer desired chemical, interfacial, mechanical and biological functions (7). Though several polymers like cellulose acetate (6), Eudragits (8, 9), ethylene vinyl acetate (10, 11) and ethyl cellulose (12) have been reported as RCM in TDDS, there are no reports in the literature on use of crosslinked SA based hydrogel films as RCM for transdermal drug delivery application. In such films, the extent of crosslinking can be monitored to control the drug diffusion rate through membrane (13).

Hence, the objective of the present investigation was to prepare and characterize the SA films as rate controlling membranes for TDDS. The drug free films of SA were prepared by mercury substrate method and films were characterized by scanning electron microscopy and differential scanning calorimetry.

2 Experimental

2.1 Materials

Diclofenac diethylamine was obtained from J. B. Chemicals & Pharmaceuticals Ltd. (Mumbai, India). Sodium alginate (SA) was purchased from Loba Chemie Pvt. Ltd. (Mumbai, India). Glutaraldehyde (GA; 25% v/v) and glycerol were purchased from S.D. Fine Chemicals (Mumbai, India). Double distilled water was used throughout the study. All other chemicals were used without further purification.

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Table 1. Composition of rate controlling membranes

Films	*SA (% w/v)*	*Glycerol (% w/w of dry polymer)*	*GA (% w/w of dry polymer)*
RCM1	2	10	3
RCM2	3	10	3
RCM3	4	10	3
RCM4	3	10	6
RCM5	3	10	9
RCM6	3	10	12

2.2 Preparation of Rate Controlling Membranes

The required quantities of SA and glycerol were dissolved in double distilled water using magnetic stirrer for 2 h to get homogeneous solution. This bubble-free polymeric solution was poured on the mercury surface (28.3 cm^2) in a petri-dish and air dried in a dust free environment for 24 h. The obtained membranes were removed from the mercury surface and crosslinked by dipping them into methanol containing different concentrations of glutaraldehyde (GA) and 1% of 1N HCl for 4 h. The crosslinked membranes were removed from methanol and repeatedly washed with distilled water to remove unreacted GA and air dried for 24 h and stored in a desiccator until further use (Table 1).

2.3 Thickness Uniformity

Thickness of the membranes was measured at five different places by a digital micrometer (MDC-25S Mitutoyo, Tokyo, Japan) having an accuracy of 0.001 mm. The average of five values was calculated.

2.4 Scanning Electron Microscopy

The membranes were mounted onto stubs using double sided adhesive tape and sputter coated with platinum using a sputter coater (Edward S 150, UK). The coated films were observed under SEM (JEOL, JSM-6360, Kyoto, Japan) at the required magnification at room temperature. The acceleration voltage used was 10 kV with the secondary electron image as a detector.

2.5 Tensile Strength Measurement

The membranes of 15 X 15 cm size were firmly fixed to the jaws of a tensile tester (Ubique, 199 LED, Pune, India) and tensile strength of the membranes was measured with an extension speed of 20 mm/min.

2.6 Differential Scanning Calorimetry

The membranes were heated from 0–300°C at a heating rate of 10°C/min under argon atmosphere using a microcalorimeter (DuPont-9900, USA) and then thermograms were obtained.

2.7 Water Vapor Permeation Study

For this study, glass vials of equal diameter were used as transmission cells. The cells were washed thoroughly and dried in a hot air oven. About 2 g of fused calcium chloride was taken in the cells and membranes (3.14 cm^2) were fixed over the brim with the help of an adhesive. The initial weight of cells was recorded and placed in a closed desiccator containing 500 ml saturated solution of potassium chloride. The humidity inside the desiccator was maintained at 84% RH. The cells were taken out and weighed at different time intervals using an electronic microbalance (Model BL-220H, Shimadzu, Japan) having an accuracy of 0.001 mg. The water vapor permeation rate was calculated from the plots of the amount of water vapor permeated vs. time (14).

2.8 Drug Diffusion through Membranes

The drug diffusion through prepared membranes was performed in phosphate buffer pH 7.4 (PBS) using a vertically assembled Keshary-Chien diffusion cell. The membrane was mounted on the donor compartment with the help of an adhesive; then it was firmly fixed on the receptor compartment of the diffusion cell. The 3 ml drug solution (diclofenac diethylamine) was poured into the donor compartment which was open to air, while the receptor compartment was filled with PBS and stirred at 100 rpm. The whole assembly was maintained at 37°C ± 5°C. The amount of drug diffused was determined by withdrawing 5 m1 samples at specific time intervals. The volume withdrawn was replaced with an equal volume of fresh PBS; the samples were analyzed in a UV spectrophotometer (Model Pharmaspec UV-1700, Shimadzu, Japan) at 254 nm using PBS as blank.

2.9 Skin Irritation Test

The primary skin irritation test was performed on healthy rats weighing between 150–200 g. Adhesive tape USP, was used as a control patch. The membranes of 2 cm^2 area were used as test patches. The test was conducted on unabraided skin of rats; a control patch was placed on the left dorsal surface of each rat, whereas test patches were placed on the identical side, on the right dorsal surface of the rat. The patches were removed after a period of 24 h with the help of an alcohol swab. The skin was examined for erythema/oedema.

3 Results and Discussion

The SA showed good film forming property. The prepared membranes were thin, flexible and smooth. The method adopted for casting the membranes on mercury surface was quite satisfactory to produce films of uniform thickness (Table 2).

Table 2. Data obtained from evaluation of rate controlling membranes

Films	*Thickness* (μ)	*Tensile strength* (Kg/cm^2)	*WVP rate* ($g/cm^2/h$)	*Diffusion rate constant* ($mg/cm^2/h$)	*Mc*	$dx \times 10^3$	*n*
RCM 1	44 ± 0.02	1.46 ± 0.65	9.86×10^{-4}	12.96×10^{-2}	2564	2.98	0.85
RCM 2	62 ± 0.01	1.76 ± 0.98	9.35×10^{-4}	12.35×10^{-2}	2501	3.24	0.89
RCM 3	86 ± 0.02	1.98 ± 0.56	8.90×10^{-4}	11.83×10^{-2}	2456	3.85	0.92
RCM 4	67 ± 0.02	1.86 ± 0.23	9.22×10^{-4}	11.91×10^{-2}	2035	5.62	0.96
RCM 5	77 ± 0.06	2.11 ± 0.46	8.60×10^{-4}	11.04×10^{-2}	1587	6.78	0.99
RCM 6	81 ± 0.02	2.42 ± 0.89	8.03×10^{-4}	9.98×10^{-2}	1135	7.85	1.08

Mc is molar mass between crosslinks, dx is crosslink density and *n* is release parameter.

3.1 Scanning Electron Microscopy

The scanning electron microscopic (SEM) study was performed to learn the surface characteristics of films. The SEM photomicrographs of neat SA film (A), RCM 2 (B), RCM 4 (C) and RCM 5 (D) and RCM 6 (D) are presented in Figure 1. The neat SA film has shown a smooth and uniform surface, while RCM 2, RCM 4, RCM 5 and RCM 6 have shown rough and dense surfaces, which may be due

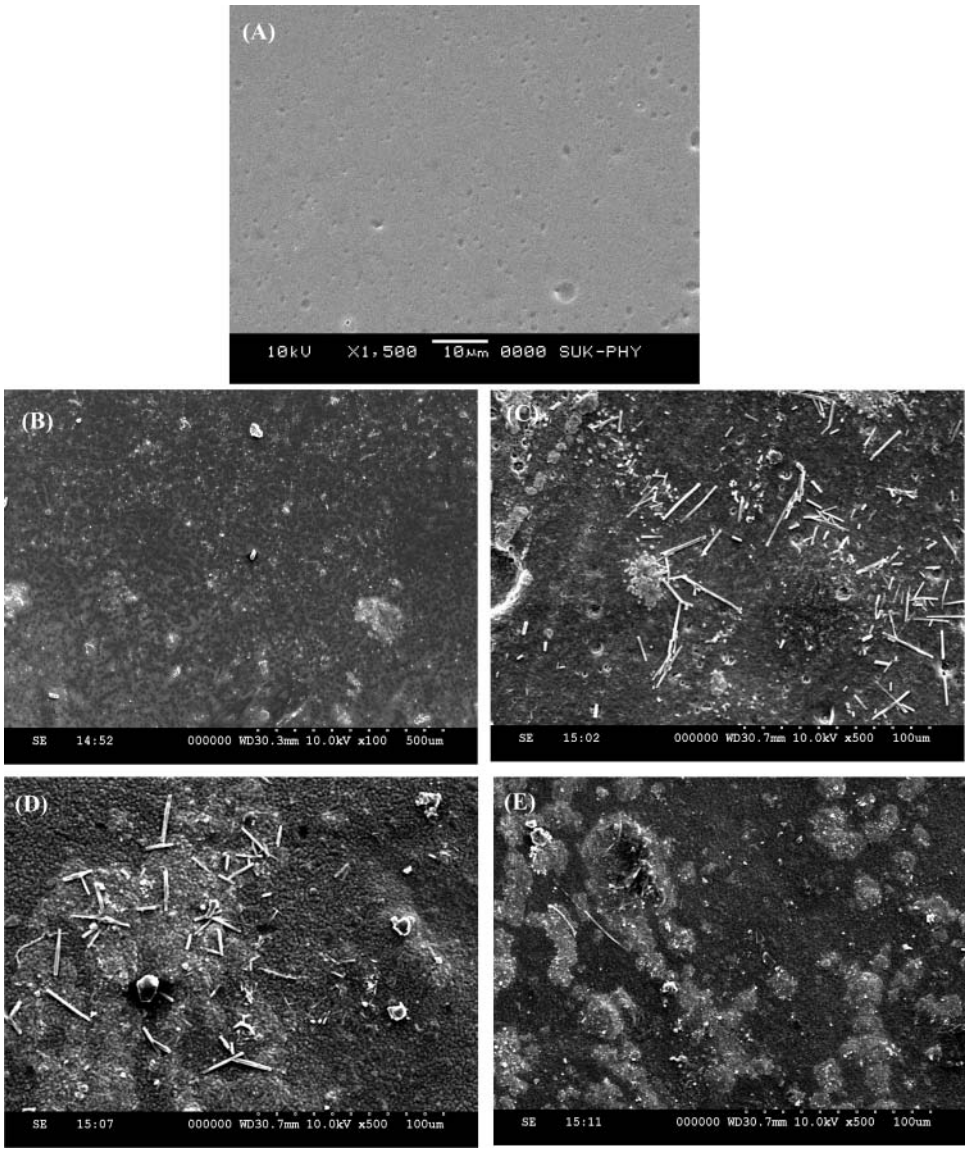

Fig. 1. SEM photographs of neat alginate film (A), RCM 2 (B), RCM 4 (C), RCM 5 (D) and RCM 6 (E).

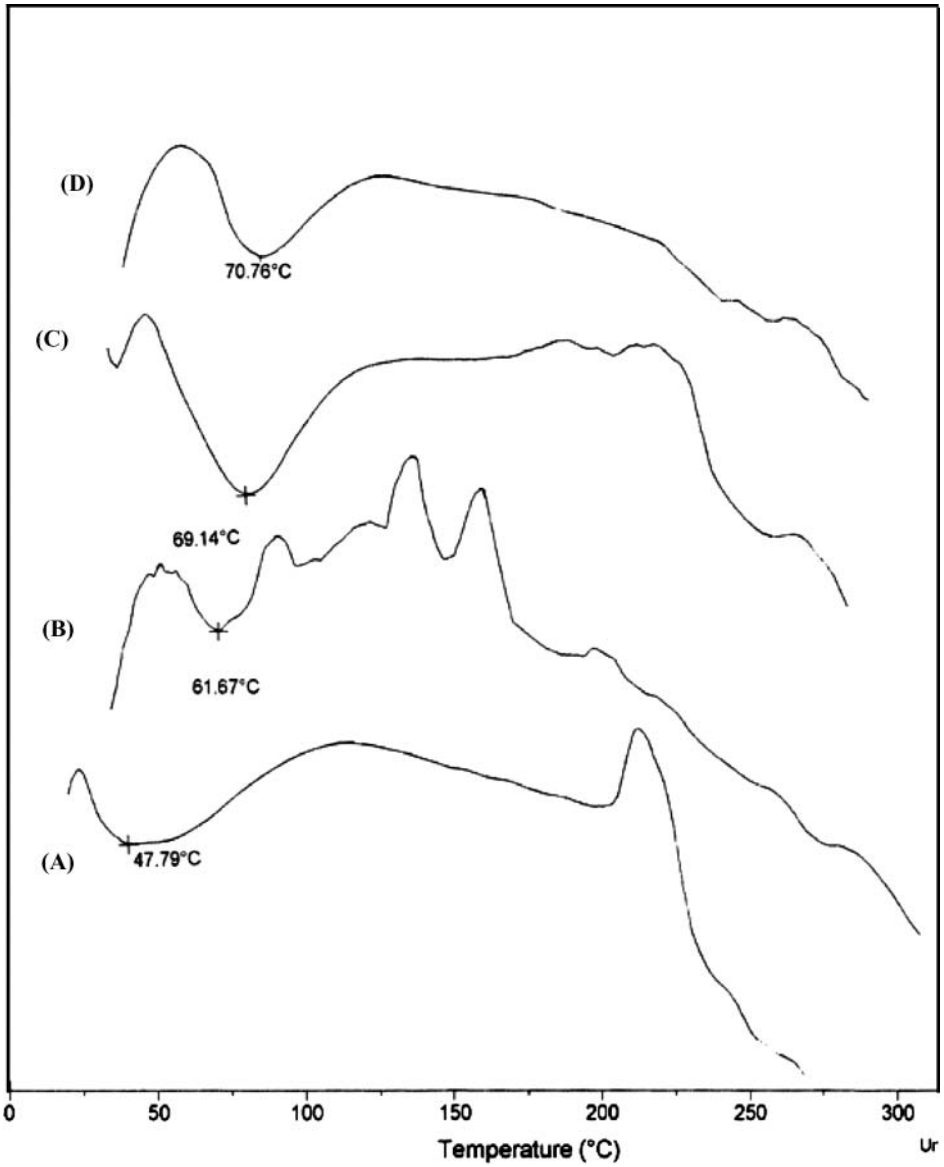

Fig. 2. DSC thermograms of neat alginate film (A), RCM 4 (B), RCM 5 (C) and RCM 6 (D).

to increase in crosslink density in the RCM. As the concentration of GA was increased, the tougher and dense membranes were formed.

3.2 Tensile Strength Measurement

The mechanical strength of the films was determined by tensile strength (TS) measurement studies. The RCM 1 film showed TS of 1.46 kg/cm^2, while, RCM 2, RCM 3, RCM 4, RCM 5 and RCM 6 films showed TS of 1.76, 1.98, 1.86, 2.11 and 2.42 kg/cm^2, respectively. Results indicate that the TS increase with increase in concentration of SA and crosslink density. This may be due to formation of a large number of links among the polymer chains as a result of crosslinking, thereby increasing strength of the matrix (13).

3.3 Differential Scanning Calorimetry

The rigidity/toughness of the prepared membranes was confirmed by DSC analysis. The thermograms for plain SA film (A), RCM 4 (B), RCM 5 (C) and RCM 6 (D) are presented in Figure 2. The plain SA film has shown a glass transition temperature (Tg) at 47°C, whereas RCM 4, RCM 5 and RCM 6 have shown the Tg values at 61°C, 69°C and 70°C, respectively. The shift in Tg values towards higher temperature indicates that polymer film rigidity/toughness increases with increase in crosslink density, which in turn affects the drug release characteristics of RCM.

3.4 Water Vapor Permeation Study

Water vapor permeation (WVP) through the RCM determines the drug permeability characteristics. All the

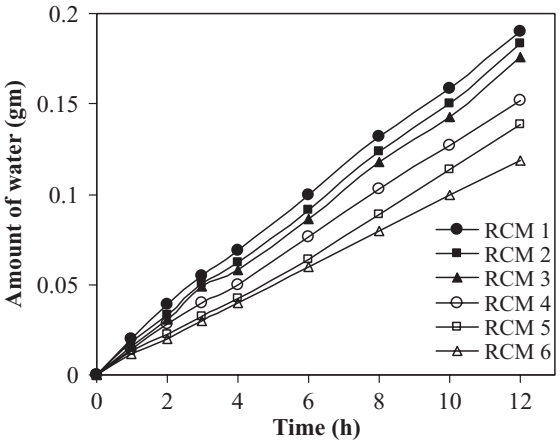

Fig. 3. Water vapor permeation profiles of different rate controlling membranes.

membranes were permeable to water vapors and permeation rate followed zero order kinetics (Fig. 3). The WVP rate of RCM was affected by the thickness and crosslink density of the films. There was a decrease in WVP with increasing film thickness which may be due to increased path length for diffusion and WVP also decreases as the concentration of GA increases in RCM, it may be attributed to increased film rigidity/toughness at higher crosslink densities.

3.5 Molar Mass Between Crosslinks and Crosslink Density

The ability of hydrogel films to release drug is a function of crosslink density. In order to know the crosslinking of the polymer network, two important parameters have been calculated, i.e., molar mass between crosslinks (Mc) and crosslink density (dx) based on the equilibrium swelling study. When a polymeric film is placed in a solvent, it swells until elastic forces balance the osmotic forces that could dissolve the polymer. These elastic forces are inversely proportional to the molar mass of the polymer between the points of cross-linking. Thus, molar mass between two junction points in a network would be rigid and exhibit limited swelling. When Mc is large, the network is more elastic and swells rapidly. The Mc values were calculated using the following equation (15):

$$Mc = -\rho p\, Vs\, \Phi^{1/3} \left[\ln(1-\Phi) + \Phi + \chi \Phi^2\right]^{-1}$$

The volume fraction, Φ of the polymer in the swollen state has been calculated as follows:

$$\Phi = \left[1 + \frac{\rho p}{\rho s}\left(\frac{Ma}{Mb}\right) - \frac{\rho p}{\rho s}\right]^{-1}$$

In the above equation, ρ_p and ρ_s are the densities of polymer and solvent, respectively; Mb and Ma are, respectively, the mass of polymer before and after swelling, and Vs is molar volume of the solvent. The interaction parameter, χ can be calculated using the equation (16):

$$\chi = \beta + \left(\frac{Vs}{RT}\right)(\delta s - \delta p)^2$$

Here, β is a lattice constant, with a value that is taken to be 0.34, Vs is molar volume of the solvent, R is molar gas constant, and T is temperature in Kelvin. The symbols δs and δp are solubility parameters of solvent and polymer, respectively. For the analysis of crosslinked structure of the hydrogel films, the crosslink density, (dx) was calculated using the following equation (17):

$$dx = \left(\frac{1}{v\, Mc}\right)$$

Here, v is the specific volume of the polymer. The results of Mc and dx are presented in Table 2. As the concentration of GA increases in the films, Mc values decreased and network becomes denser, whereas dx values increase with increase in GA concentration.

3.6 Drug Diffusion through Membranes

Figure 4 depicts the diffusion profiles of diclofenac diethylamine through rate controlling membranes. Results indicated that the membranes were permeable to diclofenac diethylamine and it was close to zero order pattern. Though an initial burst release was observed, later linearity was observed in the release profiles. The drug diffusion depends on the SA concentration and the crosslink density of RCM. Since, an increase in SA concentration increases the film thickness which in turn reduces the drug diffusion rate. On the other hand, as concentration of GA was increased in

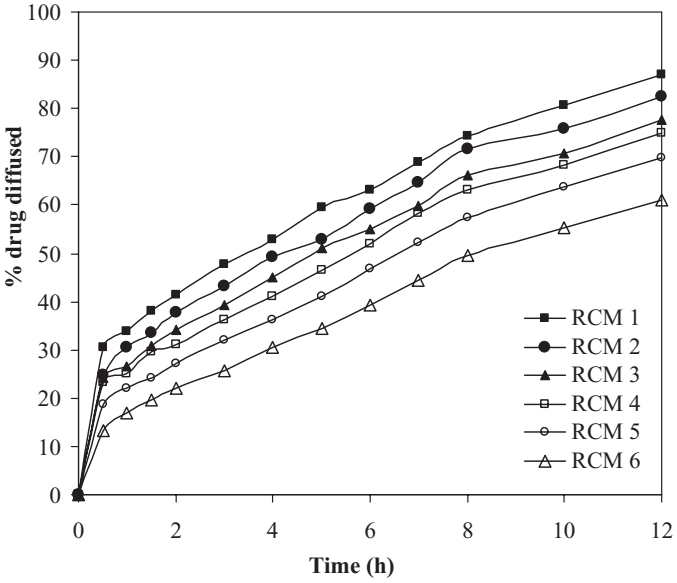

Fig. 4. Drug diffusion through various rate controlling membranes.

the RCM, drug release was decreased appreciably; this may be due to the increased rigidity and reduced porosity of the RCM at higher crosslink density, thereby hindering the transport of drug molecules through membrane.

To understand the drug release mechanism from membranes, the release data was fitted to following empirical equation (18):

$$\frac{Mt}{M_\infty} = Kt^n$$

Where M_t is the amount of drug released at time t, and M_∞ is the total amount of drug in the donor compartment, n values indicate the type of release mechanism. The n values have been calculated and given in the Table 2. The obtained n values suggest that the drug release followed nearly zero order kinetics. As the concentration of GA and SA was increased, the n values shifted towards zero order kinetics.

3.7 Skin Irritation Study

The findings of primary skin irritation test performed on albino rats for prepared RCM suggests that the test films produced very slight erythema as compared to control patch, whereas no evidence of oedema was observed, this indicates the skin acceptability of these membranes for transdermal application.

4 Conclusions

The prepared RCM were thin, flexible and smooth. Tensile strength measurement and differential scanning calorimetric analysis suggested that as the crosslink density increases, the tougher membrane were formed. The membranes were permeable to water vapors depending upon the crosslink density and thickness. The drug diffusion through films was also depended on the crosslink density and thickness. The primary skin irritation study indicated that the prepared membranes are safe for transdermal drug delivery application.

References

1. Mutalik, S. and Udupa, N. (2004) *J. Pharm. Sci.,* 93, 1577.
2. Chauhan, A.S., Sridevi, S. and Chalasani, K.B. (2003) *J. Control. Rel.,* 90, 335.
3. Cordero, J.A., Alarcon, L. and Escribano, E. (1997) *J. Pharm. Sci.,*86, 503.
4. Fang, J., Fang, C. and Hong, C. (2001) *Eur. J. Pharm. Sci.,*12, 195.
5. Hadgraft, J., Plessis, J.D. and Goosen, C. (2000) *Int. J. Pharm.,*207, 31.
6. Ramarao, P. and Diwan, P.V. (1997) *Pharmaceut. Acta Helvetiae*., 72, 47.
7. Mundaragi, R.C., Patil, S.A., Agnihotri, S.A. and Aminabhavi, T.M. (2007) *Drug Dev. Ind. Pharm*., 33, 79.
8. Kulkarni, R.V., Mutalik, S.S. and Hiremath, D. (2002) *Ind. J. Pharm. Sci.,* 64, 28.
9. Tanwar, Y., Chauhan, C. and Sharma, A. *Acta Pharm*., 57, 151.
10. Krishna, R. and Pandit, J.K. (1994) *Drug Dev. Ind. Pharm.,*20, 2459.
11. Kulkarni, R.V. and Doddayya, H. (2002) *Ind. J. Pharm. Sci.,* 64, 593.
12. Lewis, S., Pandey, S. and Udupa, N. (2006) *Ind. J. Pharm. Sci.,* 68,179.
13. Kulkarni, R.V. and Sa, B. (2008) *Cur. Drug Del.,* 5, 256.
14. Murthy, S.N., Hiremath, S.R. and Paranjothy, K.L.K. (2004) *Int. J. Pharm*., 272, 11.
15. Agnihotri, S.A. and Aminabhavi, T.M. (2005) *Drug Dev. Ind. Pharm.,* 31, 491.
16. Bristow, G.M. and Watson, W.F. (1958) *Transact. Faraday Soci*., 54, 1731.
17. Savas, H. and Guven, O. (2001) *Int. J. Pharm.,* 224, 151.
18. Kulkarni, R.V. and Sa, B. (2008) *Drug Dev. Ind. Pharm.,* 34, 1406.