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Synthesis and Characterization of Polylactic acid/Cloisite 30B (MMT) Nanocomposite for Controlled Release of Anticancer Drug Curcumin

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Subject : Nanotechnology

Abstract

PLA/Cloisite 30 B (MMT) hybrid nanocomposites were prepared by blending PLA with cloisite30B in aqueous solution. The nano composites were characterized by using FTIR, SEM and DSC analysis. From the FTIR spectra the various groups present in the gelatin blend were monitored. The homogeneity, morphology and Thermal property of the blends were ascertained from SEM and DSC data, respectively . The results indicated that an intercalated or partially exfoliated nanocomposite could be achieved and the properties of the composite were Significantly improved. The drug release kinetics were investigated using Curcumin as the drug. The kinetics of the drug delivery system has been systematically studied. Drug release kinetics was analyzed by plotting the cumulative release data vs. time by fitting to an exponential equation which indicated the non-Fickian type of kinetics. The drug release was investigated at different pH medium (pH5.8, pH7.0, pH7.4) and it was found that the drug release depends upon the pH medium as well as the nature of matrix.

Key words: *PLA, Cloisite 30 B, Curcumin, Drug delivery, Kinetics*.

Introduction :

Polylactic acid (PLA), which can be produced by ring opening polymerization of lactides and the lactic acid monomers used are obtained from the fermentation of sugar feed stocks, is a degradable thermoplastic polymer with excellent mechanical properties [1–4]. PLA has been found to degrade within a few weeks in soil environments [5]. However, PLA is not widely used because of its high cost as compared to synthetic plastics. To reduce cost, some articles have been proposed to study the composites of PLA and starch and the result shows that the blends have rather poor mechanical properties due to poor adhesion of starch and PLA [5–8]. Varying types of chemicals, such as citrate esters, have been tried to plasticize PLA [9]. Recently, plasticizers such as poly(ethylene glycol) (PEG), glucose monoesters and partial fatty acid esters [10-11] were used to improve the flexibility and impact resistance of PLA.

Polymer/montmorillonite (MMT) nanocomposites have been reported a lot recently(12-14) With only a low content of MMT, the strength, Young'smodulus, heat resistance, and solvent resistance of the composites can be greatly improved.(15-17)However, all the matrices reported are neutral synthetic polymers,where as an intercalation nanocomposite dealing with a natural amphoteric polyelectrolyte has not been reported so far. Curcumin (diferuloylmethane), a polyphenol, is a low molecular- weight active principle of the perennial herb Curcuma longa (commonly known as turmeric). Recent evidence suggests that curcumin is a highly pleotropic molecule that interacts physically with its diverse range of molecular targets including transcription factors, growth factors and their receptors, cytokines,enzymes, and genes regulating cell proliferation and apoptosis. Curcumin possesses antioxidant, anti-inflammatory, anticarcinogenic, and antimicrobial properties, and suppresses proliferation of a wide variety of tumor cells. Several clinical trials dealing with cancer have addressed the pharmacokinetics, safety, and efficacy of curcumin in humans. Despite extensive research and development, poor solubility of curcumin in aqueous

solution remains a major barrier in its bioavailability and clinical efficacy. Being hydrophobic in nature, it is insoluble in water but soluble in ethanol, dimethylsulfoxide, and acetone. To increase its solubility and bioavailability, attempts have been made through encapsulation in liposomes, polymeric and lipo- NPs,biodegradable microspheres, cyclodextrin, and hydrogels [18-23].In recent years, various controlled delivery forms, such as polymeric micro/nanospheres,liposomes, micelles, parenteral emulsion, and prodrugs have been investigated to increase its solubility, to minimize the side effects as well as to avoid the use of toxic adjuvant.

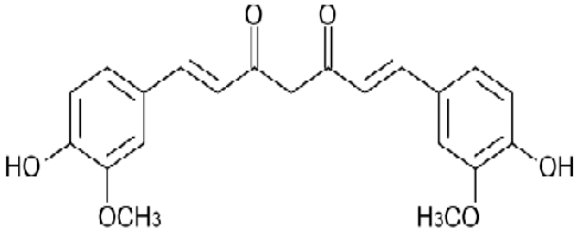

Fig-1: Curcumin structure (1*E*,6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione(IUPAC NAME**)**

PLA synthesis

There are two important methods for PLA synthesis: direct polycondensation of lactic acid and ring opening polymerization of lactic acid cyclic dimmer, known as lactide. In direct condensation, solvent is used and higher reaction times are required. The resulting polymer is a material of low to intermediate molecular weight. In the present research program, we wish to report a novel biomaterial—PLA/ MMT (Cloisite 30 B) hybrid nanocomposite for the control release of Curcumin. The nano composites have been characterized by FTIR, SEM, DSC methods. The drug delivery has been carried out at different pH conditions and the results are encouraging

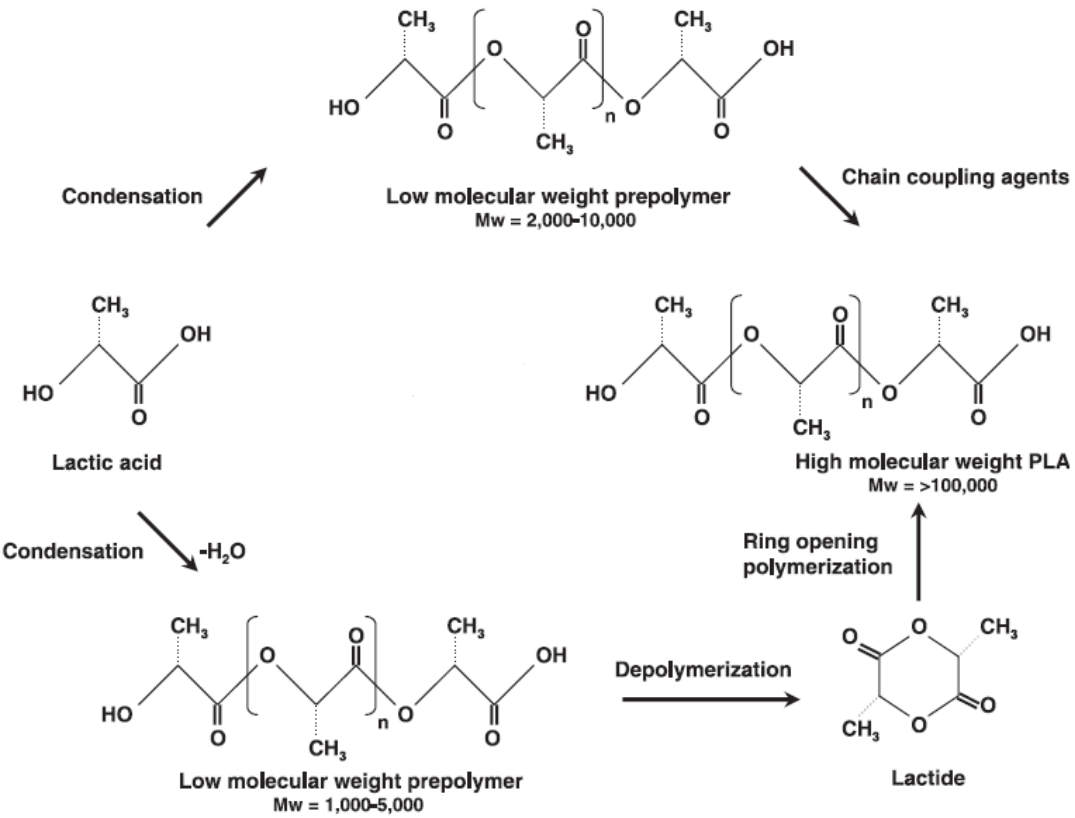

Fig-2: PLA Synthesis Method.

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EXPERIMENTAL

Materials: PLA was purchased from the Aldrich Chemical Co., (USA)..The Cloisite 30B was procured from Southern Clay Products;USA. Curcumin was purchased from Dabar Company,India. All other samples were of Analytical Grade.

Preparation of Nanocomposites

PLA was dissolved in acetonitrile solution. Calculated amount of Cloisite 30B(MMT)(1%, 2.5%) was added to this solution. The mixture was stirred for 4 hours at room temperature till a homogenate composite is formed. The product was poured into the specially self-made mold and dried at ambient temperature for several days.

Drug Loading

Curcumin-loaded PLA/ C 30B nanocomposites were prepared by emulsion/solvent evaporation method. In short, curcumin of different loadings, i.e., 1 wt%, 2.5wt%, 5 wt%, 7.5wt%, 10wt% and 15% were dissolved in ethanol with (80:20) PLA/ C 30B. The formed solution was poured into a labeled Petri dish and allowed to evaporate the solvent overnight at room temperature. This compound was used for drug delivery purposes.

Dissolution experiments

Dissolution experiments were performed at 37^0C using the dissolution tester(Disso test, Lab India, Mumbai, India) equipped with six paddles at a paddle speed of 100 rpm. About 900ml of phosphate buffer solution (pH 5.8, pH7.0 and pH7.4) was used as the dissolution media to stimulate gastrointestinal tract (GIT) conditions. A 5-ml aliquot was used each time for analyzing the curcumin content at a fixed time interval. The dissolution media was replenished with a fresh stock solution. The amount of Curcumin released was analyzed using a UV spectrophotometer (Systronics, India) at the λmax value of 420 nm.

Drug release mechanism from matrices

From time to time, various authors have proposed several types of drug release mechanisms from matrices. It has been proposed that drug release from matrices usually implies water penetration in the matrix, hydration, swelling, diffusion of the dissolved drug (polymer hydro fusion), and/or the erosion of the gelatinous layer. Several kinetic models relating to the drug release from matrices, selected from the most important mathematical models, are described over here. However, it is worth mention that the release mechanism of a drug would depend on the dosage form selected, pH, nature of the drug and, of course, the polymer used.

(i) Zero - Order Kinetics [24].

W = k1 t ……. (1)

(ii) First - Order Kinetics [25].

ln (100- W) = ln 100 - k2 t …… (2)

(iii) Hixon-Crowel's Cube- Root Equation (Erosin Model) [26].

(100- W) 1/3 = 100 1/3 – k3 t …….. (3)

(iv) Higuchi's Square Root of Time Equation (Diffusion Model) [27].

W = k4 t ……. (4)

(v) Power Law Equation (Diffusion/ Relaxation model) [28].

Mt / M∞ = k5 t n ……. (5)

Mt / M∞ is the fractional drug release into dissolution medium and k5 is a constant incorporating the structural and geometric characteristics of the tablet. The term 'n' is the diffusional constant that characterizes the drug release transport mechanism. When n = 0.5, the drug diffused and released from the polymeric matrix with a quasi-Fickian diffusion mechanism. For n >0.5, an anomalous, non-Fickian drug diffusion occurs. When n = 1, a non-Fickian, case II or Zero- order release kinetics could be observed.

Characterization

Fourier Transmission Infra Red Spectroscopy(FTIR)

The FTIR spectrum of the PLA blends were monitored using a BIORAD-FTS-7PC type FTIR spectrophotometer.

Differential scanning calorimetry.

The differential scanning calorimetry was used to study the thermal properties of blends Modulated differential scanning calorimetry (MDSC), TA Instruments Q100 was used to determine glass

transitions Tg, melting points Tm, crystallization temperatures Tc and melting enthalpies. The thermal history was erased during the first run at a high heating rate up to 190 8C followed by a fast cooling to 50 8C. Then the heating rate was modulated 1 8C/min minute with a ramp 2 8C/min to 200 8C. DSC is also explained by Menard and by Lucas and her coworkers.

Scanning Electron Microscopy (SEM):

The blending of the PLA Nanocomposites containing different concentrations was characterized using SEM (440, Leica Cambridge Ltd., Cambridge, UK). The film specimens were placed on the Cambridge standard aluminium specimen mounts (pin type) with double-sided adhesive electrically conductive carbon tape (SPI Supplies, West Chester, PA). The specimen mounts were then coated with 60% Gold and 40% Palladium for 30 seconds with 45 mA current in a sputter coater (Desk II, Denton Vacuum,Moorestown, NJ). The coated specimens were then observed on the SEM using an accelerating voltage of 20 kV at a tilt angle of 300to observe the microstructure of the gelatin composite blends.

Swelling Studies

Water absorption of the polymer-drug conjugates was measured following ASTM D 570-81. The
samples were preconditioned at 50o C for 24h and then cooled in a desiccator before being weighed. The preconditioned samples were submerged in distilled water at 25o C for 24h.The samples were removed and dried with a paper towel before weighing. Water absorption was calculated as a percentage of initial weight. The soluble material loss was checked by weighting the specimens after drying them in an oven at 50^{o} C for another 24h. The total water absorption for 24h was calculated including the soluble material loss Where, W1=Weight of Swollen composite after 24 hr., W2= Weight of Dry Composite.

$$\% \text{ Swelling} = \frac{W_1 - W_2}{W_2} \times 100$$

Where, W1=Weight of Swollen composite after 24 hr., W2= Weight of Dry Composite.

RESULTS AND DISCUSSION

Fourier Transmission Infra Red Spectroscopy (FTIR)

FTIR spectrums of the monomer and the poly(D,L-lactic acid) which was obtained from 24h of reaction. The PLA spectrum shows the bands at 2,754.94 and 2,766.51 cm^{-1} from symmetric and asymmetric valence vibrations of C-H from CH3, respectively. It is possible to observe a band shift related to the C=O stretch in the monomer in 1,727.06 to 1,757.92 cm^{-1} in the polymer. These bands that show shifts of monomer to polymer also show a difference in the peak intensity which suggests the arrangement of molecules in the polymer chain. Bands corresponding to bending vibrations of CH3 (asymmetric and symmetric) were found in 1,433.94 and 1,511,08 cm^{-1} in the polymer spectrum as greater intensity peaks compared with those from monomer found in 1,408.87 and 1,476.37 cm^{-1}. C-O-C asymmetrical and symmetrical valence vibrations were found at 1,250.73 and 1,200.59 cm^{-1} respectively; at 1,333.68 cm^{-1} is detected the C-O-C stretching vibration. The band around 3200 cm^{-1} is related to the stretching of OH group and this decreases from the monomer to the polymer due to reaction polyesterification that consumes the OH groups when they react with the acid groups to form the ester bond.

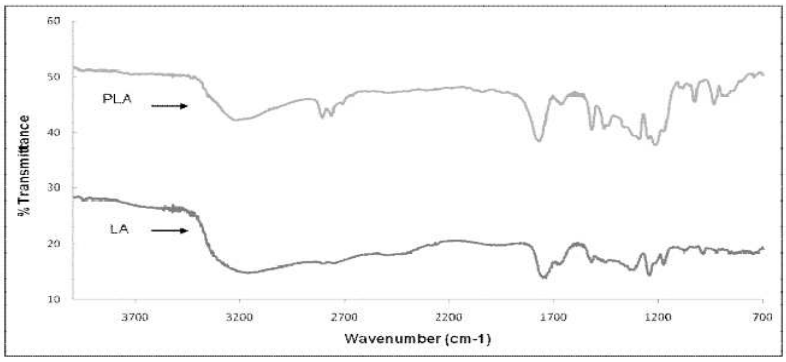

Fig-3: FTIR OF PLA AND LACTIC ACID

DSC OF PLA

DSC analysis made of products obtained show similar thermal behavior for all samples**. Figure 4** shows typical thermograms of DSC run. From the graph can observe a deviation from the baseline that was attributed to the glass transition temperature (Tg) of the material around 40-42 °C. On the other hand, sign of crystallization temperature (Tc)and melting temperature (Tm) were observed around 106 °C and 142 °C respectively. FTIR analyses were made to determine the functional groups of the products obtained in order to understand more deeply what happens in the polymerization of lactic acid. A qualitative analysis of absorption bands with reaction time shows a decrease in the intensity of some bands and, the formation of new ones, indicating the end groups which decrease and those formed due to the polymerization reaction progress.

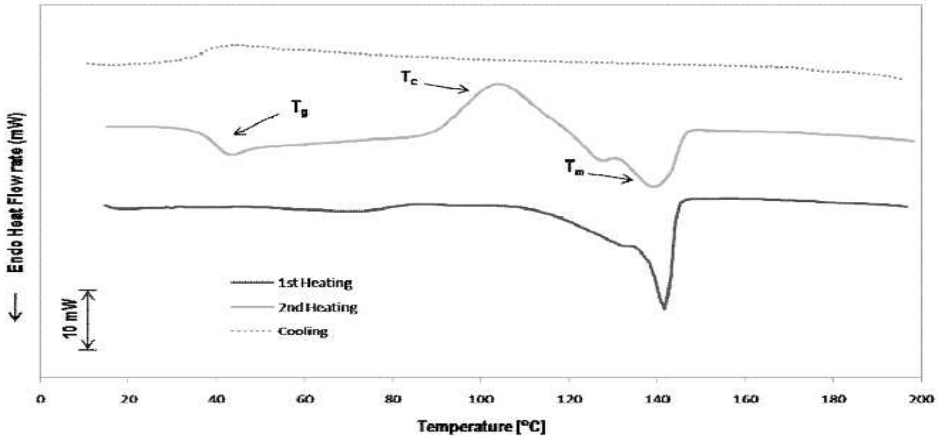

Fig. 4: DSC OF PLA

Scanning Electron Microscopy (SEM)

A scanning electron microscope (Hitachi Microscopy Model S-1400, Japan) was used to study the morphology of blends. Films from the mechanical analysis were treated with hot water at 80 8C for 24 hr, thereafter coated with gold and observed using SEM.

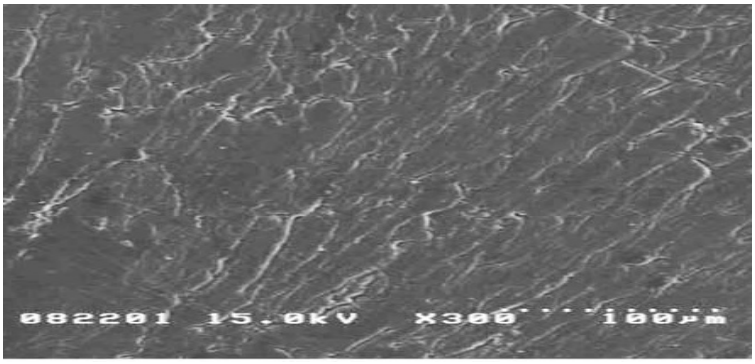

Fig.5: Scanning Electron Microscope

In-vitro Drug Release

Effect of pH, Time and Drug loading

In order to investigate the effect of pH on the swelling of PLA/C 30B composite (2.5%), we have measured the % cumulative release in pH 5.8, pH7.0 and 7.4 media. Cumulative release data presented in Figure.6, 7, 8 indicate that by increasing the pH from 5.8 to 7.4, a considerable increase in the cumulative release is observed for all composites. From Figure.6,7,8 it is seen that the 15% drug- polymer composites have shown longer drug release rates than the other composites. Thus, drug release depends upon the nature of the polymer matrix as well as pH of the media. This suggests that the drugs in the blend can be used to be suitable for the basic environment of the large intestine, colon, and rectal mucosa for which there are different emptying times. Interestingly, more than 90 wt% curcumin is released from composites at pH 7.4 within 48 hours,where as less than 70wt% of the drug is released at pH 5.8 within 48 hours. This suggests that the drugs in the composites can be used to be suitable for the basic environment. Further the electrostatic interaction of composites is more easily broken at pH 7.4 than at pH5.8.

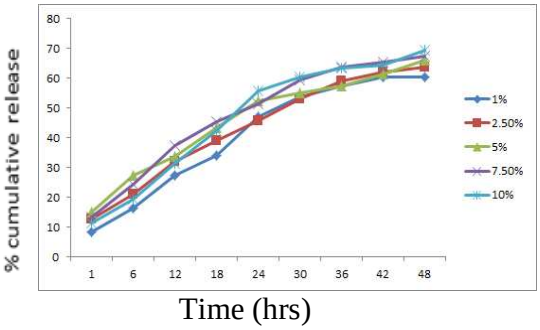

Fig-6 % Cumulative Release vs Time for Different Formulations of Curcumin Loaded in PLA-C30B in pH 5.8 media

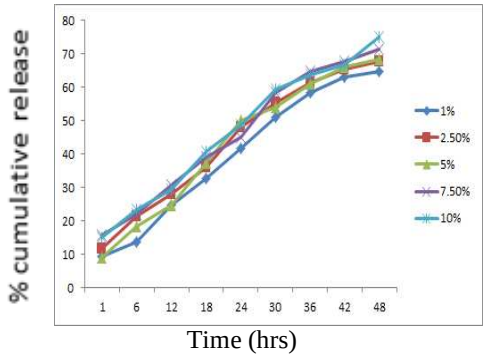

Fig-7 %Cumulative Release vs Time for Different Formulations of Curcumin Loaded in PLA-C30B in pH 7.0 media

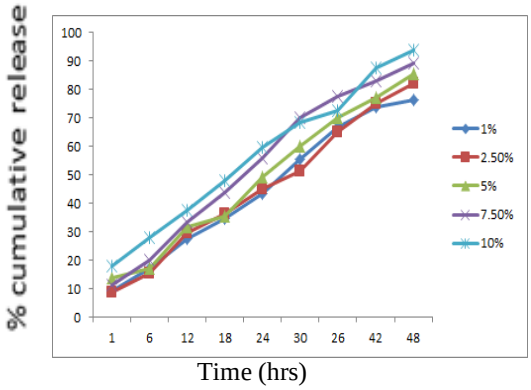

Figure 8: % Cumulative release Vs. Time for different formulation of curcumin loaded in PLA/C 30B composite film in pH 7.4 media.

leading to curcumin being released more rapidly at pH 7.4 than pH 5.8.Release data (Figure 6,7,8) showed that formulations containing highest amount of drug (10%)displayed fast and higher release rates than those formulations containing a small amount of drug loading. 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 could transport.

Drug release kinetics

Drug release kinetics was analyzed by plotting the cumulative release data vs. time by fitting to an exponential equation of the type as represented below .

$$M_t / M_\infty = K5\, t\, n$$

Here, Mt / 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 five formulations and these data are given in Table 1. The values of k and n have shown a dependence on the, % drug loading and polymer content of the matrix. Values of 'k' for composites prepared by varying the amounts of drug containing and keeping PLA/C 30B (2.5 wt %) constant ranged from 0.06 to 0.13 in pH 7.4 ,0.04 to 0.14 in pH 7.0 and 0.06 to 0.14 in pH 5.8 respectively. However, the drug loaded composites exhibited 'n' values ranging from 0.6 to 1.3 in pH 7.4 , 0.5 to 1.5 in pH 7.0 and 0.7 to 1.2 in pH 5.8 indicating a shift from erosion type release to a swelling controlled, non-Fickian type mechanism. The values of n more than 1 has also been recently reported .This may be due to a

Table-1 .Release kinetics parameter of different formulation at pH 5.8, pH 7.0, pH7.4

Curcumin		value of "k"			value of"n"	
%	pH 7.4	pH 7.0	pH 5.8	pH 7.4	pH7.0	pH 5.8
1 wt %	0.06	0.11	0.09	o.7	0.6	0.9
2 .5wt%	0.09	0.05	0.05	1.3	0.5	1.2
5wt%	0.13	0.14	0.14	0.6	0.8	0.8
7.5%	0.071	0.04	0.13	0.9	0.67	0.7
10%	0.06	0.09	0.06	1.1	1.5	1.3

reduction in the regions of low micro viscosity inside the matrix and closure of microcavities during the swollen state of the polymer. Similar findings have been found elsewhere, where in the effect of different polymer ratios on dissolution kinetics was investigated.

CONCLUSION

Controlled delivery devices that utilize biodegradable polymers have a significant advantage over competing delivery systems in that there is no need for surgical removal of the device. Further, if the polymer degrades only at the surface, the drug release process is simplified in water diffusion into the bulk is minimized and drug release rate is governed by polymer degradation rate. Novel nanocomposites of PLA blended with Cloisite 30B were prepared and characterized by FTIR spectroscopy, Differential scanning calorimetry and scanning electron microscopy. This blend was loaded with different amounts of anticancer drug curcumin to study the drug release behavior. The swelling studies of the nanocomposites have been reported. The drug was released in a controlled manner. The drug release was monitored by changing time, % drug loading and pH of the medium. It was observed that the release was much more pronounced in the basic medium than the acidic medium. The kinetics of the drug release was investigated and based on the kinetic parameters such as 'k' and 'n' values the probable drug release mechanism has been reported.

"Cite this article"

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