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Drug Release Behavior of Polyurethane/Clay Nanocomposite: Film vs. Nanofibrous Web

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ABSTRACT: In the present study, polyurethane/clay nanocomposite films have been prepared by solvent casting method. Antiseptic drug chlorhexidine acetate was intercalated into montmorillonite clay and then incorporated into the polyurethane film. For comparison, the drug was also added directly into the polymeric dope used for film casting. In addition to that, nanofibrous web containing neat drug and drug loaded clay were fabricated using electrospinning technique. The emphasis of the study was on investigating the effect of drug intercalated into nanoclay vis-à-vis direct drug loading in the polymer on the drug release behaviour of polyurethane nanocomposite films as well as nanofibrous webs. The effect of morphology (film vs. nanofibrous web) on the drug release kinetics has also been discussed. It is observed that the nanoclay is acting as a sustained release carrier of drug, and nanofibrous web exhibits higher drug release rate as compared to the film. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40824.

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INTRODUCTION

Chlorhexidine Acetate (CA), a bisdiguanide antiseptic, is effective as a bacteriostatic as well as bactericidal agent.[1,2] This cationic antiseptic has applications ranging from common disinfectant to bactericidal agent used in dentistry.[3] Chlorhexidine containing formulations are used for urinary or central venous catheter impregnation, pharmaceutical, and cosmetic industry due to its high killing rate of bacteria and fungi and nontoxicity towards the mammalian cells.[4] The mechanism responsible for the antibacterial activity of CA is the presence of two symmetrically positioned chlorophenyl guanide groups which can penetrate through the bacterial cell wall and irreversibly disrupt the cell membrane.[5] As a result of this, the microorganisms gradually die. However, for conventional topical applications, usage of Chlorhexidine formulations is restricted due to its uncontrolled release nature.[4] In addition to that, repeated application of this antibacterial agent can lead to patient discomfort. These potential adverse effects of Chlorhexidine has been overcome by using various novel drug delivery systems based on microspherical chitosan,[6] cyclodextrin,[7,8] poly (ε-caprolactone) nanocapsules,[9] ethylene vinyl acetate copolymer,[10,11] porous methacrylate based drug delivery systems, and vinyl ether-based thermosensitive hydrogel as reported in the literature.[12–14]

Montmorillonite (Mt) is one of the most commonly used smectite clay mineral in which the interlayer spacing is occupied by various exchangeable cations such as Na^+, K^+, Ca^{2+}, and Mg^{2+} which explain its high cation exchange (70–120 mequiv./100 g) capacity (CEC). It has large specific surface area and colloidal properties, good absorbability, adhesive ability, and drug-carrying capability. Unique crystalline structure of Mt clay allows expanding and contracting the interlayer spacing via substitution with various organic and inorganic cationic species including drug moieties to form the intercalation composites.[15] This clay based intercalates also has the ability of attracting and decimating the bacteria. Additionally, this drug intercalated clay mineral can be used for long-term activity such as wound healing, controlled drug delivery, and infection related diseases and therefore has attracted attention of researchers worldwide.[16,17]

Medical grade thermoplastic polyurethane chosen for this study has desirable properties such as biocompatibility, sterilizability, chemical resistance, excellent tear and wear resistance, high strength, and elastic memory and also provides patient comfort.[18] Due to these advantages, this synthetic polymer finds application as a biomaterial in the area of feeding tube, venous catheters, vascular graft, long term implants such as pacemakers, mammary prostheses, and drug delivery systems.[19]

Literature is available on the release profile of films as drug delivery system, where the neat drug is loaded in film; examples include chlorhexidine release from poly (ε-caprolactone) and polyurethane film systems,[4,20] lidocaine hydrochloride from

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

Table I. Composition of Various TPU Film Samples

Film sample abbreviation	Composition
TPU – 1% CA	10% TPU film containing 1% (w/w) CA drug wrt the dry weight of TPU polymer
TPU – 5% CA	10% TPU film containing 5% (w/w) CA drug wrt the dry weight of TPU polymer
TPU – 1% CAMt[a]	10% TPU film containing 1% (w/w) CAMt wrt the dry weight of TPU polymer
TPU – 5% CAMt[a]	10% TPU film containing 5% (w/w) CAMt wrt the dry weight of TPU polymer

[a] In 1% and 5% TPU – CAMt film sample, the amount of CAMt is taken such that the drug concentration, i.e., CA is kept 1% and 5% (w/w), respectively, with respect to 10% dry weight of TPU polymer in the dope.

polyvinyl alcohol,[21] propranolol hydrochloride release from polymeric film containing ethyl cellulose and poly (vinyl pyrrolidone),[22] release of rifampin, and amoxicillin antibiotics adsorbed on polyurethane films.[23]

Drug delivery application via electrospun nanofibers has gained attention of researchers recently due to possibility of delivering large and controlled doses of therapeutic agents at the action site via high surface area to volume ratio and high porosity and flexibility of the light weight nanofibrous system as compared to conventional drug delivery systems. In literature, polyurethane nanofibrous webs find application in drug delivery with various drugs in neat form such as ketoprofen (non-steroidal anti-inflammatory drug),[19] itraconazole (antifungal drug),[24] ketanserin (acute renal failure drug), and tetracycline hydrochloride (antibiotic).[25] In all these cases, the drug has directly been incorporated into the polyurethane nanofiber during the electrospinning stage. But till now no literature is available about drug delivery through polymeric nanocomposite based film or nanofibrous webs where nanoclay is used as a drug carrier.

In the present study, Mt nanoclay intercalated with CA drug (CAMt) via ion exchange route was used in addition to the neat Chlorhexidine acetate (CA) drug, for the preparation of thermoplastic polyurethane/clay nanocomposite films by solvent casting and nanofibrous webs by electrospinning. The synthesis of CAMt drug and its characterization is discussed in detail in our earlier paper.[26] Morphology of the electrospun nanofibers as well as film samples was studied by scanning electron microscopy (SEM). Dispersion of drug loaded clay in polyurethane matrix has been analyzed by X-ray diffraction and presented in the supporting information. Antimicrobial activity of nanofibrous web samples has been reported in detail in our previous paper.[27] Antimicrobial activity of the solvent cast film containing neat drug and drug loaded clay was determined against both gram positive and gram negative bacteria. In the present study, in vitro release profile of the cast film in phosphate buffer saline (pH 7.4) media at 37°C was investigated and compared with that of electrospun nanofibrous sample to study the effect of morphology (film vs. nanofibre) and presence of clay mineral on drug release kinetics.

EXPERIMENTAL

Materials

Chlorhexidine acetate (CA; white powder; M.W. 625.55; M.P. 156°C; Solubility: 1.49 mg/mL of water at 25°C) was obtained from Sigma–Aldrich Company Ltd. (Dorset, UK) and used as received.

Aromatic polyether-based Thermoplastic polyurethane (TEXIN® RxT85A) (M_w: 540,615 Da; measured by GPC using Polystyrene standard) was procured from Bayer Material Science LLC, Pittsburgh, PA. Sodium montmorillonite (NaMt) clay with cation exchange capacity (CEC) of 1.20 mequiv./g was procured from Southern Clay Products, Inc. (Japan) and used without further treatment.

Sodium chloride (NaCl), potassium chloride (KCl), disodium hydrogen phosphate (Na_2HPO_4), potassium dihydrogen phosphate (KH_2P0_4), and dimethyl formamide (DMF) was purchased from MERCK, India.

Preparation of Polymer Dope

Thermoplastic polyurethane chips were dried at 70°C overnight under vacuum to remove all moisture and stored in a desiccator till further use. Neat thermoplastic polyurethane solution was prepared by dissolving polymer chips in dimethyl formamide (DMF) using magnetic hot plate with stirrer (Make: Schott Instruments, Germany) at 70°C and 250 rpm to obtain a clear solution of 10% (w/w) TPU.

Pure Chlorhexidine acetate and drug loaded clay, i.e., CAMt in concentration of 1% and 5% (w/w) of 10% dry weight of TPU was loaded into polymer dope. In 1% and 5% CAMt, the amount of drug loaded clay is taken such that the drug concentration, i.e., CA is kept 1% and 5% (w/w), respectively, with respect to the dry weight of polymer. The preparation method of polymeric solution for the fabrication of film was similar to that one used for nanofibrous web.[27]

Preparation of Electrospun Nanofibrous Web

Electrospinning was carried out on Nanomate electrospinning machine (Model: Nanomate IP 607) designed and fabricated indigenously by M/s Thukral Services Pvt. Ltd. Hyderabad, India. During electrospinning syringe with 12.45 mm diameter and blunt end metal needle (Gauge-25) on a horizontal setup was used. Various parameters were standardized to prepare monolithic nanofibers from polymeric solution. During the electrospinning process, temperature and relative humidity were maintained in the range of 22–25°C and 46–50%, respectively.

After a series of standardization experiments, optimized process parameters for electrospinning were obtained as follows: applied voltage in the range of 15 kV (for neat TPU and CA loaded TPU), 20 kV (for CAMt loaded TPU), feed rate was kept constant at 5 μL/min and tip to collector distance also kept constant at 10 cm for all the samples.[27] The electrospun fibers were

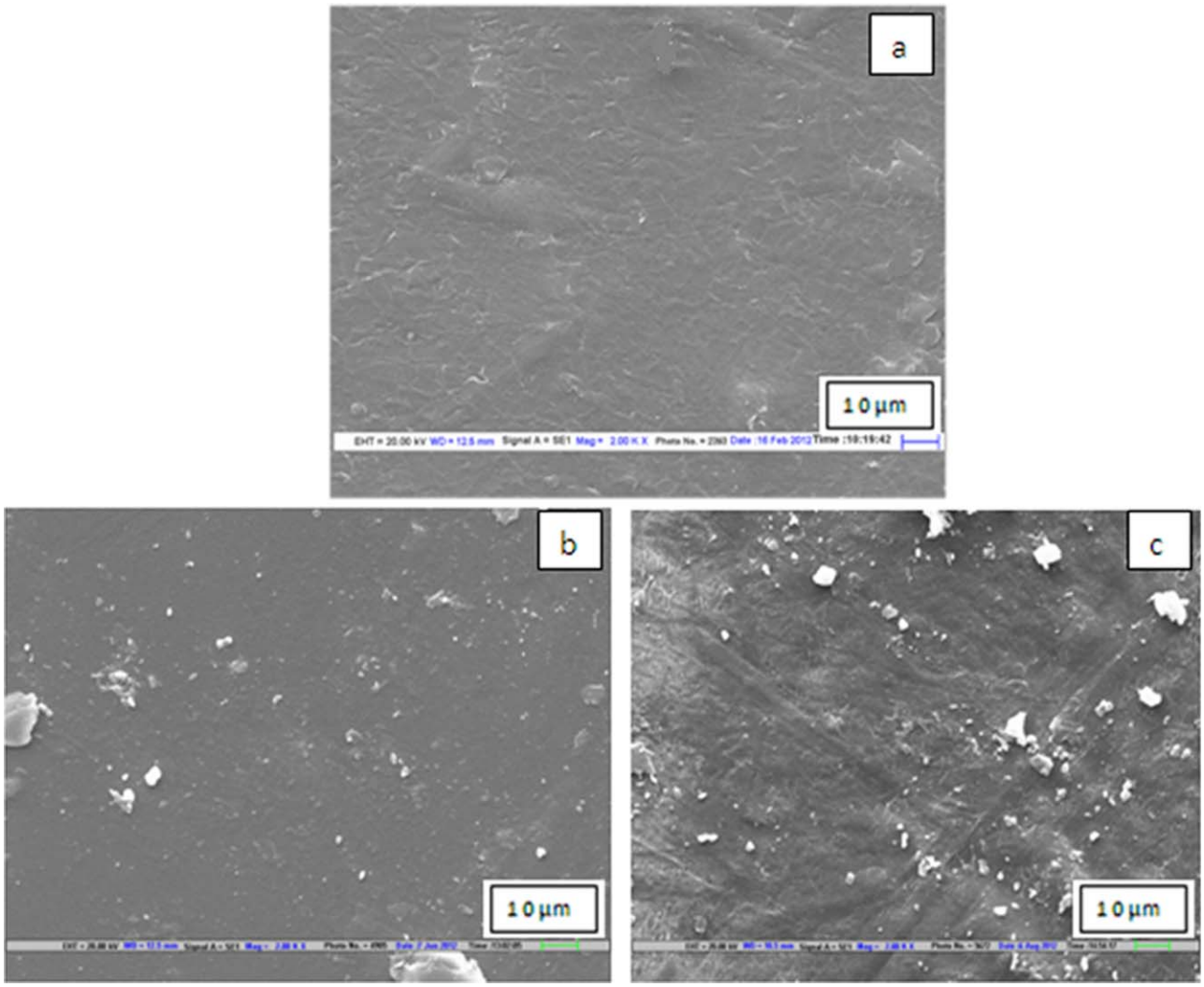

Figure 1. SEM images of (a) neat TPU film and TPU film containing (b) 5% CA and (c) 5% CAMt. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

collected onto a flat plate collector and dried overnight in a vacuum chamber at room temperature to evaporate the residual solvent from the nanofibers and stored at 4°C.

Preparation of Cast Film

Films were prepared by solvent evaporation method using dimethyl formamide as the casting solvent. Films were cast into glass petridishes and the bulk solvent was evaporated at 100°C for 4 h. Further, vacuum was applied overnight for completion of drying. Film samples were stored in a desiccator using silica gel at 4°C until required for the characterization study. Table I shows the composition of individual formulations. Film sample thickness was measured in five different positions by using Essdiel digital thickness gauze (Manufacturer: Shirley, UK). Film thickness varied in the range of 70–90 micron.

SEM Analysis

Surface morphology of the nanofibers and film was studied by Scanning Electron Microscopy (Model: ZEISS EVO 50) at an accelerating voltage of 20 kV. Samples were coated with gold prior to the SEM investigation. SEM photograph was analyzed by ImageJ Software to determine the average diameter of the deposited nanofibers onto the flat plate collector. The change of surface morphology of the neat TPU film and TPU nanocomposite film was also observed.

Antibacterial Activity: Disc Diffusion Test

Antibacterial activity of the film samples were tested against both gram positive (*Staphylococcus aureus*) and gram negative (*Escherichia coli*) bacteria by the Disc diffusion test (AATCC 90). Twenty milligrams of film sample was placed in UV chamber for 30 min for sterilization. Nutrient agar solution was made by suspending 20 g of Luria Broth in 1000 mL of DI water and 15 g of agar-agar was also added in the solution as a solidifying agent. After sterilization, about 25–30 mL of nutrient agar solution was uniformly spread on Petridishes. Ten microliters of bacterial solution was evenly spread over the nutrient agar solution. *S. aureus* and *E. coli* concentrations of around 1.2×10^6 and 1.5×10^6 CFU/mL, respectively, were used for these experiments. Sterilized samples were then placed onto the nutrient agar plate. The agar plates were kept for incubation at 37°C for 24 h.

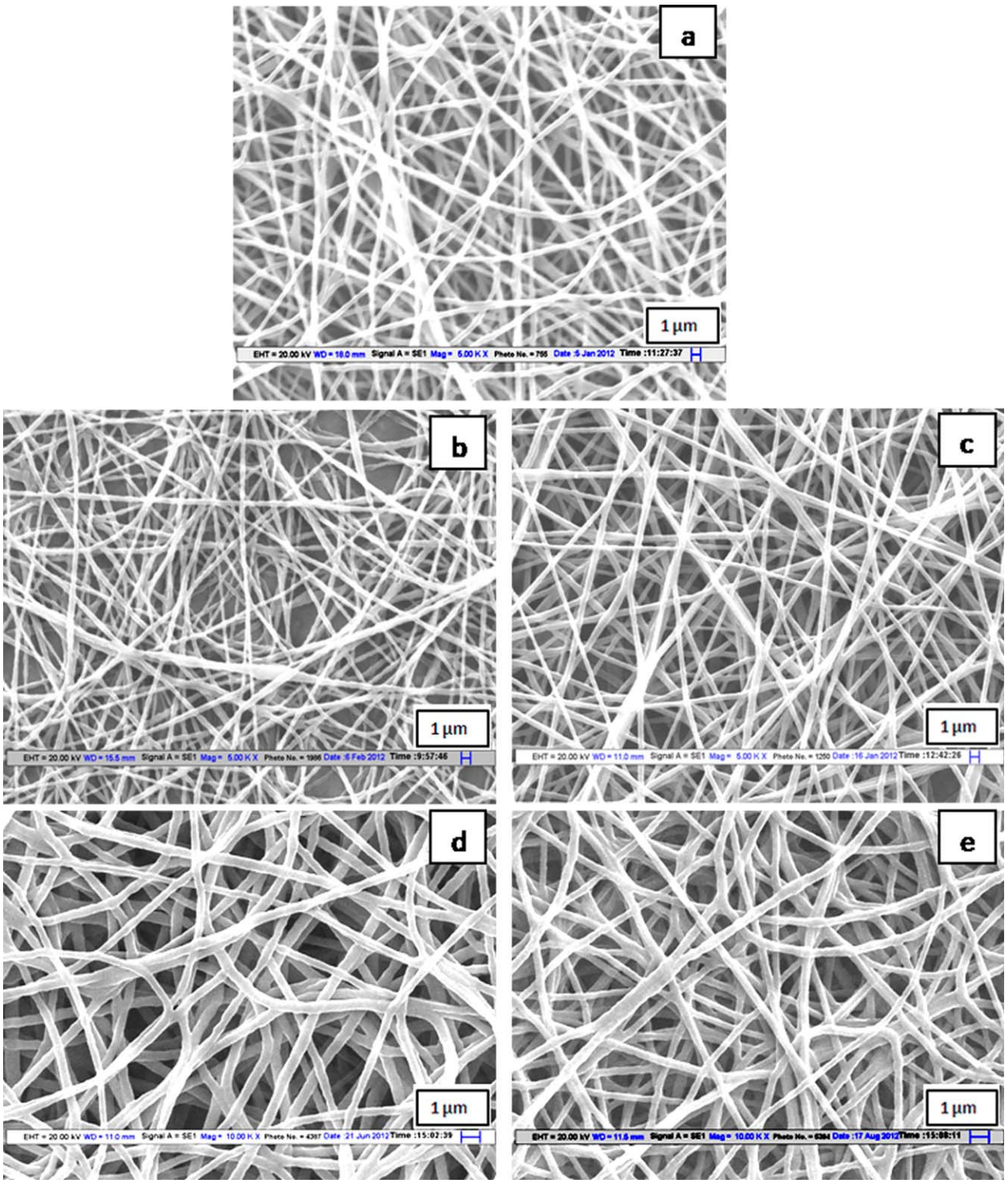

Figure 2. SEM images of (a) neat TPU nanofibrous web, TPU nanofibrous web containing; (b) 5% CA; (c) 5% CAMt with magnification 5000×; and nanofibrous web containing (d) 5% CA (e) 5% CAMt with magnification 10,000×. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

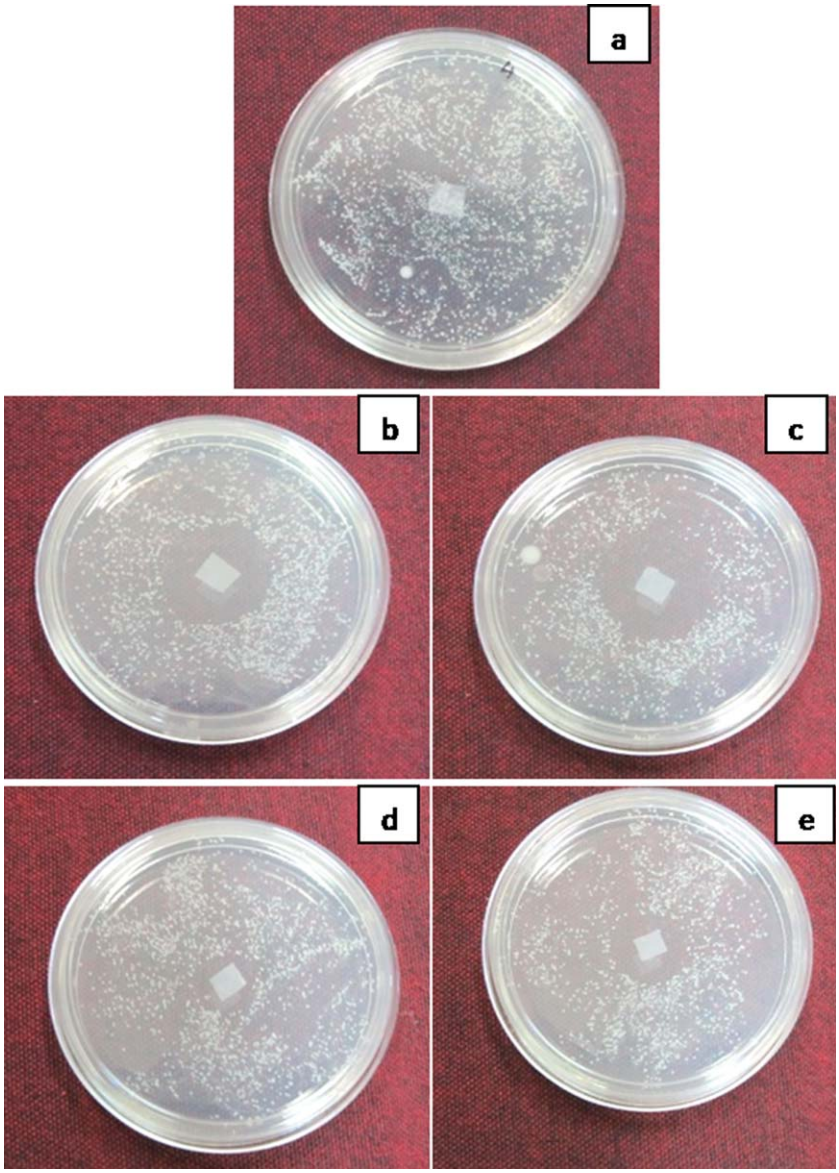

Figure 3. Photographs showing zone of inhibition of (a) neat TPU and TPU film containing (b) 1% CA, (c) 5% CA, (d) 1% CAMt, and (e) 5% CAMt against *S. aureus*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The zone of inhibition was measured after 24 h incubation period.

In Vitro Drug Release Study

Phosphate buffer saline (PBS) solution was chosen as a medium for drug release study. Preparation of PBS media is reported in our previous publication.[27]

Drug release behavior of TPU-CA and TPU-CAMt (1% & 5%) solvent cast films were studied in PBS solution of pH 7.4. About 10 mg of each film sample was taken (dimensions of the film samples remain in the range of 1 × 1 cm–1.25 × 1.25 cm by maintaining same weight for all the samples) and put in different conical flasks containing 10 mL of buffer solution which were then tightly capped and placed in an incubation chamber at 37 ± 0.1°C with stirring at 200 rpm. About 2 mL of the solution was taken at specific time intervals and the corresponding absorbance value was determined using UV spectrophotometer (Perkin Elmer Lambda 25) at $\lambda_{max} = 254$ nm, which is the characteristic peak of Chlorhexidine acetate drug. After completion of the measurement, the solution was poured back into the conical flask to maintain a constant volume. The cumulative drug concentration was calculated from the calibration curve of the model drug prepared by using CA solutions of known concentrations in PBS solution (pH 7.4). Tests were performed in triplicate and the results were recorded as an average for further analysis. Drug release profile of film samples were further compared with the nanofibrous web samples to evaluate the effect of morphology (film vs. nanofiber) and effect of clay mineral on the release kinetics.

RESULTS AND DISCUSSION

SEM Analysis

Morphology of Films. Figure 1 shows SEM images of neat TPU film and TPU film containing 5% CA and CAMt. In the

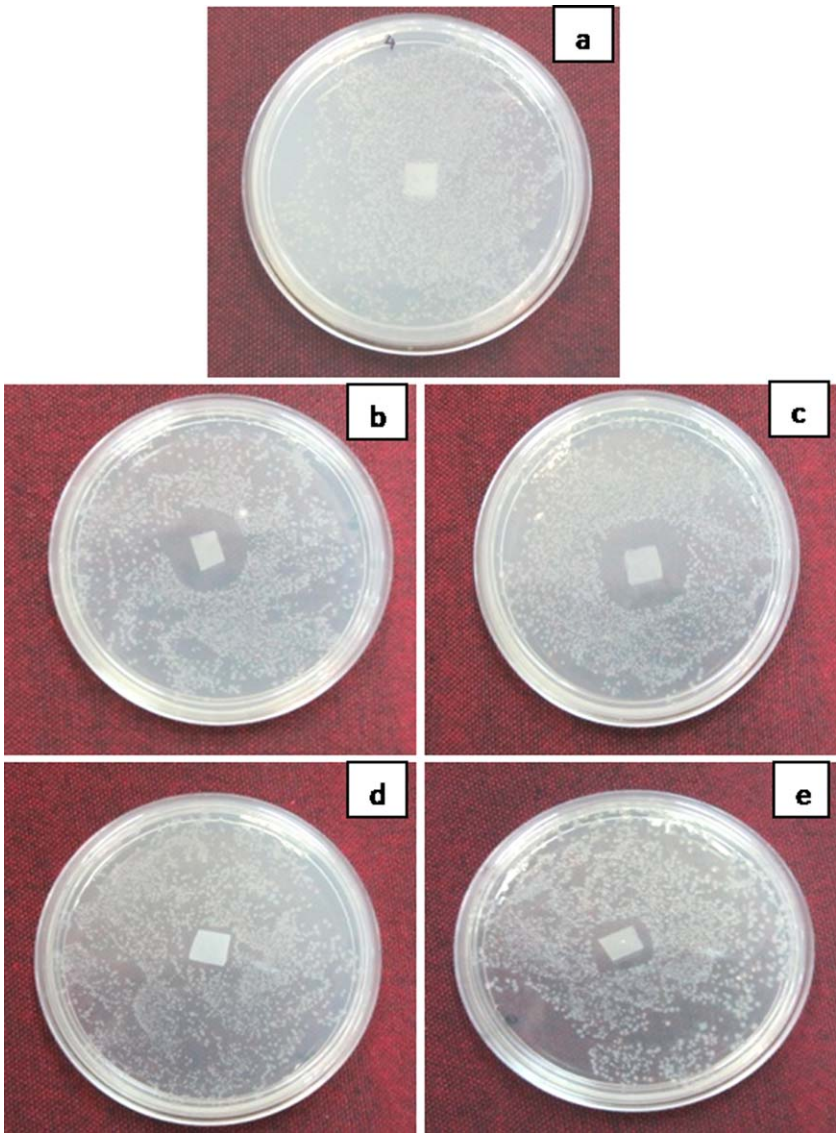

Figure 4. Photograph showing zone of inhibition of (a) neat TPU and TPU film containing (b) 1% CA, (c) 5% CA, (d) 1% CAMt, and (e) 5% CAMt against *E. coli*. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

presence of CA and CAMt, drug and clay agglomerates are found to move towards the surface and responsible for exhibiting both antimicrobial activity and drug release behavior.

Morphology of Nanofibers. Figure 2 shows selected SEM images of as-spun TPU nanofibers. Clearly, round cross-section nanofibers with smooth surfaces were obtained. For neat TPU, average diameter of nanofibers is around 410 ± 30 nm. However for drug loaded TPU (CA; 1% and 5%) nanofibers, average diameters are ranging in between 350 and 370 nm. On the other hand, SEM image analysis using ImageJ Software of TPU nanofibers containing drug loaded clay (CAMt; 1% and 5%) shown that the average diameter of the nanofibers are ranging in between 325 and 375 nm.

Antibacterial Activity: Disc Diffusion Test. The disc diffusion test results of various film samples are shown in Figures 3 and 4. Neat TPU showed no zone of inhibition for *S. aureus* and *E. coli*, reflecting no antibacterial activity [Figures 3(a) and 4(a)]. However, pure CA drug and CAMt loaded (1% and 5%) film samples show a very distinct zone of inhibition around the test specimen. The results are tabulated in Table II.

These results indicate that both CA and CAMt loaded film samples have antibacterial activity against both Gram positive and Gram negative bacteria. However, pure drug (CA) loaded samples show a larger zone of inhibition compared to CAMt loaded film samples. This is due to higher diffusion rate of pure drug into the agar as compared to CAMt in which drug is immobilized due to intercalation inside the clay interlayer gallery.

From Table II, it is also seen that on increasing concentration of CA and CAMt in the film samples, the zone of inhibition increases. The responsible mechanism for exhibiting the zone of inhibition in film sample is the bisdiguanide antiseptic which is able to disrupt the bacterial cell wall and as a result leakage of

Table II. Inhibition Zone of TPU Film as well as Nanofibrous Web Containing CA and CAMt Against *S. aureus* and *E. coli* Bacteria

	Zone of inhibition (in mm)			
	Film		Nanoweb	
	S. aureus	*E. coli*	*S. aureus*	*E. coli*
Neat TPU	Absent	Absent	Absent	Absent
TPU – 1% CA	22	18	33	32
TPU – 5% CA	25	22	37	35
TPU – 1% CAMt	15	13	25	23
TPU – 5% CAMt	19	15	28	28

intercellular component occurs. Finally, the microorganisms die and a very clear zone of inhibition is obtained.

From the table, it is also obvious that nanoweb samples exhibit larger zone of inhibition compared to film samples for both CA drug as well as CAMt loaded samples. This is due to large surface area and high porosity of the nanofibrous webs as compared to the film. The disc diffusion test results are in agreement with in vitro drug release studies discussed in detail in the following section.

In Vitro Drug Release Study: Film vs. Nanofibrous Web

The cumulative amount of drug released (reported as the percentage of the actual amount of drug present in the drug loaded samples) from the pure drug and CAMt nanocomposite loaded film samples in phosphate buffer saline media of pH 7.4 at 37°C is shown in Figures 5 and 6.

From Figure 5, it is obvious that the CA drug from the film sample is continuously released for over 195 h. A higher concentration of CA drug release, i.e., 22% and 29% from the 1% and 5% CA drug loaded film samples were observed in the first 25 h followed by a gradual release thereafter. Based on the release profile at pH 7.4, a maximum release of 80% of pure drug was observed in case of 5% drug loaded film sample whereas only 44% release was attained for 1% drug loaded film. The amount of drug released increases monotonically with increase in initial drug loading from 1% to 5% in TPU film. But 100% drug de-intercalation was never attained as per the principles of ion exchange equilibrium reaction.

On the other hand, in case of CAMt loaded TPU film the drug starts releasing after a time lag, i.e., it take 3 h for initial drug release as seen in Figure 6. This kind of sustained release occurs due to the presence of bulky and immobilized drug cation into the clay interlayer spacing which cannot be exchanged easily with the small Na^+, K^+ cationic species present in the buffer media. Only 16% and 20% of drug release occurred during the initial 25 h from 1% and 5% CAMt loaded film samples, respectively. After that, the drug release rate diminishes for next 196 h in comparison to the neat drug. The maximum release of drug from 1% and 5% CAMt was observed in the range of 28% and 51% respectively, as compared to 44% and 80% in case of 1% and 5% neat CA incorporated into the film sample.

The cumulative amount of drug released from neat CA and CAMt loaded nanofibrous webs in PBS media at pH 7.4 and 37°C is shown in Figure 7. In case of neat drug loaded nanofibrous web samples, burst release was observed for initial 5 h followed by a slower release pattern for about 4 days. In that

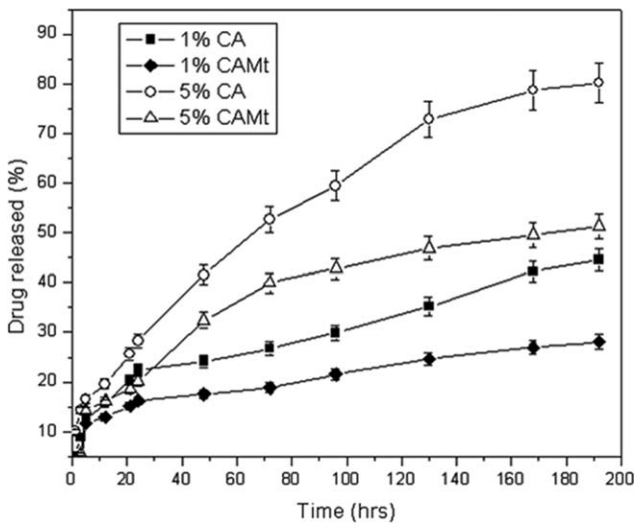

Figure 5. Release profile of CA and CAMt loaded film samples in PBS media at 37°C.

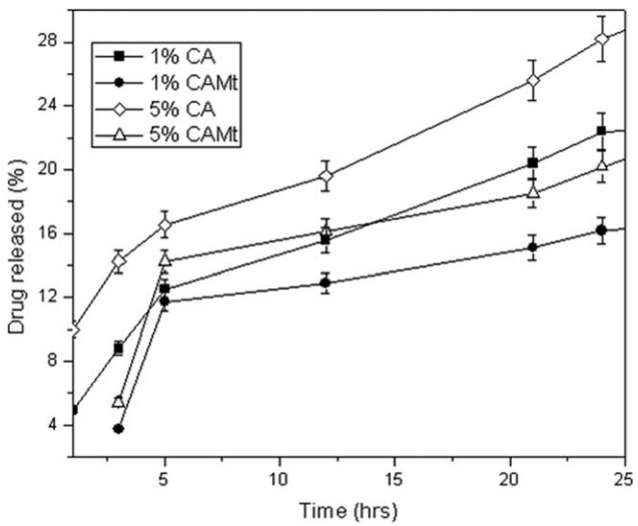

Figure 6. Release profile of CA and CAMt film samples in PBS media for initial 25 h.

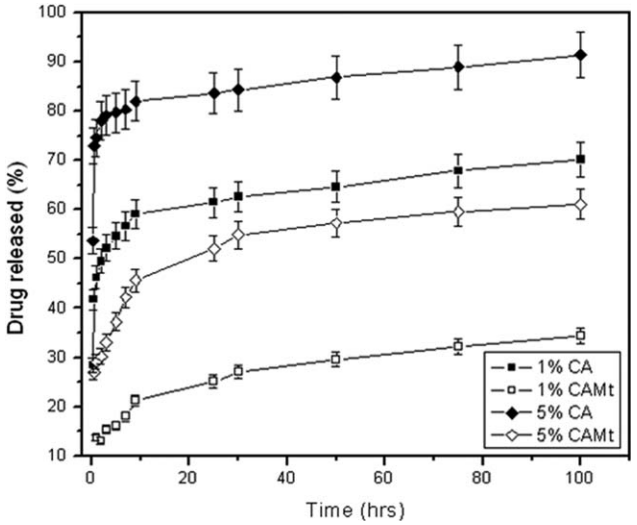

Figure 7. Release profile of neat CA and CAMt nanofibrous webs in PBS media at 37°C.

case, 70% and 91% drug was released from 1% and 5% drug loaded nanofibrous samples after about 100 h, respectively. Comparatively only 44% and 80% drug was released for film samples even after 196 h. Both film and web samples exhibit first order release kinetics where the drug release rate is proportional to drug concentration with initial burst release associated only with nanofibrous samples.

Similarly in case of CAMt loaded nanofibrous web, drug starts releasing from the clay intergallery in the range of 30–60 min. However, the drug starts releasing after 3 h from CAMt loaded TPU film. The maximum release of drug from 1% and 5% CAMt loaded nanofibrous was observed in the range of 35% and 61%, respectively, as compared to 28% and 51% (Figure 8) for 1% and 5% CAMt loaded film, respectively.

Therefore, it can be concluded that morphology has a significant influence on drug release behaviour. Nanofibrous web sample exhibits higher drug release rate as compared to the film sample as shown from the release profile. In addition to that, burst release was associated only in case of nanofibrous samples. These results can be explained due to large surface area to volume ratio of electrospun fibers, porosity of the electrospun webs, and high flexibility of the light weight nanofibrous system as compared to conventional drug delivery through film form.

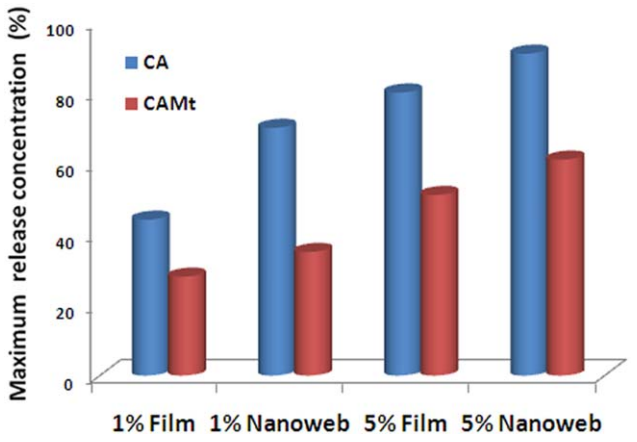

Figure 8. Bar diagram depicting maximum drug release concentration of film and nanofibrous webs in PBS media. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

The effect of drug immobilization in the clay intergallery also has a significant impact on the drug release profile as compared to neat drug and the effect is prominent in case of nanofibrous sample. Neat drug loaded nanofibrous web exhibits burst release followed by first order kinetics whereas nanofibrous nonwoven web containing drug loaded clay follows zero order kinetics with sustained release characteristics.

Additionally, film sample containing drug intercalated clay also has a remarkable effect in terms of release behaviour. Pure drug loaded film exhibits first order release kinetics. This kind of release kinetics is advantageous where long term action is necessary, such as infection related diseases prevention and control. However, TPU film sample containing drug loaded clay exhibits sustained zero order release characteristics. For a drug delivery carrier, this kind of release kinetics is beneficial for non-infected wound healing application. In conclusion, both kinds of drug release follow the Fickian diffusion mechanism but it transforms from first to zero order after drug intercalation into the clay interlayer spacing.

CONCLUSION

Film as well as nanofibrous web form of thermoplastic polyurethane containing neat drug (CA) and drug loaded clay (CAMt) were prepared and evaluated for drug release kinetics. SEM analysis of electrospun nanofibrous web shows smooth, uniform, and beadless nanofiber formation at optimized process conditions whereas film sample shows drug and drug loaded clay agglomerates on the film surface which accounts for the presence of antimicrobial activity against both gram positive and gram negative bacteria.

The drug release profile of film as well as nanofibrous sample containing pure drug into PBS media indicates first order kinetics whereas intercalated species exhibited zero order release kinetics. Moreover, nanofibrous forms exhibited higher drug release due to larger surface area as compared to the film sample. In addition to that, burst release was associated only with electrospun web samples.

Overall drug release rate depends upon initial drug loading concentration, immobilization of drug onto the clay interlayer spacing and also on the morphological form of the polymer (film vs. nanofibrous web) which acts as a vehicle for drug delivery. The potential application for these TPU-CA and TPU-CAMt film samples can range from infection control to wound healing in which long-term action is necessary whereas nanofibrous web samples are useful for both topical drug delivery and infected wound treatment where immediate action as well as sustained activity is the prime consideration.

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