Journal of Applied Polymer Science

Dextrin Crosslinked with Poly(lactic acid): A Novel Hydrogel for Controlled Drug Release Application

Dipankar Das,[1] Raghunath Das,[1] Jayanta Mandal,[1] Animesh Ghosh,[2] Sagar Pal[1]

[1]Polymer Chemistry Laboratory, Department of Applied Chemistry, Indian School of Mines, Dhanbad, Jharkhand 826004, India

[2]Department of Pharmaceutical Sciences, Birla Institutes of Technology, Ranchi, Jharkhand 835215, India

Correspondence to: S. Pal (E-mail: sagarpal1@hotmail.com) or A. Ghosh (E-mail: aghosh@bitmesra.ac.in)

ABSTRACT: A new class of biodegradable crosslinked hydrogel, consisting of hydrophobic polylactic acid (PLA) and hydrophilic dextrin in presence of crosslinker *N*,*N*-methylene bisacrylamide (MBA) has been synthesized by free-radical polymerization technique using potassium persulfate (KPS) as initiator. By variation of crosslinker concentration, a series of hydrogels have been prepared and the optimized grade has been selected on the basis of higher crosslinking efficiency as well as lower equilibrium swelling characteristics, XRD analysis. The hydrogels have been characterized by FTIR spectra, ^{13}C-NMR spectra, CHN analysis, SEM analysis, swelling characteristics, and toxicity study. *In vitro* release study of model drugs (ciprofloxacin and ornidazole) from hydrogel matrix has been performed in various buffer solutions at 37°C. The drug release kinetics and mechanism have been studied using zero order, first-order kinetic models, Korsemeyar–Peppas model, Higuchi model, Hixson–Crowell model, and nonlinear Kopcha model. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40039.

KEYWORDS: crosslinking; drug delivery systems; gels; polysaccharides; swelling

Received 22 May 2013; accepted 6 October 2013

DOI: 10.1002/app.40039

INTRODUCTION

The development of controlled release drug delivery systems (CRDDS) in biomedical and pharmaceutical fields has increased dramatically in last few years. Controlled drug release at a desired rate has numerous advantages over conventional drug release such as maintaining the drug concentration level in patient's blood, minimizing deleterious side effects, prolonging efficiency time, heightening bioavailability, improve patient compliance,[1] protecting sensitive drugs from enzymatic or acid degradation in the gastrointestinal tract, masking peculiar odors, etc.[2] Different types of drug delivery systems have been proposed over the last few decades. Out of which, the simplest system is the matrix device where the drug is dispersed within a polymer network.[3] Thus, the composition or the structure of the polymeric system plays an important role in altering the drug release rate. In recent years, polysaccharides/modified polysaccharides based stimuli-responsive crosslinked hydrogels are extensively used as drug delivery matrix which improve or adjust the release of the drug in a required time and manner.[4–7]

The use of natural polymers, mainly polysaccharides/biopolymers over synthetic polymers in the field of drug delivery has increased dramatically because of their biodegradability, low cost, easy availability, and nontoxicity.[8] However, they are having certain drawbacks like uncontrolled rate of hydration, microbial contamination, and drop in viscosity during storage etc.[9] By crosslinking of synthetic polymers on polysaccharide backbone in the presence of chemical crosslinker; it is possible to develop hydrogels having improved functional properties, which finds potential application in the field of controlled drug delivery.[10] Lower crosslinker concentration forms crosslinked network which increase the rate of swelling and decrease the gel strength.[11] On the other hand, higher crosslinker concentration forms crosslinked network that decreases the swelling ratio and increases the gel strength, may be a suitable candidate for controlled/sustained drug release application.

Hydrogels are physically or chemically crosslinked natural or synthetic 3D polymer network which swell but do not dissolve when added to water or biomedical fluid, maintaining its form until an equilibrium state is achieved. Stimuli-responsive hydrogels exhibit remarkable changes in their swelling behavior, network structure, permeability and mechanical strength in response to a number of external stimuli, including pH,[12] ionic strength,[13] temperature,[14] magnetic field,[15] electric

Additional Supporting Information may be found in the online version of this article.

Table I. Synthesis Details, % Crosslining, Equilibrium Swelling, and Rate of Erosion of Dextrin and Various Hydrogels

Hydrogel	Amount of crosslinker (mole × 10^{-3})	% Crosslinking[a]	% Equilibrium swelling at 6 h (pH = 1.2)	% Equilibrium swelling at 6 h (pH = 7.4)	% Erosion (pH = 7.4)
DXT-*g*-PLA 1	3.25	62.74	167.04 ± 4.17	221.88 ± 4.29	12.88 ± 1.02
DXT-*g*-PLA 2	4.06	70.54	162.55 ± 4.06	195.82 ± 3.91	11.45 ± 1.33
DXT-*g*-PLA 3	4.87	85.85	158.55 ± 4.75	184.79 ± 4.95	10.85 ± 1.14
DXT-*g*-PLA 4	6.49	61.50	170.51 ± 3.41	247.81 ± 4.90	14.20 ± 1.88
DXT-*g*-PLA 5	8.11	60.40	184.66 ± 3.69	264.36 ± 3.51	15.33 ± 1.08
Dextrin (DXT)	–	–	–	–	76.50 ± 1.64

Amount of dextrin: 1 g (0.0062 moles); amount of KPS (initiator): 0.0025 g (9.25×10^{-6} moles); amount of LA (monomer): 25 mL ($3.36 \times 10\times^{-1}$ mole); amount of Tin (II) 2-ethyl hexanoate (catalyst): 1 mL (3.08×10^{-3} mole); used in all the synthesis.

[a] %cross linking= $\frac{\text{Wt. of hydrogel}-\text{Wt. of polysaccharode}}{\text{Wt. of monomer}+\text{Wt. of crosslinker}} \times 100$

field,[16] etc. This important characteristic of hydrogel makes it to be appropriate in controlled release applications.[17–20] The pH-sensitive hydrogels are generally prepared by incorporating pendant acidic or basic functional groups to the polymer backbone.[21]

For oral administration of drug delivery, there is a need for safe, nontoxic and biocompatible matrix. Poly-α-hydroxy acids, because of their biodegradable and biocompatible nature, are often used as a matrix for drug delivery systems for treatment of cancer,[22] reproduction,[23] tissue regeneration,[24] etc. As one of the prominent synthetic biodegradable polymers, PLA is widely used in the field of biomedical science.[25–28] Further, these materials degrade in aqueous media to form monomers which are easily metabolized to yield water and carbon dioxide as natural compounds. On the other hand, dextrin is enzymatically degradable, hydrophilic natural polysaccharide. Both polymers are biocompatible also.[26] As a model compartmentalized material, hydrogels composed of PLA-based and dextrin-based polymers may draw a great attention in the field of CR of drugs. This assertion is based on the fact that the PLA is hydrolytically degradable and hydrophobic, dextrin, on the other hand, as a natural polymer, is degradable and hydrophilic.

Hence the main objective in the present article is to synthesize and characterize a novel hydrogel by grafting PLA onto a dextrin backbone using MBA as crosslinker and investigate the feasibility of this novel hydrogel as a new drug delivery system for ciprofloxacin and ornidazole drugs based on a strategy that the hydrophilic part ensures swelling of the hydrogel in an aqueous media, whereas the presence of hydrophobic constituent regulates the mechanical property and swelling behavior of the hydrogel. As far as it is concerned, there is no report regarding the use of this novel hydrogel for the controlled delivery of model drugs ciprofloxacin and ornidazole, which has been addressed in the present article.

EXPERIMENTAL

Materials

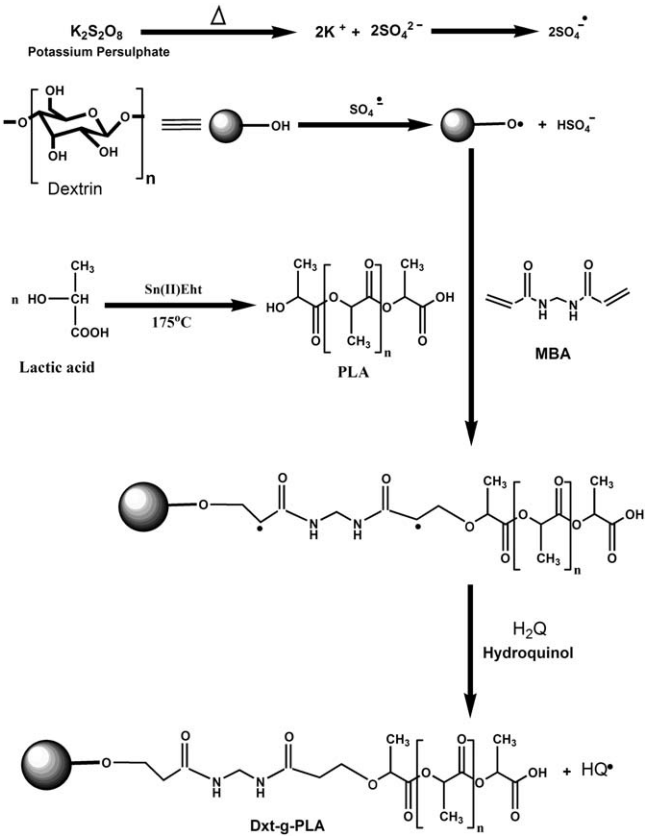
Dextrin was purchased from Fluka, Switzerland. *N*,*N*′-methylene bisacrylamide was acquired from Loba Chemie Pvt., Mumbai, India. Potassium persulfate (KPS) was supplied by Qualigens Fine Chemicals, Mumbai, India. Lactic acid (LA) and acetone were obtained from E-Mark (I) Pvt., Mumbai, India. Tin (II) 2-ethyl hexanoate was purchased from Sigma-Aldrich Chemie GmbH, Germany. Polyvinyl pyrollidone (PVP) was acquired from Spectrochem Pvt., Mumbai, India. Hydroxypropyl methyl cellulose (HPMC) was obtained from Lancaster, UK. Ornidazole was a gift sample from Endoc Pharma, Rajkot, India. Ciprofloxacin was obtained as a gift sample from Department of Pharmaceutical Sciences, BIT, Mesra, Ranchi. Double distilled water was used in all experimental works.

Preparation of Hydrogel

Synthesis of PLA from LA. A total of 25 mL LA was taken in a three-necked round bottom flask and kept at 110°C for 4 h in an oil bath for removal of water. After that, a condenser was fitted with RB and temperature was raised to 175°C. Thereafter, 1 mL tin (II) 2-ethyl hexanoate was added to this anhydrous LA and allowed to stir (at 400 rpm) at the same temperature for 24 h. Finally, the product (i.e., PLA) was recovered by centrifugation and dried in hot air oven at 40°C for 6 h.

The synthesized PLA has been characterized through GPC analysis (Model: 2414; Make: Waters (I) Pvt., USA), ^{13}C NMR spectroscopic analysis.

Synthesis of Dxt-g-PLA Hydrogel. The dextrin crosslinked with PLA hydrogel was synthesized by free-radical polymerization technique using KPS as initiator. For the synthesis, 1 g of dextrin was slowly dissolved in 40 mL DMSO in a three-necked round bottom flask equipped with an electrically operated magnetic stirrer (Tarsons, Model: Spinot Digital) and kept in an oil bath maintained at a temperature of 80°C, with constant stirring under nitrogen atmosphere. Subsequently, required amount (Table I) of KPS dissolved in 5 mL DMSO followed by MBA solution (desired amount of MBA was dissolved in 5 mL DMSO) was added under constant stirring condition (400 rpm). Then, PLA synthesized as above (dissolved in 25 mL DMSO) was added to the reaction system and allowed to stir at the same temperature (80°C) and stirring speed (400 rpm) for further 3 h. Finally, the reaction was terminated using saturated solution of hydroquinol. The resultant solution was dispersed in DCM and the product was recovered



Scheme 1. Schematic representation for the synthesis of hydrogel.

by centrifugation. The product was dried at 40°C under vacuum until and unless the constant weight of the gel was achieved. The synthesis of hydrogel follows the steps as shown in Scheme 1.

Characterization

CHN Analysis. The CHN analysis of dextrin and various hydrogels developed in this study has been investigated using an Elemental Analyzer (Perkin Elmer, Series-II, CHNS/O analyzer-2400)

FTIR Spectroscopy. FTIR spectra of the dextrin, various hydrogels prepared under study, ciprofloxacin, ornidazole and drug loaded hydrogel (i.e., tablet) were recorded using KBr pellet method (Model IR-Perkin Elmer, Spectrum 2000). The scan range was 500 and 4000 cm^{-1}.

^{13}C-NMR Spectroscopy. Solid state ^{13}C nuclear magnetic resonance (NMR) spectra of dextrin, PLA and various hydrogels were recorded at 500 MHz on a Bruker Advance II-500NMR spectrometer.

Scanning Electron Microscopy. The surface morphology of neat dextrin, various crosslinked hydrogels and drug loaded hydrogel (i.e., tablet formulation) was investigated using scanning electron microscopy. After complete drying, the samples were sputter-coated with gold, and the surface morphologies were analyzed using scanning electron microscopy (Model: S-3400N, HITACHI, Japan).

X-ray Diffraction. Wide angle X-ray diffraction (XRD) behavior of Dxt-*g*-PLA 3, ciprofloxacin, ornidazole and triturated content of tablets was carried out in a Bruker X-ray diffractometer (Bruker, D8-Fecus, Germany).

Swelling Characteristics and Swelling Kinetics of Dextrin and Crosslinked Hydrogels. The equilibrium swelling ratio (ESR) of hydrogels was assessed at 37°C in pH 1.2 and pH 7.4 buffer solutions. A total of 0.05 g of sample was immersed in buffers and then left to swell for 10 h to achieve equilibrium swelling (equilibrium swelling was attained at ~6 h). The swollen hydrogel was withdrawn after specific time intervals (after every 1 h) and the excess water was removed carefully with tissue paper and reweighed. The % ESR has been calculated using eq. (1):

$$\mathrm{ESR}(\%) = \frac{W_{eq} - W_d}{W_d} \times 100 \quad (1)$$

where W_d and W_{eq} are weights of dried gel and swollen gel at equilibrium, respectively.

For swelling kinetics, water absorption of hydrogels has been measured at consecutive time intervals until equilibrium was accomplished. To determine the pH-sensitivity of the hydrogel, the swelling was measured in different buffer media. Voigt model [eq. (2)] is the fundamental model to find out the swelling rate of the hydrogel.[29,30]

$$S_t = S_e(1 - e^{-t/\tau}) \quad (2)$$

where S_t (g g^{-1}) is the swelling at time t, S_e (g g^{-1}) is the equilibrium swelling, t is the time (min) for swelling, and τ (min) stands for the rate parameter. Using eq. (2), the rate parameter (τ is obtained, which is a measure of the swelling rate, i.e., lower will be the rate parameter value (τ higher will be the swelling rate.[30]

Acute Oral Toxicity Study. Acute oral toxicity study of Dxt-*g*-PLA hydrogel was executed as per the "Organization of Economic Co-operation and Development (OECD) guideline for the test of chemicals" 425, adopted "December 17, 2001." Five nulliporous and nonpregnant 5 weeks old female mice (*Swiss albino* strain) were taken for this study. The study protocol was prior approved by the Animal Ethics Committee of Birla Institute of Technology, Ranchi, India. Mice were housed in polycarbonate cage with sufficient food and deionized reverse osmosis water was available to them *ad libitum* at 20–25°C and 40–70% relative humidity in a 12 h light on/off cycle. A single dose of 2000 mg/kg body weight of the gel was administered by gavages using a stomach tube to the first animal. The same dose was administered to the remaining four animals after survival of the first animal. The animals were kept under the continuous observation up to 4 h after dosing. The observation was continued up to 14 days. The mortality rate was evaluated by visible observation and reported accordingly.

Preparation of Hydrogel-Based Tablets and *In Vitro* Drug Release Study

Dextrin and different hydrogels (450 mg) were used for the preparation of ciprofloxacin (500 mg) and ornidazole (500 mg) tablets. The hydrogel was swelled with minimum amount of hot water to form dough like mass, to which PVP-K 30 (50 mg) and model drug (500 mg) was added to form granule. The

granule was completely dried at 40°C. Afterward, the tablet was lubricated with talc (10 mg) and magnesium trisilicate (10 mg). Finally, the tablets were compressed at an average weight of 1 g using a tablet punching machine at a pressure of 2–3 t/cm^2. Eventually, the drug loading (for both ciprofloxacin and ornidazole) of each tablet was 500 mg.

During drug release, some tablets disintegrated partially. The degree of erosion (D) was calculated using eq. (3) based on the difference between the initial dry weight of the tablet (W_i) and the dry weight of the tablet ($W_{d(t)}$) at time t, considering the initial amount of drug in tablet (W_d) and fraction of drug release at time t (M_t/M_∞),

$$D(t)(\%) = \frac{W_i - W_{d(t)} - W_d\left(1 - M_t/M_g\right)}{W_i} \times 100 \qquad (3)$$

The *in vitro* release of the encapsulated ciprofloxacin and ornidazole from corresponding tablets were determined at pH 1.2 and pH 7.4 buffers. The controlled drug release was conducted by Dissolution Test Apparatus (Lab India, Model: DS 8000), in 900 mL of buffer solution maintained at the physiological temperature (37 ± 0.2°C) under a constant rotation of 60 rpm. Aliquots were withdrawn from the release media after every 60 min and replaced by an equal volume at each sampling time. The amount of drug release was measured with the help of UV–visible spectrophotometer (Shimadzu, Japan; Model—UV 1800).

To determine the release kinetics and mechanism of the drug release from hydrogel based matrix, various mathematical models were used such as zero order kinetic and first-order kinetic models, Korsemeyar–Peppas model, Higuchi model, Hixson–Crowell model, and nonlinear Kopcha model.

Stability Study

Final tablets containing ciprofloxacin and ornidazole were undergone accelerated stability study for one month to confirm the stability of drugs in the present hydrogel matrix (Dxt-*g*-PLA 3) to check the compatibility in accelerated conditions. Tablets were packed in a glass bottle and placed in the humidity chamber where temperature was kept at 40 ± 2°C and relative humidity (RH) was maintained at 75 ± 5% throughout the study period.

RESULTS AND DISCUSSION

Synthesis of Hydrogel

Here, the free-radical polymerization technique was used for the preparation of a novel crosslinked hydrogel using KPS as initiator and MBA as crosslinker. The synthetic route has been represented in Scheme 1. At first, the PLA was synthesized from LA by catalysis polycondensation reaction. In this reaction tin (II) 2-ethyl hexanoate acts as catalyst and the polycondensation takes place at 175°C as shown Scheme 1. The synthesized PLA is characterized using GPC analysis and the results have been given in Supporting Information (Fig. S1 and Table S1).

The PLA crosslinked dextrin hydrogel was prepared, based on the assumption that potassium persulfate (KPS) generates free-radical sites on dextrin. In presence of crosslinker MBA, because of its polyfunctionality,[31] a new macroradical would be formed that has four reactive sites[31] and these sites can be linked with the radical generated on dextrin as well as on the PLA backbone as shown in Scheme 1. This result in the formation of three-dimensional crosslinked network hydrogel. The reaction was carried out using DMSO as a solvent because of its high boiling point (189°C) and lower rate of thermal decomposition (<2% on 24 h). Also, aqueous solvent can cause trans-esterification reaction. To observe the effect of crosslinking concentration, several grades of hydrogels were prepared (Table I) and the optimized one was selected with respect to its higher % crosslinking and lower % equilibrium swelling. It has been observed that with increase in crosslinker concentration from 3.25×10^{-3} to 4.87×10^{-3} moles, the % crosslinking increases (Table I), beyond which it declines. This indicates that 4.87×10^{-3} mole is the optimum crossliner concentration for various hydrogels prepared in this study.

Table II. CHN Analysis Result

Polymer	% C	% H	% N
Dextrin	39.65	6.83	0.00
Dxt-*g*-PLA 1	36.39	7.45	0.717
Dxt-*g*-PLA 2	37.40	7.12	0.824
Dxt-*g*-PLA 3	**38.45**	**6.88**	**1.105**
Dxt-*g*-PLA 4	37.24	6.94	0.704
Dxt-*g*-PLA 5	38.26	7.04	0.672

Bold value indicates that this hydrogel is optimized one.

Characterization of Hydrogel

CHN Analysis. The results of CHN analysis of dextrin and various hydrogels have been reported in Table II. Dextrin does not have any presence of nitrogen. However, it has been found that there is certain amount of nitrogen in the hydrogels, which is accounted for the presence of crosslinker in the hydrogel moiety. In the series of graft copolymers based hydrogels, the variation in the nitrogen content, although not much, is significant in case of Dxt-*g*-PLA 3. The higher nitrogen content in Dxt-*g*-PLA 3 may be due to higher % crosslinking in compared to other hydrogels.

FTIR Analysis. From the FTIR spectrum of dextrin [Figure 1(a)], it has been observed that the peak at 3495 cm^{-1} is due to the stretching vibrations of O—H, a small peak at 2940 cm^{-1} is attributed to the C—H stretching vibrations. The peaks at 1092 and 1026 cm^{-1} are assigned to C—O—C stretching vibrations. Figure 1(b–f) represents the FTIR spectra of various hydrogels based on Dxt-*g*-PLA. For all hydrogels, there are few additional peaks in compared to pure dextrin. The O—H stretching band of dextrin and N—H stretching band of crosslinker (i.e., MBA) overlap with each other and lead to a broad peak, which appear at 3307 cm^{-1} (for Dxt-*g*-PLA 3 hydrogel). One intense peak at 1741 cm^{-1} is attributed to —COOH groups of grafted PLA moiety (for Dxt-*g*-PLA 3 hydrogel). Two peaks at 1640 and 1522 cm^{-1} are due to amide-I and amide-II bands of MBA (for Dxt-*g*-PLA 3 hydrogel). C—N stretching and C—H stretching peaks appear at 1375 and 2922 cm^{-1}, respectively (for Dxt-*g*-PLA 3 hydrogel). It has been observed that all

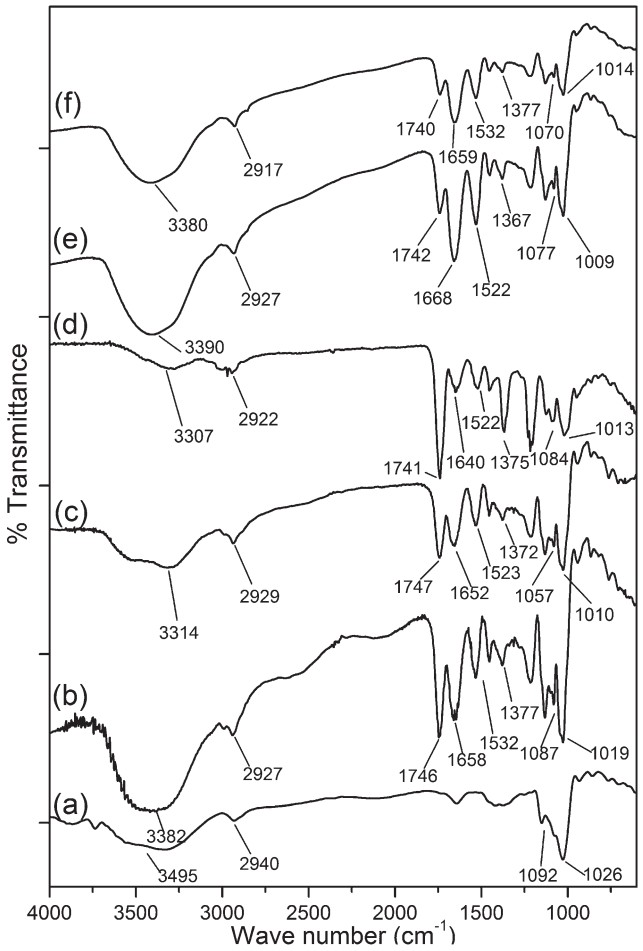


Figure 1. FTIR spectra of (a) dextrin, (b) Dxt-*g*-PLA 1, (c) Dxt-*g*-PLA 2, (d) Dxt-*g*-PLA 3, (e) Dxt-*g*-PLA 4, and (f) Dxt-*g*-PLA 5 hydrogels.

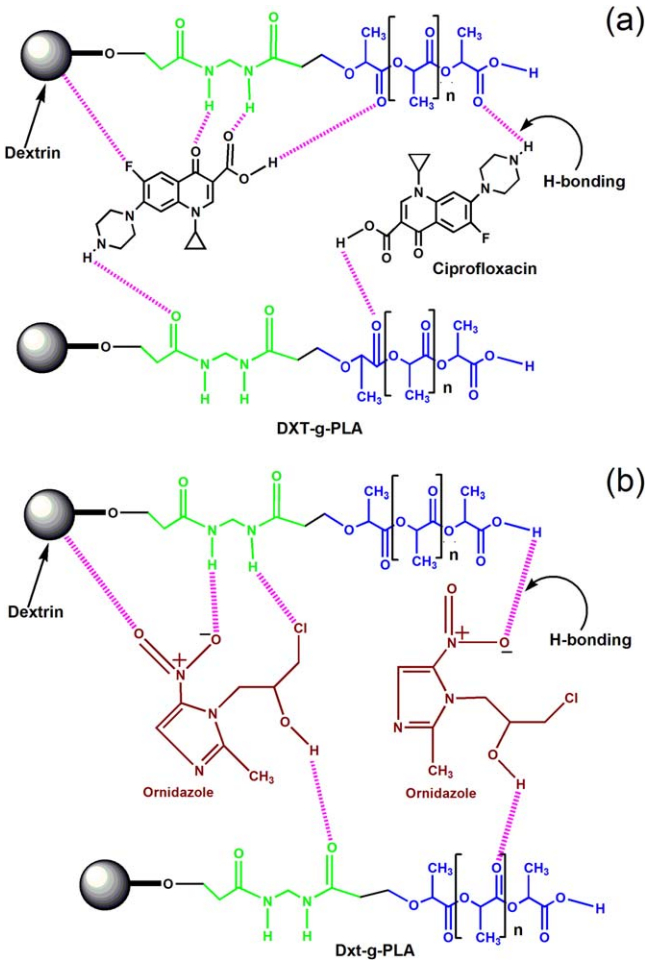


Figure 2. Interaction between (a) hydrogel and ciprofloxacin drug, (b) hydrogel and ornidazole drug. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

characteristics peaks of dextrin, MBA and PLA are present in the FTIR spectra of DXT-*g*-PLA based hydrogels. This indicates the successful incorporation of PLA moiety onto dextrin backbone in presence of MBA as crosslinker.

Supporting Information Figure S2 represents the FTIR spectra of Dxt-*g*-PLA 3 hydrogel, model drugs (i.e., ciprofloxacin and ornidazole) and triturated contents of tablets. In FTIR spectrum of ciprofloxacin (Supporting Information Fig. S2b), two prominent characteristic peaks have been observed at 3527 and 3371 cm^{-1}, which are assigned to stretching vibration of OH groups and intermolecular hydrogen bonding. Peaks at 3084 and 2928 cm^{-1} represents alkene and aromatic C—H stretching, mainly $\upsilon_{=C-H}$. The peak at 1712 cm^{-1} attributes the carbonyl C=O stretching, i.e., $\upsilon_{C=O}$. The peak at 1630 cm^{-1} is assigned to quinolones, i.e., for N—H bending. The peak at 1497 cm^{-1} represents υ_{C-O} and 1271 cm^{-1} is due to the bending vibration of O—H group. The absorption peak at 1040 cm^{-1} is assigned to C—F group. Supporting Information Figure S2d, explains the FTIR spectrum of ornidazole. For ornidazole, peaks at 3313 and 3175 cm^{-1} are due to —O—H stretching mode and C—H stretching mode respectively. For asymmetric NO_2 stretching the peak appears at 1536 cm^{-1}. The peaks at 1364–1274 cm^{-1} are due to the symmetric stretching mode of NO_2 group. A total of 1150 cm^{-1} is due to C—O stretching vibration. The peaks at 826 and 744 cm^{-1} are attributed to C—N, i.e., carbon atom connected with NO_2 group and stretching frequency of C—Cl bond vibration respectively. For ciprofloxacin tablet (i.e., ciprofloxacin loaded Dxt-*g*-PLA 3 hydrogel) (Supporting Information Fig. S2c) and ornidazole tablet (i.e., ornidazole loaded Dxt-*g*-PLA 3 hydrogel) (Supporting Information Fig. S2e), it is apparent that all characteristics peaks are present in the tablet formulation, which specifies the compatibility between the drug and the hydrogel. However, the peak values of —COOH and amide-I groups of hydrogel shifted towards lower region (In case of both the drugs). This indicates that the interaction between hydrogel and drugs is through H-bonding as shown in Figure 2.

^{13}C-NMR Spectral Analysis. The solid state ^{13}C NMR spectrum of dextrin [Figure 3(a)] reveals four distinct peaks at $\delta = 103.9$, 83.5, 73.5, and 62.4 ppm, which are assigned to the anomeric carbon atom, carbon atoms connected by —OH groups (i.e., the carbon atoms in the six member ring except anomeric carbon atom-C-2 to C-4), the carbon atom of —CH_2OH group and C-5 carbon atom, respectively. The PLA synthesized in authors' laboratory is also having four characteristics peaks (Supporting Information Fig. S3) at 171.4, 72.9, 62.4, and 19.1 ppm. It is obvious from the spectra that all the hydrogels are

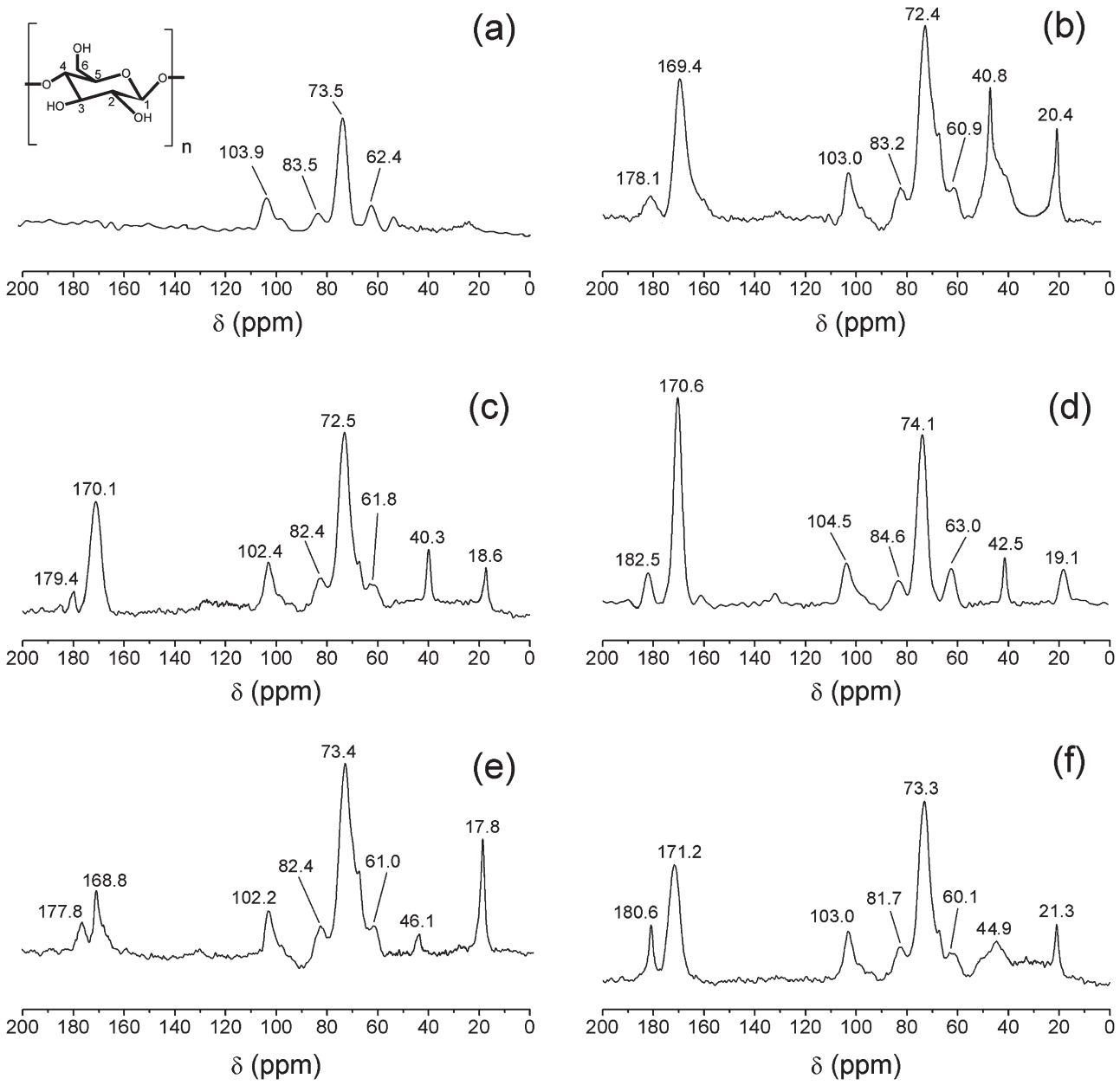


Figure 3. ^{13}C NMR spectra of (a) dextrin, (b) Dxt-*g*-PLA 1, (c) Dxt-*g*-PLA 2, (d) Dxt-*g*-PLA 3, (e) Dxt-*g*-PLA 4, and (f) Dxt-*g*-PLA 5 hydrogels.

having four additional peaks in compare to neat dextrin. For the hydrogel Dxt-*g*-PLA 3 [Figure 3(d)], the peaks at 170.6 and 19.1 ppm are responsible for carboxylic carbon and methyl carbon of grafted PLA respectively. The peak at 182.5 ppm is responsible for the —C═O group of MBA. The another peak at 42.5 ppm is a result of sp^3 hybridized carbon atom from crosslinker MBA, which has been produced during crosslinking between dextrin backbone and PLA moiety as shown in Scheme 1. The presence of these additional peaks in the spectra of hydrogels confirms that PLA has been successfully grafted on the dextrin backbone in presence of MBA crosslinker.

Scanning Electron Microscopic Analysis. Figure 4 depicts the SEM micrographs of dextrin and various hydrogels, taken at ×1.40 K magnification. The surface morphology of dextrin indicates that it is granular in nature. Compared to dextrin, the surface of the hydrogels has been appeared as rough, irregular and aggregated. This is because of the presence of crosslinked PLA chains in the dextrin backbone, which got agglomerated during polymerization reaction. The irregular and rough surface of the hydrogel favor the drug loading. Compared with the hydrogel, the morphology of tablet formulations (for both ciprofloxacin and ornidazole drugs) (Supporting Information Fig. S4) shows smooth surface which clearly indicates that the drug has been entrapped onto the surface of the hydrogel and the interaction between the gel and the drug is completely physical.

XRD Analysis. The X-ray diffractogram of hydrogel, ciprofloxacin, ornidazole, and triturated content of tablets has been represented in Supporting Information Fig. S5. It has been found

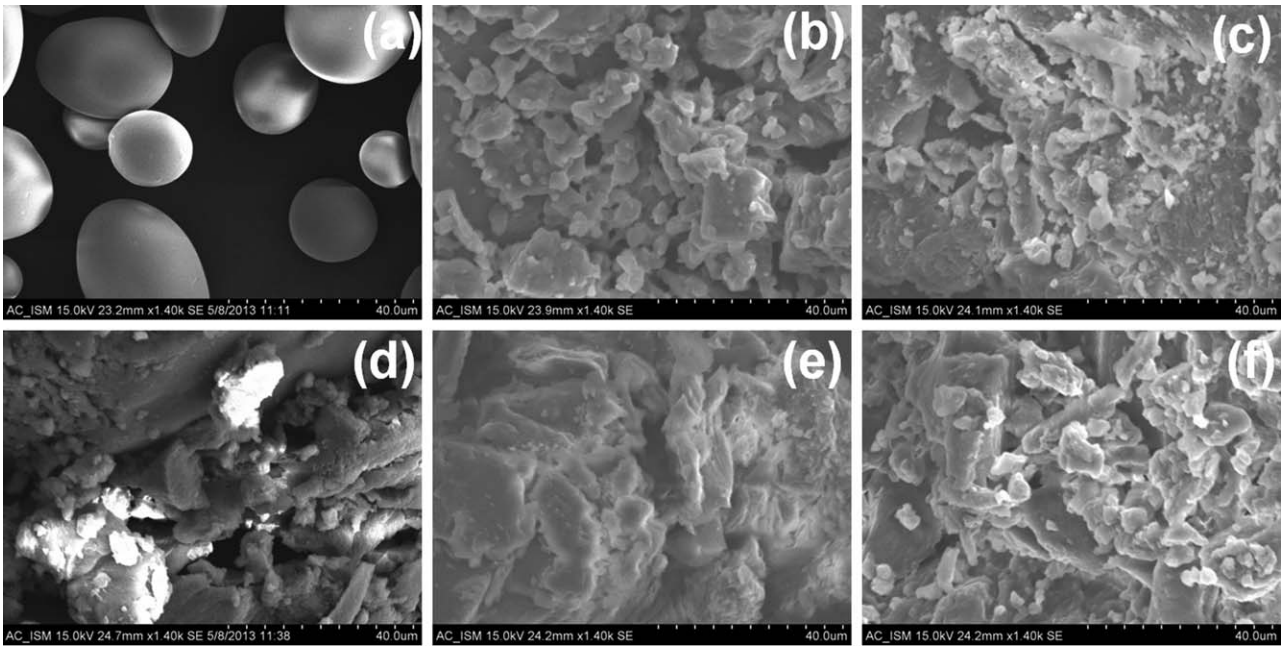


Figure 4. SEM micrographs (×1.40 K magnification) of (a) dextrin, (b) Dxt-*g*-PLA 1, (c) Dxt-*g*-PLA 2, (d) Dxt-*g*-PLA 3, (e) Dxt-*g*-PLA 4, and (f) Dxt-*g*-PLA 5 hydrogels.

that the hydrogel is amorphous and on the other hand, both drugs are crystalline in nature. However, from the XRD of tablets formulation, it is apparent that there is no sign of incompatibility between the drugs and the excipients.

Swelling Characteristics of Hydrogel. The equilibrium swelling properties of dextrin and synthesized hydrogels were investigated in pH 1.2 and pH 7.4 buffer solutions at 37°C. Equilibrium swelling was attained at ~6 h (Figure 5) in both the buffer media for various hydrogels. It is obvious that the hydrogels demonstrate a faster swelling rate than that of dextrin (Figure 5). Here, it is to be mentioned that dextrin shows declining nature of swelling with time which is because of its solubility in aqueous solution. The higher swelling behavior of Dxt-*g*-PLA can be explained by the fact that hydrogels are more hydrophilic in nature and facilitates the hydration as well as expansion of the network. In addition to that, the porous morphology of the hydrogel also enhances the diffusion of water into the hydrogel network. It has also been observed that the hydrogels show higher rate of swelling at pH 7.4 than that in pH 1.2. This may be due to the fact that the hydrophilic groups present in the hydrogel network get protonated in pH 1.2 and hindered the formation of H-bonding with water, which results less swelling in compared to pH 7.4. This is because, in pH 7.4,

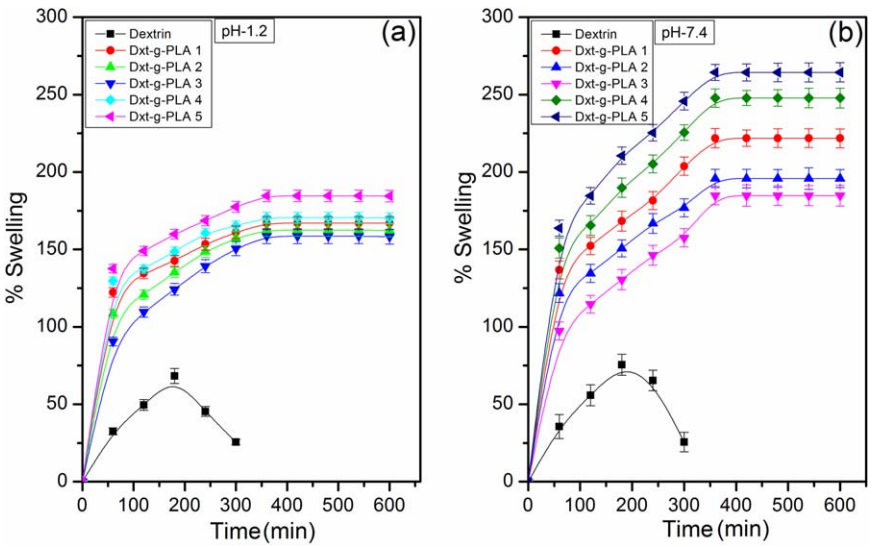


Figure 5. Swelling characteristics of dextrin and various hydrogels at (a) pH 1.2 and (b) pH 7.4. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Table III. Toxicity Test Results

	Mortality				
Observation time period	Animal 1	Animal 2	Animal 3	Animal 4	Animal 5
30 min	O	O	O	O	O
4 h	O	O	O	O	O
1st day	O	O	O	O	O
3rd day	O	O	O	O	O
7th day	O	O	O	O	O
14th day	O	O	O	O	O

O, survival; X, death.

all the hydrophilic groups remain free and also some of the carboxylic acid groups would be ionized to carboxylate and thus able to form more H-bonding with the media. This will result higher ESR value. Of various hydrogels, DXT-*g*-PLA 3 shows lowest equilibrium swelling (Table I), as this composition has maximum % crosslinking ratio, which in turn will make the hydrogel structure more rigid. Thus it will swell less as compared to other hydrogels which are having lower % crosslinking.

From the swelling curve (Figure 5), it has been observed that initially the rate of water absorption increases, after which it reaches equilibrium (~6 h). The data has been fitted with Voigt model according to eq. (2). The value of rate parameter (τ can be obtained from the slope value of ln $(1 - S_t/S_e)$ vs. t plot.[30] In case of crosslinked hydrogels, the value of rate parameter (τ (Supporting Information Table S2) is more in pH 1.2 than in pH 7.4. The decrease in τ of hydrogels with increase of pH indicates faster swelling rate in alkaline media than acidic media, since the τ value is a measure of the swelling rate (i.e., the lower the τ value, higher will be the rate of swelling).[30] At pH 7.4, some of the carboxylic acid groups ionize to carboxylate ion and the electrostatic repulsion between $-COO^-$ groups stretched the hydrogel network widely causes an enhancement of the swelling capacity. But in acidic media (pH 1.2), hydrophilic groups present in the hydrogel gets protonated, which oppose the interaction with water, resulting lower swelling capacity. The responsiveness and fast swelling behavior may be of the significant importance in case of drug delivery in alkaline medium.

Acute Toxicity Study. The acute toxicity results are shown in Table III. It is obvious that there was no mortality found within the observation period of 14 days after dosing. As per the OECD guideline for the test of chemicals 425, adopted "December 17, 2001" Annexure 4, the LD_{50} value is greater than 2000 mg/kg dose is recognizing the need to protect animal welfare, testing in animal is discouraged. As per the globally harmonized system (GHS), if LD_{50} value is greater than the 2000 mg/kg dose then the test product will be fallen under the "Category 5" and toxicity rating will be "zero." So, Dxt-*g*-PLA is under the Category 5 and its toxicity rating is zero.

In Vitro Drug Release Studies

Controlled Release of Ciprofloxacin. The release profile of ciprofloxacin from dextrin and various hydrogels as a function of time has been graphically represented in Figure 6(a). The release study was performed in pH 1.2 for 2 h followed by at pH 7.4 for further 16 h. It is obvious that dextrin was failed to retard the drug release and has been found to release the entire drug in 9 h. On the other hand, all the hydrogels release the drug in more sustained way. The release rate has been found to be very less for first 2 h, since the dissolution was carried out at pH 1.2 and at this pH, the swelling rate was very less (details of explanation has been given in swelling section). Thus, at pH 1.2, the drug was unable to diffuse from the hydrogels.[32] However, few amount of drug release was observed, may be because of the drug remaining at the surface of the gel, which was not loaded effectively within the hydrogel network.[32,33] The ciprofloxacin release rate was increased at pH 7.4 because of the higher swelling ratio of the hydrogels. Among the various hydrogels, Dxt-*g*-PLA 3 shows most controlled ciprofloxacin release (~51% release after 18 h) behavior. This is because of its higher % crosslinking and lower rate of swelling. Finally, the lower rate of erosion of different hydrogels compared to dextrin (Table I) supports the controlled ciprofloxacin release behavior.

Controlled Release of Colon Specific Drug Ornidazole. Release behavior of ornidazole from the hydrogels as well as from dextrin as a function of time is shown in Figure 6(b). The nature of hydrogel affects the drug release behavior. The higher swelling ratio of hydrogels create a larger surface area for diffusion of drug from inside of hydrogel to the environment.[30] It has been found that the rate of drug release is higher at pH 7.4 than that of pH 1.2. This may be because of the fact that at pH 1.2, the network hydrogel is in collapsed state, resulting lower rate of swelling and hence the drug was unable to diffuse from the hydrogels. However at pH 7.4, because of higher swelling ratio, drug diffusion rate from the hydrogel based matrix enhanced, resulting higher rate of drug release. Out various hydrogels, Dxt-*g*-PLA 3 shows more sustained drug release [Figure 6(b)] behavior. This is because of its lower swelling ratio as well as lower rate of erosion. Finally, the % of ornidazole release is much higher at simulated intestinal fluid (i.e., pH 7.4) than that of simulated gastric fluid (i.e., pH 1.2), which indicates that the developed hydrogel is a good candidate for colon specific delivery of ornidazole.

The drug release behavior of the best hydrogel was compared with hydroxypropyl methyl cellulose (HPMC), which is a usual

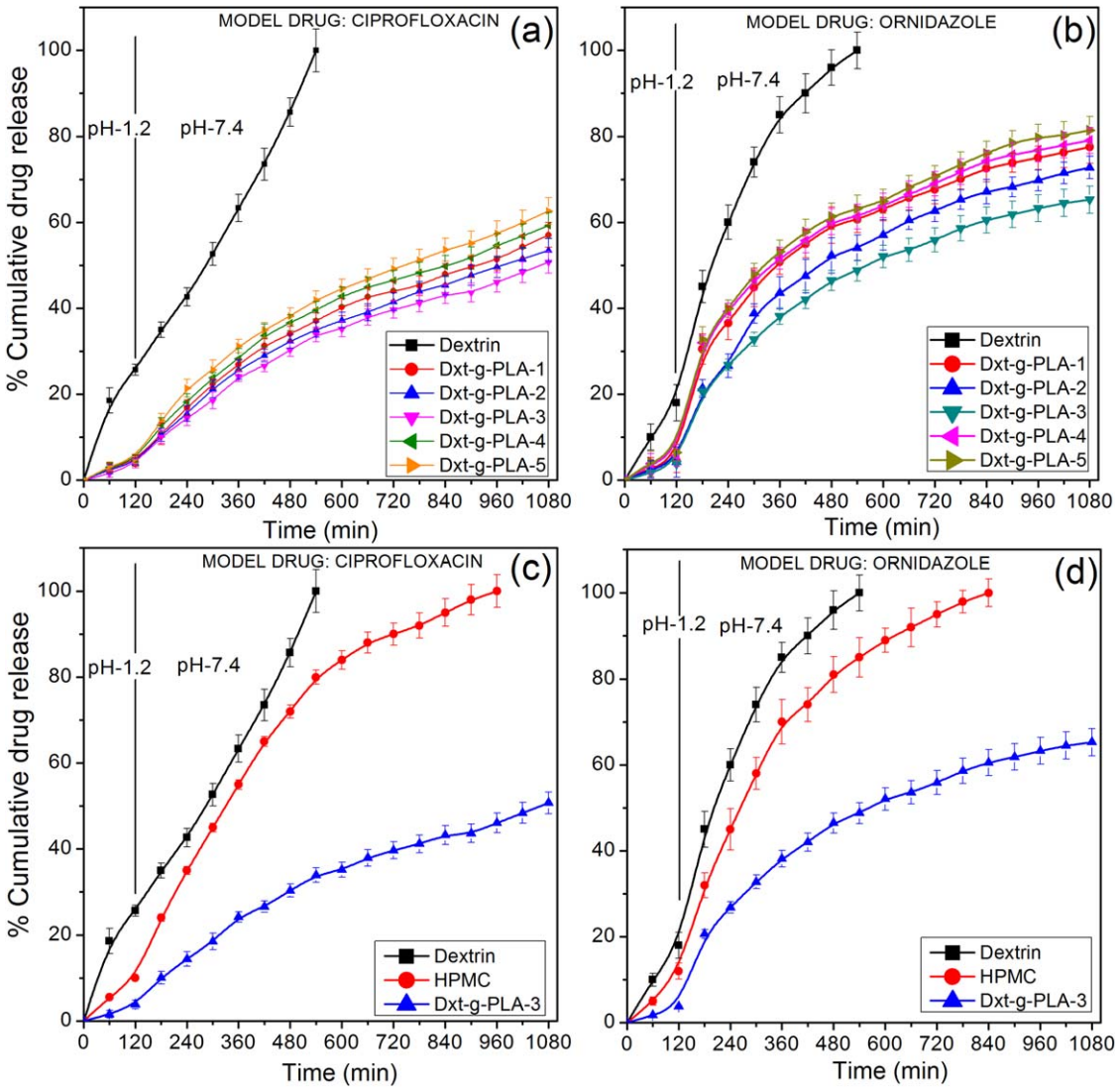


Figure 6. (a) Ciprofloxacin release study using dextrin and various hydrogels, (b) ornidazole release study using dextrin and various hydrogels, (c) ciprofloxacin release study using dextrin, Dxt-*g*-PLA 3 and HPMC hydrogels, (d) ornidazole release study using dextrin, Dxt-*g*-PLA 3 and HPMC hydrogels. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

hydrogel material for sustained release tablet. It is apparent from Figure 6(c) (for model drug: ciprofloxacin) and Figure 6(d) (for model drug: ornidazole) that Dxt-*g*-PLA 3 (optimized hydrogel) shows much better sustained release behavior than that of HPMC.

Kinetics and Mechanism of Drug Release. To analyze the *in vitro* release data, two different kinetic models namely zero order and first orders were used to describe the release kinetics. The zero order kinetic [eq. (4)] model is utilized to describe the drug dissolution from transdermal systems, as well as matrix tablets with low soluble drugs, coated forms, osmotic systems, etc.[34]

$$Q_t = Q_0 + K_0 t \tag{4}$$

where Q_t is the amount of drug release in time t, Q_0 is the initial amount of drug in solution (most times, $Q_0 = 0$) and K_0 is the zero order release constant expressed in units of concentration/time and t is the time.

The first-order kinetic model [eq. (5)] describes the release from systems those containing water soluble drugs in porous matrices, where the drug release is proportional to the amount of drug remaining in its interior.[35]

$$\log Q_t = \log Q_0 + \frac{K_1 t}{2.303} \tag{5}$$

where Q_0 and Q_t is the initial amount of drug in tablet and amount of drug release at time t, respectively. K_1 is first-order release constant.

In the hydrogel system, for controlled release of drug, the release should follow three steps. First step is the penetration of the dissolution medium in the tablet matrix (hydration). Second step is the polymer relaxation or erosion of the matrix and third step is the transport of the dissolved drug,

Table IV. Kinetic Data of Dextrin and Different Hydrogels at pH 7.4

Polymers	Zero-order model R^2	First-order model R^2	Higuichi model R^2	Hixson–Crowell model R^2	Korsemeyar–Peppas model		Kopcha model		
					n	R^2	A	B	R^2
Model drug: Ciprofloxacin									
DXT-g-PLA 1	0.9542	0.9949	0.9942	0.9422	0.58	0.9927	1.97	0.99	0.9924
DXT-g-PLA 2	0.9615	0.9990	0.9959	0.9479	0.58	0.9949	1.63	0.61	0.9986
DXT-g-PLA 3	0.9549	0.9815	0.9924	0.9418	0.59	0.9931	1.41	0.71	0.9909
DXT-g-PLA 4	0.9520	0.9949	0.9923	0.9389	0.55	0.9940	1.82	0.69	0.9912
DXT-g-PLA 5	0.9601	0.9917	0.9962	0.9471	0.52	0.9954	1.97	0.91	0.9915
Dextrin	0.9899	0.9900	0.9998	0.9899	0.64	0.9777	0.15	0.51	0.9896
HPMC	0.9095	0.9865	0.9468	0.8825	0.84	0.9970	1.10	0.40	0.9942
Model drug: Ornidazole									
DXT-g-PLA 1	0.9111	0.9804	0.9850	0.9102	0.54	0.9852	1.45	0.88	0.9981
DXT-g-PLA 2	0.9058	0.9752	0.9609	0.9086	0.72	0.9759	1.82	0.91	0.9965
DXT-g-PLA 3	0.9289	0.9864	0.9769	0.9289	0.67	0.9898	1.55	0.80	0.9992
DXT-g-PLA 4	0.9256	0.9872	0.9741	0.9033	0.51	0.9891	1.67	1.01	0.9907
DXT-g-PLA 5	0.9284	0.9896	0.9749	0.9108	0.52	0.9872	1.61	0.74	0.9946
Dextrin	0.9700	0.9854	0.9855	0.9700	0.84	0.9859	0.46	0.85	0.9931
HPMC	0.9782	0.9840	0.9892	0.9782	0.81	0.9895	1.23	0.77	0.9974

either through the hydrated matrix or from the parts of the eroded tablet to surrounding dissolution medium.[36] The absorption of water from the environment changes the dimensions and physicochemical properties of the system and thus affects the drug release kinetics. Three types of diffusion mechanism of drug from polymer matrix have been proposed-Fickian diffusion, non-Fickian diffusion and Case II diffusion.[37]

Korsemeyar–Peppas model is very crucial to find out the mechanism of drug release from a polymer matrix.[38] For this purpose first 60% drug release data was fitted in eq. (6).

$$\frac{M_t}{M_\infty} = Kt^n \tag{6}$$

where M_t/M_∞ is the fractional release of drug in time t, "k" is the constant characteristic of the drug-polymer system, and "n" is the diffusion exponent characteristic of the release mechanism. The n value is used to characterize different release mechanisms. $n \leq 0.45$ indicates Fickian diffusion, in which the rate of diffusion is less than that of relaxation and release is primarily controlled by diffusion process. The value of n in the range of $0.45 < n < 0.89$ indicates the mechanism is non-Fickian diffusion or anomalous diffusion, where the diffusion and relaxation rates are comparable and drug release depends on both diffusion as well as on erosion of the matrix. When $n > 0.89$, the major mechanism of drug release is Case II diffusion (relaxation-controlled transport) where release is mainly controlled by polymer relaxation process.

Higuchi model describes the release of drugs as a diffusion process from insoluble matrix based on Fick's law of diffusion [eq. (7)].[39]

$$Q_t = Q_0 + K_H t^{1/2} \tag{7}$$

where Q_0 is the initial amount of drug in solution, Q_t is the amount of drug release after time t, and K_H is the Higuchi dissolution constant.

The Hixson–Crowell cube root law [eq. (8)] illustrates the release from systems where there is a change in surface area and diameter of particles or tablets, i.e., it supports erosion of matrix is the main principle of drug release.[40]

$$W_0^{1/3} - W_t^{1/3} = K_{HC} t \tag{8}$$

where W_t is the amount of drug remaining after time t, W_0 is the initial amount of the drug in tablet and K_{HC} is the rate constant for Hixson–Crowell rate equation.

The Kopcha model [eq. (9)] can also be used to quantify the relative contributions of diffusion and polymer relaxation to drug release.[41]

$$Q_t = At^{1/2} + Bt \tag{9}$$

where "A" is diffusional exponent and "B" is erosion exponent. A is much greater than B indicates that the drug release from matrix is primarily controlled by Fickian diffusion process.

To investigate the drug release kinetics as well as release mechanism of ciprofloxacin and ornidazole drugs in pH 7.4, the drug release data were fitted in various models as shown in Supporting Information Figs. S6 and S7. In the present investigation, it has been observed that the drug release profile follow first-order kinetics (with higher R^2 value). Again, the values of n (Table IV) points out that the release of

drugs from drug entrapped hydrogel in release medium (i.e., pH 7.4 buffer) occurs through non-Fickian diffusion process. The best linearity obtained from Higuchi model (Table IV) suggested that most of the drug is released by diffusion process. It is, further confirmed by nonlinear Kopcha model, where the value of diffusion coefficient (*A*) and erosion coefficient (*B*) (Table IV) indicates that both diffusion as well as rate of erosion controlled the drug release. However, the diffusion process controlled the drug release more quantitatively than erosion process.

Stability Study

Stability study of the final tablets containing ciprofloxacin and ornidazole was performed. The results are shown in Supporting Information Table S3. It is obvious that the formulation remains stable at 40°C/75% RH up to 1 month.

CONCLUSIONS

A novel crosslinked network hydrogel composed of dextrin and PLA has been successfully synthesized using MBA as crosslinker and KPS as free-radical initiator. Various characterization techniques confirm the formation of hydrogel. Through introducing poly-(lactic acid) onto dextrin backbone, the porous and rough morphology of hydrogel was attained and swelling property was enhanced. This observation indicates that the presence of hydrophilic, hydrophobic segments, and crosslinker moiety in the network structure control the swelling ratio, which helps the release of the enclosed drug in more sustained way. The developed hydrogel demonstrates excellent potential as novel matrix for controlled release of ciprofloxacin as well as for controlled release of colonic drug ornidazole. The drug release from dissolution media follows first-order kinetic and non-Fickian diffusion mechanism.

ACKNOWLEDGMENTS

The first author wishes to acknowledge University Grant Commission, New Delhi, India (Ref. No.19-06/2011(i) EU-IV; Sr. No. 2061110303, Dated: 30.11.2011) for providing financial assistance Under Junior Research Fellowship (NET-UGC-JRF) Scheme. The authors earnestly acknowledge the financial support from Department of Science and Technology, New Delhi, India in form of a research grant (NO: SR/FT/CS-094/2009) to carry out the reported investigation.

REFERENCES

1. Uhrich, K. E.; Cannizzaro, S. M.; Langer, R. S.; Shakesheff, K. M. *Chem. Rev.* **1999**, *99*, 3181.
2. Qiu, X. P.; Leporatti, S.; Donath, E.; Möhwald, H. *Langmuir* **2001**, *17*, 5375.
3. Osuna, B.; Ferrero, C.; Jimenez-Castellanos, M. R. *Eur. J. Pharm. Biopharm.* **2008**, *69*, 285.
4. Sinha, V. R.; Kumria, R. *Int. J. Pharm.* **2001**, *224*, 19.
5. Cao, Y.; Gu, Y.; Ma, H.; Bai, J.; Liu, L.; Zhao, P.; He, H. *Int. J. Biol. Macromol.* **2010**, *46*, 245.
6. Wu, W.; Aiello, M.; Zhou, T.; Berliner, A.; Banerjee, P.; Zhou. S. *Biomaterials* **2010**, *31*, 3023.
7. Vandamme, T. F.; Lenourry, A.; Charrueau, C.; Chaumeil, J. C. *Carbohydr. Polym.* **2002**, *48*, 219.
8. Huang, X.; Nayak, B. R.; Lowe, T. L. *J. Polym. Sci. Part A: Polym. Chem.* **2004**, *42*, 5054.
9. Vijan, V.; Kaity, S.; Biswas, S.; Isaac, J.; Ghosh, A. *Carbohydr. Polym.* **2012**, *90*, 496.
10. Singh, B.; Sharma, N. *Carbohydr. Polym.* **2008**, *74*, 489.
11. Korsmeyer, R. W.; Peppas, N. A. *J. Membr. Sci.* **1981**, *9*, 211.
12. Strehin, I.; Nahas, Z.; Arora, K.; Nguyen, T.; Elisseeffv, J. *Biomaterials* **2010**, *31*, 2788.
13. Rasool, N.; Yasin, T.; Heng, J. Y. Y.; Akhter, Z. *Polymer* **2010**, *51*, 16873.
14. Zhao, Z. X.; Li, Z.; Xia, Q. B.; Xi, H. X.; Lin, Y. S. *Eur. Polym. J.* **2008**, *44*, 1217.
15. Meenach, S. A.; Hilt, J. Z.; Anderson, K. W. *Act. Biomater.* **2010**, *6*, 1039.
16. Kim, S. J.; Kim, H.; Park, S. J.; Kim, I. S. *Sen. Act. A: Phys.* **2004**, *115*, 146.
17. Cheauril, F. N.; Corrigan, O. I. *Int. J. Pharm.* **2009**, *366*, 21.
18. Eeckman, F.; Moes, A. J.; Amighi, K. *Eur. Polym. J.* **2004**, *40*, 873.
19. Anumolu, S. S.; Singh, Y.; Gao, D.; Stein, S.; Sinko, P. J. *J. Controlled Release* **2009**, *137*, 152.
20. MilašinovicÇ, N.; KrušicÇ, M. K.; KneževicÇ-JugovicÇ, Z.; FilipovicÇ, J. *Int. J. Pharm.* **2010**, *383*, 53.
21. Zhang, R.; Tang, M.; Bowyer, A.; Eisenthal, R.; Hubble, J. *Biomaterials* **2005**, *26*, 4677.
22. Wang, Y.; Liu, P.; Qiu, L.; Sun, Y.; Zhu, M.; Gu, L.; Di, W.; Duan, Y. *Biomaterials* **2013**, *34*, 4068.
23. González, D.; Santos, V.; Parajó, J. C. *Chem. Eng. J.* **2011**, *167*, 278.
24. Cai, X.; Tong, H.; Shen, X.; Chen, W.; Yan, J.; Hu, J. *Act. Biomat.* **2009**, *5*, 2693.
25. Onyari, M. J.; Huang, S. J. *J. Appl. Polym. Sci.* **2009**, *113*, 2053.
26. Dev, A.; Binulal, N. S.; Anitha, A.; Nair, S. V.; Furuike, T.; Tamura, H.; Jayakumar, R. *Carbohydr. Polym.* **2010**, *80*, 833.
27. Yang, X.; Liu, L. *J. Appl. Polym. Sci.* **2009**, *112*, 3209.
28. Lee, W. F.; Cheng, T. S. *J. Appl. Polym. Sci.* **2013**, *128*, 230.
29. Omodian, H.; Hashemi, S. A.; Sammes, P. G.; Meldrum, I. *Polymers* **1998**, *39*, 6697.
30. Anirudan, T. S.; Sandeep, S.; Divya, P. L. *RSC Adv.* **2012**, *2*, 9555.
31. Singh, B.; Sharma, N.; Chauhan, N. *Carbohydr. Polym.* **2007**, *69*, 631.
32. Vaghani, S. S.; Patel, M. M.; Satish, C. S. *Carbohydr. Res.* **2012**, *347*, 76.
33. Prabaharan, M.; Gong, S. *Carbohydr. Polym.* **2008**, *73*, 117.
34. Donbrow, M.; Samuelov, Y. *J. Pharm. Pharmacol.* **1980**, *32*, 463.
35. Gibaldi, M.; Feldman, S. *J. Pharm. Sci.* **1967**, *56*, 1238.

36. Kiortsis, S.; Kachrimanis, K.; Broussali, T.; Malamataris, S. *Eur. J. Pharm. Biopharm.* **2005**, *59*, 73.

37. Peppas, N. A. *Pharm. Acta. Helv.* **1985**, *60*, 110.

38. Korsemeyer, R. W.; Gurny, R.; Doelker, E.; Buri, P.; Peppas, N. A. *Int. J. Pharm.* **1983**, *15*, 25.

39. Higuchi, T. *J. Pharm. Sci.* **1961**, *50*, 874.

40. Hixson, A. W.; Crowell, J. H. *Ind. Eng. Chem.* **1931**, *23*, 923.

41. Kopcha, M.; Lordi, N. G.; Toja, K. J. *J. Pharm. Pharmacol.* **1991**, *43*, 382.