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RESEARCH ARTICLE

Synthesis of cellulose acetate nanofibers and its application in the release of some drugs

Fatemeh Mehrabi[1,2]*; Tayebeh Shamspur[1]*; Ali Mostafavi[1]; Asma Saljooqi[1,2]; Fariba Fathirad[1,2]

[1]*Department of Chemistry, Shahid Bahonar University of Kerman, Kerman, Iran*

[2]*Young Research Societies, Shahid Bahonar University of Kerman, Kerman, Iran*

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ABSTRACT

Objective(s): The purpose of this study was to compare novel sandwich-structured nanofibrous membranes, and coaxial and usual methods, to provide sustained-release delivery of morphine for drug delivery. In this work, synthesis of nanofibrous cellulose acetate (NFC) was carried out by electrospinning.

Methods: A weighed amount of cellulose acetate (CA) powder was dissolved in 3:1 v/v acetone/dimethylformamide (DMF) to obtain a CA solution at a concentration of 8 to16% w/v. Acetaminophen or morphine-loaded CA solutions were prepared by dissolving CA powder and Acetaminophen (A) or morphine in the weight ratio of 5:1, in an acetone/DMF mixture. Under optimum condition, they were electrospun into sandwich structured membranes with the coaxial method and cellulose acetate as the surface layer and cellulose acetate/drugs as the core.

Results: Characterization of the radius of fiber is shown as 52.9 ± 0.1nm with scanning electron microscopy (SEM). The full range drug release profiles of nanofibers are shown as 80.7% of the contained drug in 8h. The drug release from nanofiber was controlled through a typical Fickian diffusion mechanism from the cellulose acetate matrix by a release exponent value of 0.24 for conventional nanofiber, 0.35 for coaxial nanofiber and 0.40 (less than 0.45) for sandwich nanofibers.

Conclusions: All the cellulose acetate nanofibers showed that they could release large amounts of drugs in vitro for more than one day. However, among these three methods, the best one is a sandwich method because its release is slower than that of the other methods.

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INTRODUCTION

The release of drugs such as acetaminophen and morphine by conventional means, such as taking a tablet or injection every eight hours, results in constantly changing systemic drug concentrations in the blood stream. This often produces a sharp initial increase in drug concentration to a level above the therapeutic range and is followed by a fast decrease in drug concentration below the therapeutic range [1]. Drug delivery systems (DDS) with controlled release, attempt to maintain drug concentrations in the therapeutic level over a specified period. Thus, they offer several advantages over immediate release systems, including precise control of dose, decreased number of dosages, reduction in harmful side effects, and improvement in patient compliance and convenience [2]. Nanotechnology can provide superior drug delivery systems for better management and treatment of diseases. The nanostructures employed as drug delivery systems have many advantages which make them superior to conventional delivery systems. The aim of this

* Corresponding Author Email: *shamspur@gmail.com*
f_mehrabi2010@yahoo.com

study was to produce systems based on NFC as matrix maker that would sustain release of a drug for a long period of time (for example, up to 24 h) and longer than when nanofibrous cellulose acetate (NFC) biodegradable polymers are used for DDS [3].

Drug-loaded nanofibers can be prepared by co-dissolving solutions of active pharmaceutical ingredients and the host polymer by traditional single-fluid electrospinning [4,5].

For these nanofibers, the initial burst effect is inevitable because of the large nanofiber surfaces, drug distribution on the nanofiber surfaces, and possibly, the amorphous status of the linear drug release membrane prepared by a modified coaxial electrospinning process and sandwich method.

Cellulose and its derivatives like cellulose acetate (CA) have a long history in pharmaceutical technology, mainly as excipients in oral solid dosage forms. In higher plants, cellulose is organized in morphologically complex, hierarchical structures consisting of β(4$_{\leftarrow}$1) D-glucopyranose chains. These are laterally bound by hydrogen bonds to form microfibrils with a diameter in the nanoscale, which are further organized in microfibril bundles [6]. Furthermore, cellulose molecules are intimately associated with other polysaccharides (hemicelluloses) and lignin in plant cell walls, resulting in even more complex morphologies [7]. The cellulose nanoscale fibers can be released from the highly ordered structure by a mechanical process combined with enzymatic pretreatment [8]. The resulting material named nanofibrillar cellulose, nanocellulose, cellulose nanofibers or microfibrillated cellulose has recently found applications in various areas [9,10] including biomedical and pharmaceutical applications [11-14]. NFC has been successfully used for immobilization of drug nanoparticles in suspension as well as stabilization of emulsion systems [14,15].

Cellulose fibers on the nanoscale are usually prepared in four different ways: (1) bacterial cellulose nanofibers, (2) cellulose nanofibers by electrospinning, (3) microfibrillated cellulose plant cell fibers and (4) nanorods or cellulose whiskers. However, electrospinning is easier than the others and preferred in the industry [16].

Electrospinning is an attractive process for fabricating ultrafine fibers with average diameters in sub-micrometer down to nanometer range. These fibers show several attractive characteristics, for example, they have a high surface area to mass or volume ratio, a small inter-fibrous pore size with high porosity and vast possibilities for surface functionalization. These advantages make electrospun polymeric fibers good candidates for a wide variety of applications, including filters [17], composite reinforcements [18], drug carriers [18-21] and tissue-engineered scaffolds [22-24]. A method for preparing twisted ultrafine fiber from electrospun fiber mat has also been introduced lately [25]. A focal point of research over the years has been the choice of solvent system for electrospinning CA fibers. The selection of suitable solvents has been conventionally based on trial and error, results from similar systems or solubility models limited by a physicochemical database [26]. Tungprapa et al. [27] reported the effect of various single and mixed solvent systems on the morphology and fiber diameter. The individual solvent systems are made up of chloroform, N, N-dimethylformamide (DMF), acetone, formic acid, dichloromethane (DCM), methanol (MeOH) and pyridine. Chloroform-MeOH, acetone-dimethylacetamide (DMAc) and DCM-MeOH were amongst the mixed solvent systems. The shear viscosity, surface tension, and conductivity of these solvent systems have been evaluated to be critical solution parameters in generating bead free or beaded fibers. The ternary solvent system of acetone/DMF/trifluoro-ethanol has also been evaluated for electrospinning cellulose acetate [28]. The current work describes the preparation and characterization of NFC material and evaluates the ability of drugs such as acetaminophen and morphine in solution, to diffuse through NFC. For this purpose, UV spectroscopy was used to determine and analyze the amount of drug in bulk. The effect of pH on the various in vitro environments (different points of the body) was investigated to determine the mechanism of release of drugs.

MATERIALS AND METHODS

Cellulose acetate (CA; white powder; Mw= 30,000 Da; acetyl content=39.7 wt%), acetone, N,N-dimethylformamid (DMF), Na_2HPO_4, NaH_2PO_4, Na_2CO_3, HCl, KCl and $KHCO_3$ were purchased from Aldrich (Germany). Acetaminophen and morphine were purchased

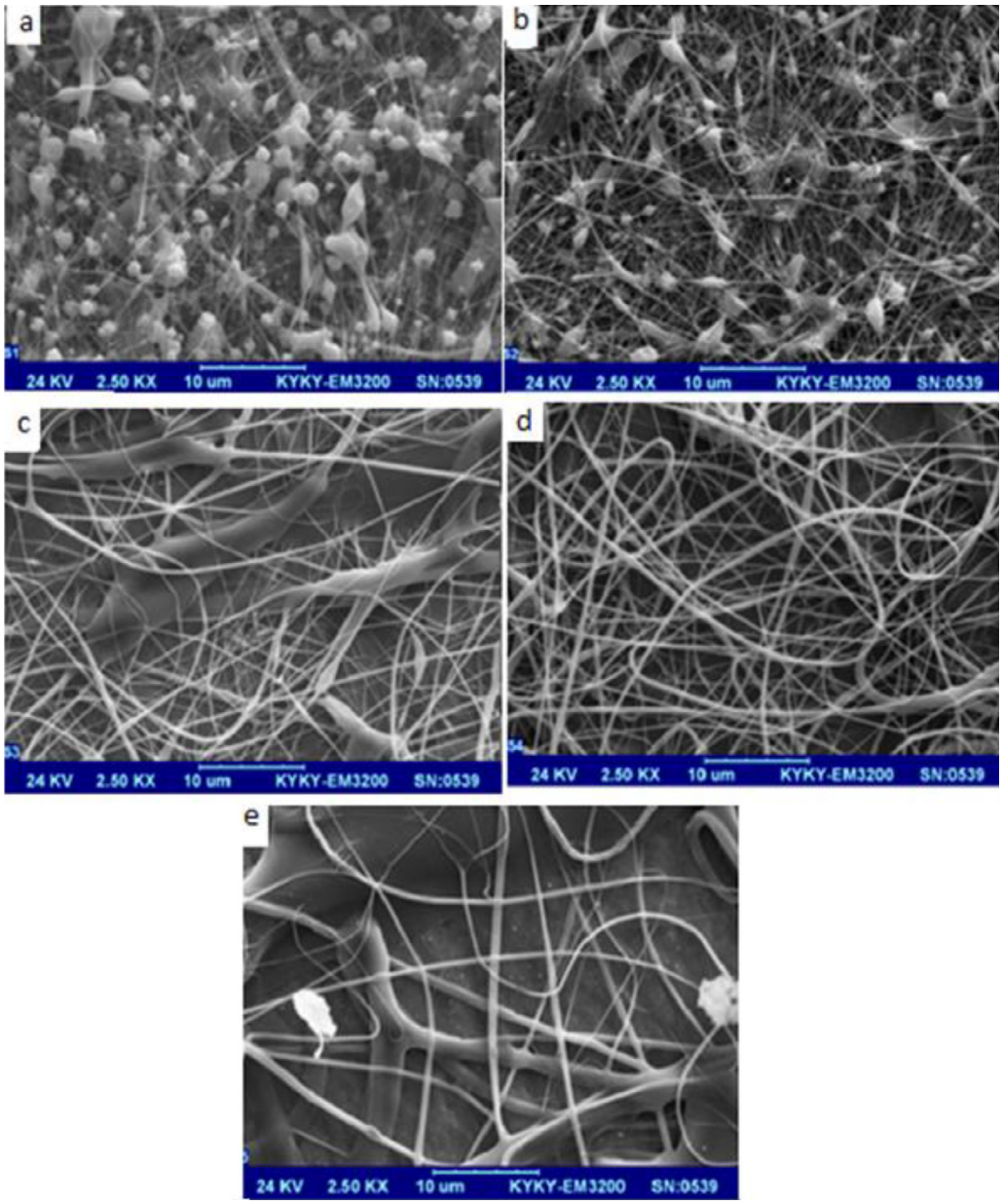

Fig.1. SEM images of as-spun CA fiber mats from different amount of CA solution in 3:1 (v/v) acetone/DMF. Field strength: 30 KV/8 cm.

from Jalinous Company. Acetaminophen was supplied in tablet form for oral administration. Acetaminophen, 4'-hydroxyacetanilide, a slightly bitter, white, odorless and crystalline powder, is a non-opiate, non-salicylate analgesic and antipyretic. Acetaminophen is often combined with other ingredients such as codeine, cough and cold ingredients. Morphine sulphate is the white and crystalline powder. In this work, Acetaminophen and Morphine used were pure. Dialysis tube (Dialysis sacks Avg. flat width 25 mm (1.0 in.), MWCO 12,000 Da) was purchased from Aldrich (Germany).

Electrospinning of the solution was carried out by connecting the emitting electrode of positive polarity from FANAVARAN NANO-MEGHYAS (Fnm-ES1000, Tehran, Iran). Electron microscopy images were scanned using a SEM (KYKY SBC-12 SEM, China). Diameters of the individual fibers in the as-spun fiber mats were measured directly from

the SEM images obtained. Fourier transformed infrared spectroscopy (FTIR) was conducted using a MATTSON 1000 FTIR SPECTROMETER over the scanning range of 400-4000 cm^{-1} with a resolution of 16 cm^{-1}. UV–VIS absorbance of the samples was recorded in the 200-400 nm range with a UV spectrometer (CARY 50, Varian Australia Pty Ltd, Australia).

Preparation of solution

Preparation of buffer (pH: 1, 7.4, 10)

For preparation of buffer with pH 1 (equal to stomach pH), the following formula were used. HCl 0.4 N : A, KCl 0.4 N : C, x ml A+ (100-x) ml C, x=55. For preparation of buffer with pH 7.4 (equal body pH), the following formula were used. NaH_2PO_4 0.13 N : A, Na_2HPO_4 0.13 N : C, x ml A+ (100-x) ml C, x=37. For preparation of buffer with pH 10 (equal gut pH), the following formula were used. Na_2CO_3 0.1 N : A, $KHCO_3$ 0.1 N : C, x ml A+ (100-x) ml C, x=37

Preparation of acetate cellulose solution

A certain amount of CA powder was dissolved in 3:1 v/v acetone/DMF to obtain a CA solution at the concentration of 8 to 16% w/v. Acetaminophen or morphine-loaded CA solutions for the usual method and core solution of coaxial and sandwich methods were provided by dissolving CA powder and acetaminophen or morphine in the weight ratio of 5:1, in an acetone/DMF mixture.

Electrospinning of the solutions

The solutions were ultra-sonicated for 5 min and then electrospun. A fixed electrical potential of 30±0.2 KV was applied across a distance of 8.0 cm between the tip of the nozzle and the outer surface of the drum. The rotational speed of the rotating drum was adjusted to 2000±200 rpm. The feed rate of the solutions was controlled at 1.0 ml/h. Electrospinning was carried out at room temperature (21±3°C).

Release studies

In vitro dissolution tests were carried out by dialysis tube. 12 mg of cellulose acetate electrospun nanofiber was put into 100 mL of 3 different buffers and the temperature was maintained at 37±3°C (equal body temperature). At predetermined time points, samples of 3.0 mL were withdrawn from the dissolution medium and replaced with fresh medium to maintain a constant volume. Letters involving acetaminophen were analyzed at 244nm and another that consists of morphine was analyzed at 285nm using a UV-Vis spectrophotometer for this purpose. The time of release of the drug was checked at different times (3, 6, 9, 12, 15, 30, 45, 60, 90, 120, 150, 180, 240, 300, 360, 420, 480, 540, 600, 660, 720 and 1440 min). The cumulative amount of drug released at each time point was calculated from the data obtained from a determined calibration curve.

RESULTS AND DISCUSSION

Characterization of CA fiber

Morphological appearance of CA fiber was observed by a KYKY scanning electron microscope (SEM).

Morphology and fiber size

A representative SEM image of CA is depicted in Fig.1. The morphology of fibers shows that different concentrations of cellulose acetate solution result in different radius and morphology. When the concentration is low, the fiber is smooth along with beads, and as the concentration increases, the radius of the fibers also increase (Fig.1 a to e).

Further characterization

DSC and XRD measurements determined the physical status of fig.1a in the nanofibres. Otherwise, these measurements illustrate that the pure drug is a crystalline material but was converted into an amorphous. This indicates that the drug completely dissolved in nanofibres.

DSC thermograms are shown in Fig.2. The DSC curve of pure A showed a single endothermic response corresponding to its melting point of 169.8°C. As amorphous polymers, raw CA powder and A-CA nanofibres do not show melting peaks or phase transitions [29, 30]. DSC thermograms of the A-CA nanofibres did not show any peak characteristic of A melting, indicating that the drug was no longer present as a crystalline material but had been converted into an amorphous state. As shown in Fig.3, the presence of many different reflections in the XRD pattern of pure A illustrate that the pure drug is a crystalline material [30, 31]. The diffraction patterns of raw CA powders and nanofibres from electrospinning exhibit a

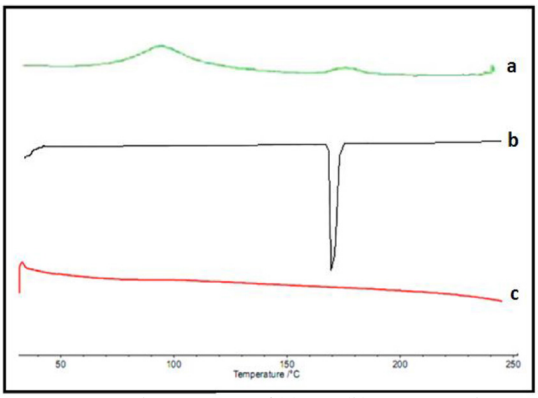

Fig.2. DSC thermograms of (a) CA, (b) acetaminophen and (c) drug-containing NFC.

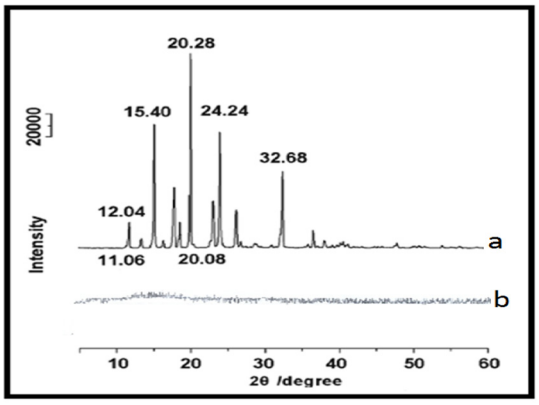

Fig.3. XRD pattern of (a) pure acetaminophen and (b) drug-containing NFC.

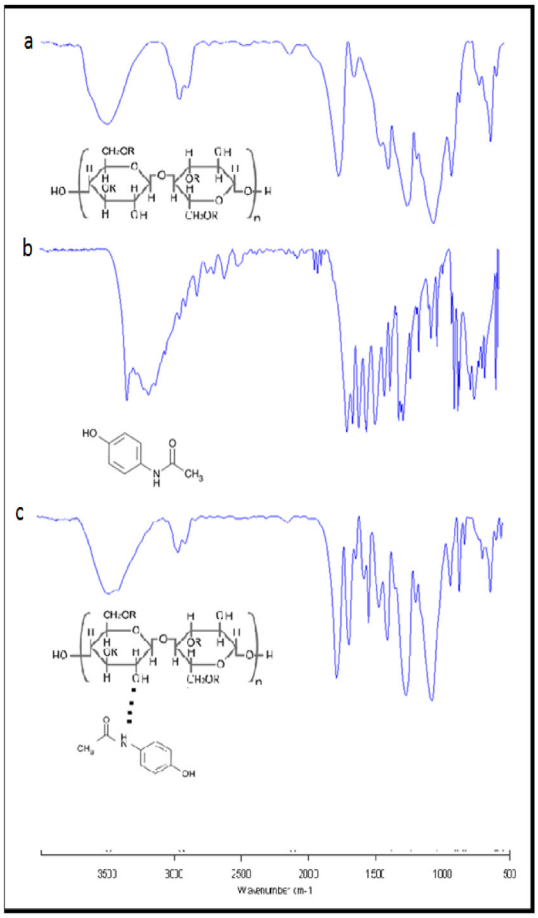

Fig.4. FTIR spectra of (a) NFC, (b) acetaminophen and (c) drug-containing NFC.

diffuse background pattern with one diffraction halo, indicating that the polymer is amorphous. In the patterns of the A-loaded nanofibres, the absence of characteristic reflections of A and only a hump characteristic of amorphous materials were observed, showing that A was no longer present as a crystalline material but was converted into an amorphous state in the fibre composites.

The DSC and XRD result confirms that A was highly dispersed in the CA nanofibre matrix and present in an amorphous mode where the original structure of the pure materials had been lost. This observation supports that from SEM, where no separate particles could be discerned on the surfaces and cross-sections of A-CA nanofibres. Compatibility among components is essential for the production of high-quality, stable nanofibres. Often, second-order interactions, such as electrostatic interactions, hydrogen bonding, and hydrophobic interactions, improve compatibility. Both A and CA molecules possess free hydroxyl (acting as potential proton donors for hydrogen bonding) and carbonyl groups (potential proton receptors). Therefore, as shown in FTIR, hydrogen bonding interactions can be said to occur within the A-loaded CA nanofibres.

The FTIR spectrum for CA is shown in Fig.4, A. The spectrum of CA has characteristic peaks from stretching vibrations of C-H groups at 3000 cm^{-1}, OH at 3500 cm^{-1}, C=O at 1850 cm^{-1} and C-O at 1250 cm^{-1}. Fig.4 B and C show the FTIR spectrum for acetaminophen and the breakage of acetaminophen (A) dimers, and the formation of hydrogen bonds between the CA carbonyl and the hydroxyl groups of A, respectively. Although, there may be secondary interactions between A or morphine and CA involving electrostatic and hydrophobic interactions through the A or morphine benzene ring, it is thought to be essentially the A or morphine–CA hydrogen bonding interactions that

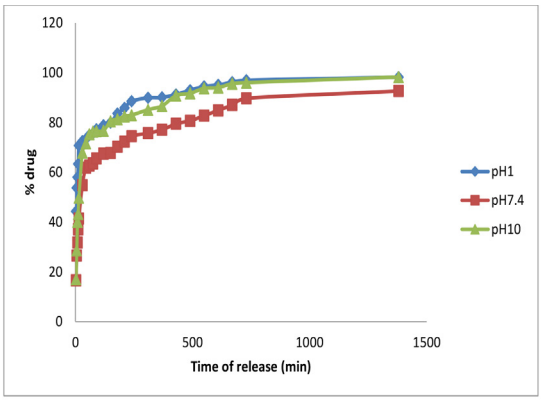

Fig.5. In vitro release profiles of A in different pHs.

prevent A or morphine crystallization in the fibers. These interactions stabilize A or morphine in an amorphous state in the nanofibers. Therefore, the drugs were capsulated by cellulose nanofibers.

In vitro release experiment

Preparation of releasing media

For this purpose, 100 ml buffer was used and placed in a dialysis tub that contained the nanofiber containing drugs. In this step of the experiment, 3.0 mL of samples were withdrawn from the dissolution medium and replaced with fresh buffer to 100 ml. Equation 1 was used to determine the concentration of drugs in solution.

Equation 1:

$$C = \mathrm{C} + \frac{v}{V}\sum_{s}^{n-1} c$$

where *C* is the concentration at each time point, C is the concentration measured by UV spectroscopy at each time point, v is the entry volume at each time period, *V* is the total volume, n is the number of entry volumes and s is the total number of samples [32, 33].

Effect of pH

There is an obvious need for studies which would clarify the influence of factors affecting the drug release from the matrices. This knowledge could then also be used as a tool for drug screening when choosing suitable drug candidates for the NFC-containing drug formulations. Thus, drug permeation tests were performed through plain NFC films as a quick technique to estimate the rate of drug diffusion through a porous NFC network. Series of permeation tests at different pH-values

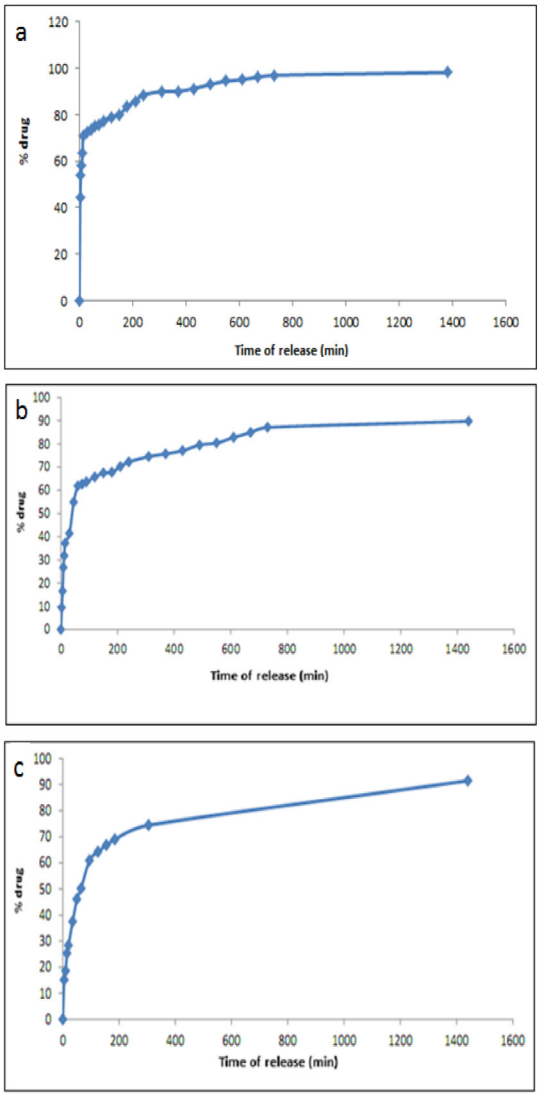

Fig.6. In vitro release profiles of morphin
a) from conventional nanofibers, b) from coaxial nanofibers and c) from sandwich nanofibers.

were conducted using model compounds with different sizes. It was shown that the ability of NFC to slow down the drug diffusion did not change significantly with small increases in the molecular size of the permeating compounds. A pH change in the medium also did not significantly change the membrane structure and, thus, did not influence the drug diffusion rate.

UV analysis

Absorbance was recorded to determine the measurement of release of the drug into the medium. In this step, standard concentrations of

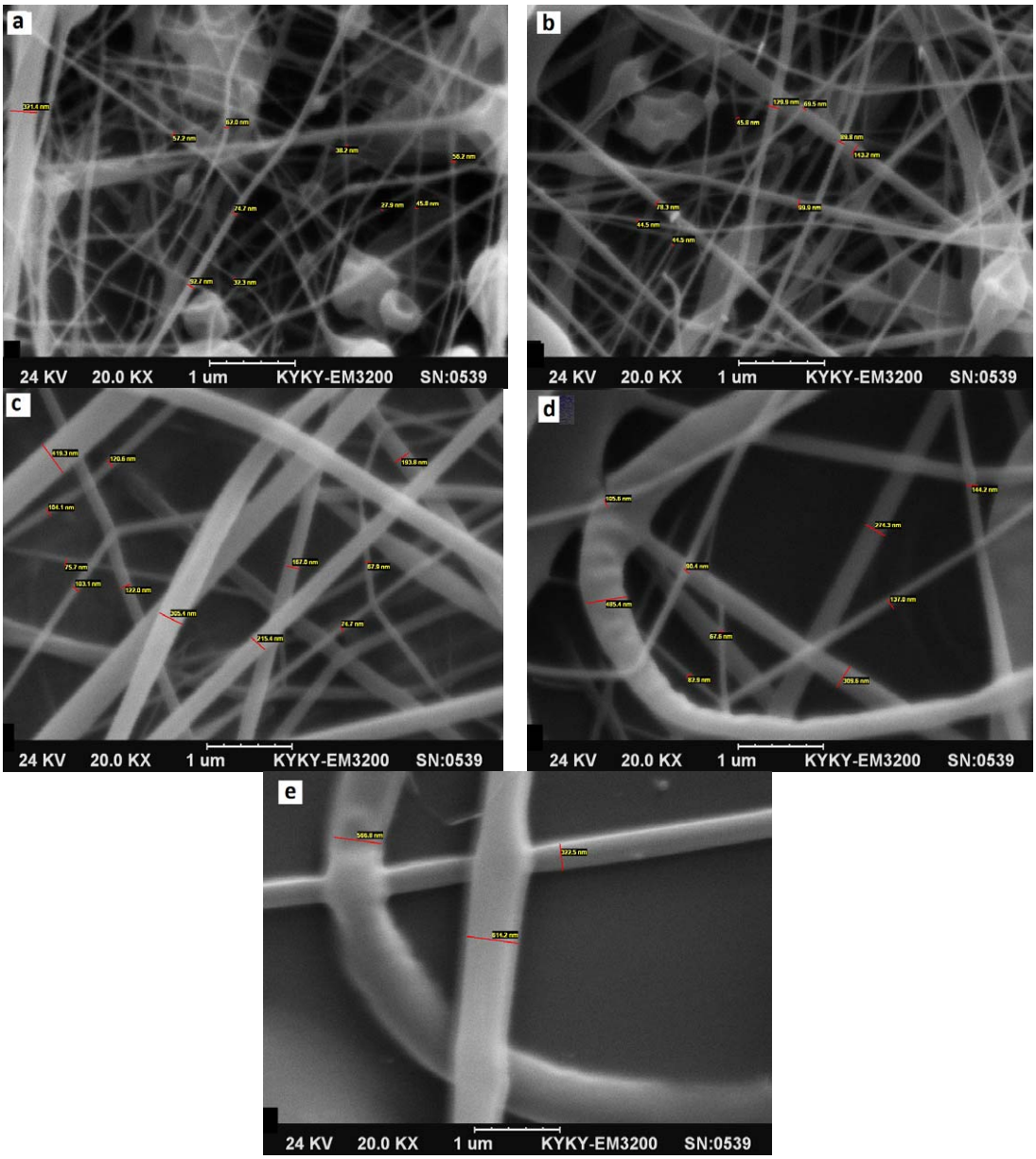

Fig.7. SEM images of as-spun CA fiber mats from different amounts of CA solutions ((a) 8%, (b) 10%, (c) 12%, (d) 14% and (e) 16%) in 3:1 (v/v) acetone/DMF.

morphine and A was prepared, and these were analyzed with UV-spectrophotometer and by estimating the relationship between concentration and absorbance using regression method for morphine and A separately.

The full range drug release profiles of nanofibers are shown in Fig.5. Nanofiber released 80.7% of the contained drug in 8 h and later entered the tailing-off release period for slow exhaustion. The A release profiles for nanofiber can be analyzed by the Peppas equation (Equation 2) [34].

Equation 2:

$$Q=kt^n$$

Where Q is the drug release percentage, t is the release time, k is a constant reflecting the structural and geometric characteristics of fibers and n is the release exponent that indicates the drug release mechanism. As shown in Fig.6, the regressed equation for conventional nanofiber between 0 and 8h is $Q=18.05t^{0.24}$ ($R^2=0.9844$), acetate for coaxial nanofiber between 0 and 8 h is $Q=11.41t^{0.35}$ ($R^2=0.9826$) and for sandwich nanofiber between 0

and 8 h is $Q=8.61t^{0.40}$(R^2=0.9901), indicating that the drug release from nanofiber was controlled through a typical Fickian diffusion mechanism from the cellulose acetate matrix by a release exponent value of 0.24 for conventional nanofiber, 0.35 for coaxial nanofiber and 0.40 (less than 0.45) for sandwich nanofibers. This result showed that sandwich structure has slower release as compared to the others.

Process of preparing suitable electrospinning solutions

The concentration of CA in the spinning solutions was determined. The experiment was as follows: 5 different spinning solutions were used. When the concentration of CA was low, SEM showed numerous disordered beads. When the CA concentration increased to 16%, SEM exhibited uniform fibers with fewer beads. Fair results were obtained when CA concentration was 12%, and SEM showed smooth and uniform fibers with lower beads. SEM for different CA concentrations was investigated. The electrospinning conditions were similar. The optimum drug to polymer ratios was 1:5, which led to polymer contents of 20% of the drug. According to SEM observations, the prepared Acetaminophen codeine-CA fibers were estimated as 52.9 ± 0.1 (Fig.7.A), 82.3±0.1 (Fig.7.B), 107.3± 0.1 (Fig.7.C), 139.5±0.1 (Fig.7.D) and 501.2±0.1 nm (Fig.7.E).

Minor differences were found between thinner fibers and thicker ones both for acetaminophen morphine-CA release behavior in pH=7.4. Initially, fibers tended to release drug faster which could reduce time to reach the maximum drug content in the medium.

Fig. 8s shows the in vitro release profiles of A form different nanofibers which were synthesized in different cellulose acetate concentrations and the release profile of morphine from the optimum fibers in pH=7.4. As can be seen, the release of morphine occurs at lower rate and longer time.

CONCLUSIONS

NFC was tested as a novel pharmaceutical excipient. Standard methods for tablet production were used to evaluate the applicability of electrospinning NFC as filler for tablet manufacturing. An electrospinning process was developed to produce drug loaded NFC nanoparticles for long-lasting controlled drug release. NFC fibers formed network structures during this process, entrapping the drug within the nanoparticles. This network is tight enough to sustain the release of drug for up to one day. The results of this study indicated that the thickness of nanofiber and pH change of the used medium did not greatly change the membrane structure and, thus, did not influence the drug diffusion rate. Moreover, the pH did not affect drug release, and hence the drug can be used in various ways such as oral and injectable. Three methods for making carrier nanofibres were used here. The results of drug release were studied using UV–VIS data and using the peppas equation the degree of release was obtained. This result showed sandwich method is better than for drug delivery because of release slower than other methods.

ACKNOWLEDGEMENT

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: http://www.nanomedicine-rj.com/jufile?ar_sfile=312341

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