# Controlled delivery systems of cellulose matrix for oxytetracycline: *In vitro* dissolution

Disha Mishra [a], Puja Khare [a,*], K. Shanker [b], Dhananjay K. Singh [c], Suaib Luqman [c]

[a] Agronomy and Soil Science Division, CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow 226015, India
[b] Analytical Chemistry Division, CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow 26015, Uttar Pradesh, India
[c] Molecular Bioprospection Department of Biotechnology Division, CSIR-Central Institute of Medicinal and Aromatic Plants, Lucknow 226015, India

## ARTICLE INFO

## ABSTRACT

Microfibrillated cellulose (MFC) has recently been explored as a novel nanostructured system for controlled drug delivery. The present study examines the releasing behavior and antibacterial efficacy of cellulose (CC) and tempo-oxidized- microfibrillated cellulose (TO-MFC) loaded with oxytetracycline at three different physiological pH (2.1, 6.8 and 9.0). The releasing mechanism from cellulosic matrix was assessed by applying zero order, first order, and second order & Ritger-Peppas model. The well diffusion assay was carried out to investigate the antibacterial efficacy of the prepared MFCs. Results indicate that the stability for the drug loaded on TO-MFC at all the pH was significant. TO-MFC and CC both showed sustained release of OTC and followed Ritger-Peppas model signifying the diffusion process. The sustained antibacterial activities of these cellulosic matrixes were also observed. Results indicate that both drug delivery systems retained their medicinal properties against bacteria. The application of MFC could be very promising since it allows a sustained release of drug conserving long-term antibacterial efficiency.

**Focal points:**

- Microfibrillated cellulose (MFC) loaded with oxytetracycline at three different physiological pH (2.1, 6.8 and 9.0) was examined.
- The OTC and RO-MFC drug delivery system was stable at all pH.
- Riteger-peppas model was favourable for the drug release phenomenon signifying the diffusion process.
- The antibacterial activities of three matrixes appear in the similar manner as reported for releasing.

## 1. Introduction

Recently, plant based engineered materials have attracted the interest of many researchers due to its vast applications in many area of science such as drug delivery. The materials are engineered in such a way that the active agent in the matrix should be released with an appropriate rate, balancing the minimum effective dose and toxic threshold dose [1]. Currently microfibrillated cellulose (MFC) is used as promising source for the controlled release study [2,3]. MFC could be obtained from plant and bacterial cellulose through different recognized processes. Cellulose an ubiquitous and economic compound produced by biomass contains anhydroglucose unit (AGU), containing three hydroxyl groups, which brought together into larger units known as elementary fibrils [4] and further create larger units called MFC. The diameter of MFC could be between 20–50 nm, and length generally exceeds more than 1 μm [5]. The size of MFCs mainly depends on the origin of the MFC and on the production process. Presently for reduction of energy consumption process several other techniques like enzymatic pre-treatment and TEMPO mediated oxidation are in use [3]. Due to its unique properties, MFC has been used for many years in different industries like pharmaceutical, coating, food and cosmetic [6]. The properties such as biocompatibility, a high elastic modulus (similar to steel), a low thermal expansion coefficient, optical transparency and anisotropy, negative diamagnetic anisotropy and flexible surface

\* Corresponding author.
*E-mail address:* kharepuja@rediffmail.com (P. Khare).

chemistry making it of interest in applications such as composites, security papers, wound dressings and medical implant. The very large surface area and negative charge of MFCs suggests that large amounts of drugs might be bound to the surface of this material with the potential for high payloads and optimal control of dosing [7]. Nanocellulosic materials are currently the focus of extensive research due to a combination of promising properties of nanocellulose and better drug sustainability. Therefore, they are potential bio-based candidates to achieve a controlled release of an active desired agent. Chlorhexidine digluconate [8], Amoxicillin trihydrate [9], Ornidazole [10] and Camptothecin [11] are some examples of control released formulations loaded on cellulosic matrix. Oxytetracycline (OTC) is an antimicrobial extensively used in human and veterinary medicine all over the world and also for the treatment of bacterial diseases [12]. Its approved uses in human include the treatment of respiratory, genitourinary, and cutaneous infections. Among available formulations in the market, we can find pills, drops, and ointments of OTC. It inhibits bacterial protein synthesis by binding the 30 s ribosomal subunit, specifically the aminoacyl site A. Their indiscriminate use in animal feed lead to important sanitary risks for humans such as bacterial resistance, allergies, ossification and dentition problems, and carcinogenic effects. Control release drug delivery system could offer advantages for the administration and delivery of drugs that may be useful to prevent and overcome problems derived from overuse and resistance mechanism [13]. Polymeric nanoparticles, liposomes, solid lipid nanoparticles, nanoemulsions, and dendrimers have been widely investigated as antimicrobial drug delivery systems [27]. However, the inclusion of OTC in nano-vehicles may be difficult because of its high affinity towards water.

In this study, we prepared the OTC composites with MFCs and compared it with the commercial drug. The study was carried out at three physiological pH 2.1, 6.8 and 9.0. The aim was to bring insight into how the chemical binding of the carrier is influencing the antimicrobial efficacy of nanocomposites based on controlled released drug delivery system. It was examined against pathogenic microorganism: *Pseudomonas aeruginosa*. To the best of our knowledge, our work is the first of its kind where TEMPO-MFC for oxytetracycline drug delivery was developed at different physicological pH.

## 2. Materials and methods

The waste biomass after oil extraction of Citronella grass (*Cymbopogon citratus*) was collected from the farm of CSIR-Central Institute of Medicinal and Aromatic Plant, Lucknow, India for the preparation of cellulose. All other chemicals used in the study were of analytical grade. *Pseudomonas aeruginosa* (MTCC No. 741) was procured from Microbial Type Culture Collection facility of CSIR-Institute of Microbial Technology, Chandigarh, India. Oxytetracyclin (OTC) used in the study was obtained from Sigma Aldrich, while commercial tablets of OTC was purchased from the local market of Lucknow, India.

### 2.1. Preparation and characterization of drug delivery system

The isolated cellulose (CC) [14] and TEMPO modified cellulose (TO-MFC) [15] material were selected for the synthesis of drug delivery system with OTC. Different concentration of OTC (100, 500 and 750 mg/g) were loaded on the matrix material of CC and TEMPO-MFC (w/w) separately. The prepared system was homogenized for 6 h to ensure proper interaction of drug and matrix material. After that the material was freeze dried. The material was extracted and characterized by using FTIR (Perkin Elemer Spectrum BX), particle size and zeta potential (Malvern

mastersizer). The matrix material was also characterized for morphological features using SEM (SEM) (JEOL (Make), JSM-6100), and crystallinity index using XRD (ULTIMA IV, Rigaku, Japan).

### 2.2. pH dependent swelling behavior of matrix material

The swelling index of CC and TO-MFC at pH 2.1, 6.8, and 9.0 was determined by calculating the volume occupied by the sample before and after swelling. The swelling index was calculated according to the method given by Amin, 2012 [16]. The swelling index was expressed in ml/g of the dried weight of sample.

### 2.3. In vitro release behavior of OTC

In order to study the releasing behavior of OTC, three medium resembling the physiological pH were prepared. The medium of pH 2.1 was obtained using HCl, pH 6.8 using phosphate buffer saline (10 mM), pH 9.0 using NaOH respectively. OTC loaded material (2 mg) was immersed in different physiological media (300 μL). The samples (100 μL) were withdrawn at 0, 15, 30, 45, 60, 120, 240, 360, 480 min and upto 24 h. Then the system was again replenishing using media (100 μL). The amount of OTC released in the medium was detected using HPLC system equipped with solvent delivery pump (WATER-600), Autosampler (WATERS-717), Column C-18 – X select ($4.6 \times 250$ mm, 5 μm) and PDA detector ($\lambda_{max}=254$). The water (1% acetic acid) and acetonitrile (**30:70**) at the flow rate of 1 ml/min. A calibration curve was constructed to quantify the OTC in different solution. For this different concentration of OTC 200–800 (μg/ml) were adjusted to get a calibration curve. The peak area of the chromatogram was plotted against the concentration of OTC in the medium to obtain the calibration curve.

### 2.4. Release kinetics of drug

Several kinetic models are available for studying the behavior of drug in a controlled release through various matrices. To overcome the drawback of *in vivo* performance of drug dissolution, kinetic model provides a valid *in vitro* behavior of drug release. The mechanism of drug release from CC and TO-MFC was predicted after applying zero, first, second order kinetics and Ritger-Peppas model dependent kinetics. Peppas and Ritger have proposed an empirical power equation to follow drug release [20].

$$Mt/M_\propto = Kt^n$$

where Mt and $M_\propto$ are the absolute cumulative amounts of drug released at time (t) and at infinite time, respectively, k is a constant relating to the properties of the matrix and the drug, structural and geometric characteristics of the device; and n is a dimensionless number.

### 2.5. Antibacterial efficacy of OTC

Antibacterial efficacy was measured by well diffusion assay and results were expressed as zone of inhibition (ZOI) [29]. Nutrient agar plates were seeded with the *P. aeruginosa* as described before [28]. Well of identical diameter was bored on the surface of agar plates using sterile borer. The aliquot (25 μL) collected at different time interval was placed in the each hole. Supernatant containing drug only was served as control. The plates were incubated at 37 °C for 24 h and the zone of inhibition (ZOI) was measured in mm after incubation.
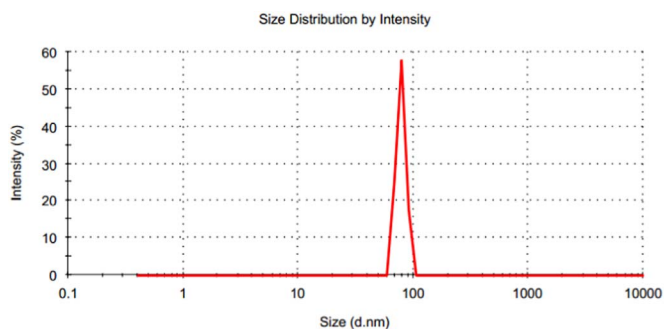
**Fig. 1.** Particle size of TO-MFC.

**Table 1**
Particle size, zeta potential and aspect ratio of TEMPO-oxidized matrix and drug delivery system.

| Sample name | Particle size (μm) | Zeta potential | Aspect ratio |
|---|---|---|---|
| TO-MFC | 4.8 | − 37 | 0.09 |
| TO-100 | 4.5 | − 14.9 | 0.1 |
| TO-500 | 2.2 | − 3.83 | 0.15 |
| TO-750 | 4.4 | − 3.65 | 0.11 |

## 3. Results and discussion

### 3.1. Preparation and characterization of oxytetracycline –TO-MFC

SEM image of the tempo-oxidized crystalline cellulose is shown in the Supplementary (S-1). It persist fibril thread like networks. An average diameter of the TO-MFC was 78 nm, determined using particle size analyser (Fig. 1). It posses good crystallinity (56%), high surface charge (9.34 mmol/g) and aspect ratio (0.09) (Table 1). The detail XRD characteristics of TO-MFC are shown in the Supplementary materials(S-II). This value agrees well with dimensions for similar MFC fibers found in the literature [8,17]. While CC showed average diameter of 0.5 μm with the zeta potential of − 9.34 mV (data not shown here). Presently, various types of MFC are created from various methods and source which leads the variations in the aspect ratio and dimensions of each type of MFC fiber [18]. Thus, SEM was used to verify that the MFC suspensions were homogeneous and that it had no large fibers (with diameter higher than 10 μm). Moreover, the suspension used for drug loading is stable with a Zeta potential of − 17.4, which are characteristic of nano-scale features. After loading of oxytetracycline (OTC), not much variation in particles size was observed. Zeta potential of composite material was increases with the increase in the amount of drug loaded and shifted towards more colloidal unstability due to of neutralization of total surface charge of nanocellulose.

The preparation of carboxylated nanocellulose using TEMPO-mediated oxidation is a successful method for disintegration and oxidation of microcellulose. It could introduce the stable negative electrostatic charges on the CC surface and thus induces electrostatic stabilization to obtain a homogeneous dispersion in water [19]. This is confirmed by the FTIR spectroscopic study which suggested that OTC loaded TEMPO modified MFCs exhibited all the characteristics peaks of cellulose backbone as well as amide binding between the TO-MFCs and OTC (Fig. 2). The strong bands at 3340 cm$^{-1}$ and 2900 cm$^{-1}$ were due to the stretching vibrations of O–H groups and symmetric C–H vibrations, respectively in both the original materials. Peak at 1056 cm$^{-1}$ was due to symmetric C–O vibrations. The peaks around 1120 and 665 cm$^{-1}$ were attributed to stretching vibrations of intermolecular ester bonding and C–OH out of plane bending mode. After loading of OTC on the
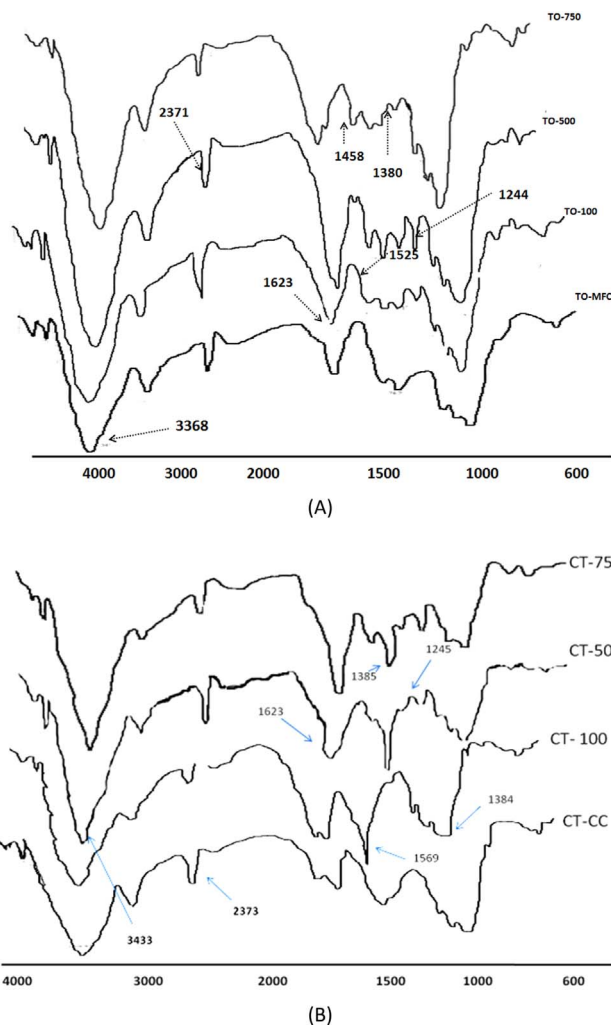


**Fig. 2.** FTIR of (A) TO-MFC, (B) CC, with loaded and unloaded OTC.

cellulosic materials, the spectra clearly revealed the presence of OTC on the surface of both fiber however the intensity of bonding between OTC and hydroxyl or carboxyl group present at the surface area of both the template materials is quite different. The peak intensity at 1639 cm$^{-1}$ represents carbonyl moiety of amide group, while peak at 1620–1579 denotes amide (–N–H) bonds of oxytetracyclin. These two peaks collectively represents –CONH$_2$ moiety of oxytetracyclin molecule. The aromatic C=C vibration bands appear in the region 1430–1310 cm$^{-1}$ and the –C–N bond vibration were located between 1216–1280 cm$^{-1}$ in both the materials. In case of cellulosic materials the extent of hydrogen bonding might be possible between surface hydroxyl group of cellulose and –C–N bond of drug, which is apparent by the disappearance of peak between 1216–1280 cm$^{-1}$ (phenolic –OH group) in FTIR of drug loaded cellulose. Phenolic group of drug may also form hydrogen bond with hydroxylic group of cellulose which is evident by reduction in peak intensity of phenolic group at 1160 cm$^{-1}$. In case of TEMPO modified fiber, the hydrogen bonding between the carboxyl groups of the TO-MFC with the amide linkage of drug may be possible. This was corroborating with the FTIR spectra, which showed the disappearance of intensity of peaks between 1680–1592 cm$^{-1}$ belongs to carbonyl moiety of amide group. It indicated that the major interaction between drug and nanocellulose was due to hydrogen bonding (Scheme 1).
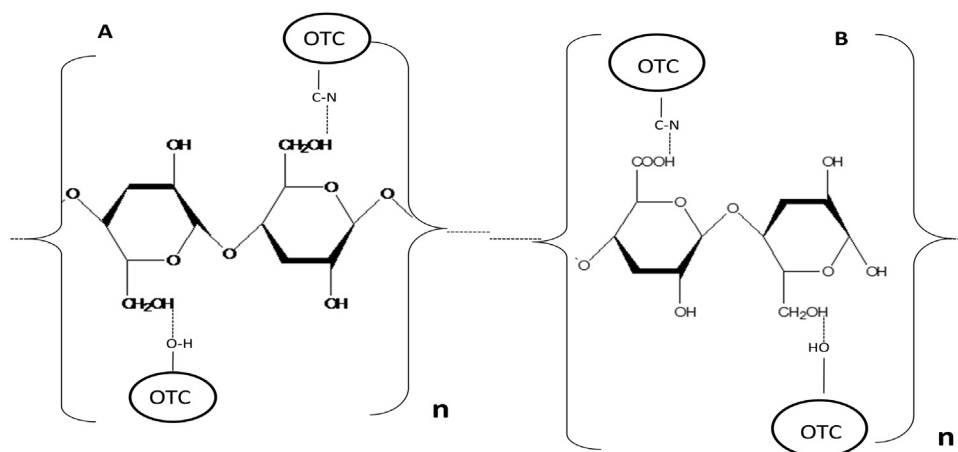
**Scheme 1.** Possible bonding of drug with (A) cellulose and (B) TO-MFC.

### 3.2. Analysis of cumulative drug release at different pH

The OTC release study comprises three steps: (1) response of drug dose, (2) affect of pH, and (3) the intermittent diffusion experiments of the species into an aqueous media. At the end, a comparison was made between (i) commercial tablet as control, (ii) the cellulose loaded with OTC, and (iii) TO-MFC loaded with OTC. The release of cellulose and TO oxidized cellulosic fibrils loaded with different amount of OTC were subjected for examination of release behavior from matrix at different pH 2.1, 6.8 and 9.0 that mimicked the varying pH of gastrointestinal tract [20]. After preparation, the surface of each sample was placed on the meniscus with solution to study the release of the OTC.

The *in vitro* cumulative release of drug at different time is shown in the Fig. 3. The $t_{50\%}$ and $t_{90\%}$ values for the release of OTC at different loading concentration and pH are shown in the Table 2. Releasing of drug exhibited different pattern for different dose and pH. $t_{50\%}$ for CC was up to 1.3 h at pH 2.1 while TO-MFC the same value obtained at pH 6.8 with loading of 500 mg/g. The release rate of OTC with time in the case of the commercial tables reaches a plateau after 10 min of release in solution. However, the CC and TO-MFC promote the slow release. Even if the slope at the origin is moderately slower for the CC and TO-MFC, the inclines of the curves for all samples are roughly identical.

At lower loading concentration, the release of OTC was swift within 10 min for commercial tablet and 2hrs for cellulosic matrix. The cumulative release pattern of both cellulosic materials was quite similar despite the different behavior at different pH. In case of cellulose due to presence of more amorphous region the maximum concentration of OTC moves towards outer surface during freeze drying, which results in the burst release in the initials hours. TO-MFC have sufficient cellulose I due to ultrasonication during production consequently limits the release of OTC initially, but as the time passes due to sufficient swelling ability of material the release was majorly governed by swelling behavior of both the materials. The OTC loading over cellulosic surface generates more amorphous form than loaded over TO-MFC. The amorphous form of drug helps in the increase dissolution rate and maintaining oral bioavailability of drugs [21]. In addition, charged nature of functional sites of OTC and almost same chemical architecture of fibrils network might be the reason for the almost equal sustained release of OTC from the fibril surface than commercial tablet [22]. After one hour when 50% release was occurred, the matrix causes the delay of water penetration for some time thus diffusion of drug from matrix takes some time. With the replacement of the aqueous media, the equilibrium of the system was shifted toward increased diffusion of OTC in one direction and the OTC was attracted by the new aqueous media, which further accelerates their release [3]. But later the swelling of network dominates over diffusion for sustained release up to 10 h in cellulosic and nano-cellulosic networks. Overall, compared with commercial tablet, the OTC release rate of CC and TO-MFC significantly slowed down. For commercial tablet, the drug release generally reached the equilibrium in 6 h. On the contrast, approximately 10 h was needed for cellulosic matrix to reach the equilibrium, demonstrating the high potential of CC and TO-MFC for pharmaceutical applications.

### 3.3. Effect of pH on the releasing behavior of OTC

In addition, the drug release from cellulosic matrix was not only highly pH dependent but also loading concentration. The $t_{50\%}$ and $t_{90\%}$ calculated from Fig. 3 are shown Table 2. At all the pH, $t_{90\%}$ values of all matrix loaded with 100 mg/g drug concentration were approximately 8 h. For the higher loading, $t_{90\%}$ values were higher for alkaline pH. At this pH, CC showed highest extended release of drug at a loading of 750 mg/g. However, maximum sustain drug release in TO-MFC was observed for 500 mg/g loading at pH 6.8 (Table 2). Results indicate that alkaline condition favors the extended release of OTC from CC and TO-MFC. At acidic pH, formation of ionic bond dominates. Acidic pH favors the protonation of amide group and leads to ionic interaction between surface hydroxyl or carboxyl group of cellulosic surface and OTC. The quick breakage of this bond could be responsible for the initial burst release at this pH. Alkaline conditions favors the swelling of fibers, so the penetration of water delays thereby the release lasts up to 10 h. The swelling performed at different pH at different interval of 1, 2 and 4 h. The results revealed swelling properties were varied for two materials at different pH (S-III). At lower pH cellulose and TO-MFC were swelled maximum at 2 and 4 h, respectively. At the physiological pH (6.8), both the materials exhibited maximum swelling at 2 h. At alkaline pH the trend was found quite different. No swelling was observed in cellulose at this pH, while the TEMPO modified fiber swell maximum up to 4 h. These results demonstrated a remarkable pH responsiveness of the cellulosic matrix. For clinical practices, the TO-MFC could slow down the initial burst release of OTC in stomach and bring more drugs to the intestinal tract for a targeted drug delivery. This would not only reduce the side effects on stomach but also improve the absorption efficiency of drugs.

### 3.4. Mechanism of in vitro drug release

To understand the mechanism of *in vitro* drug release, zero order, first order, second order and Ritger-Peppas equations were
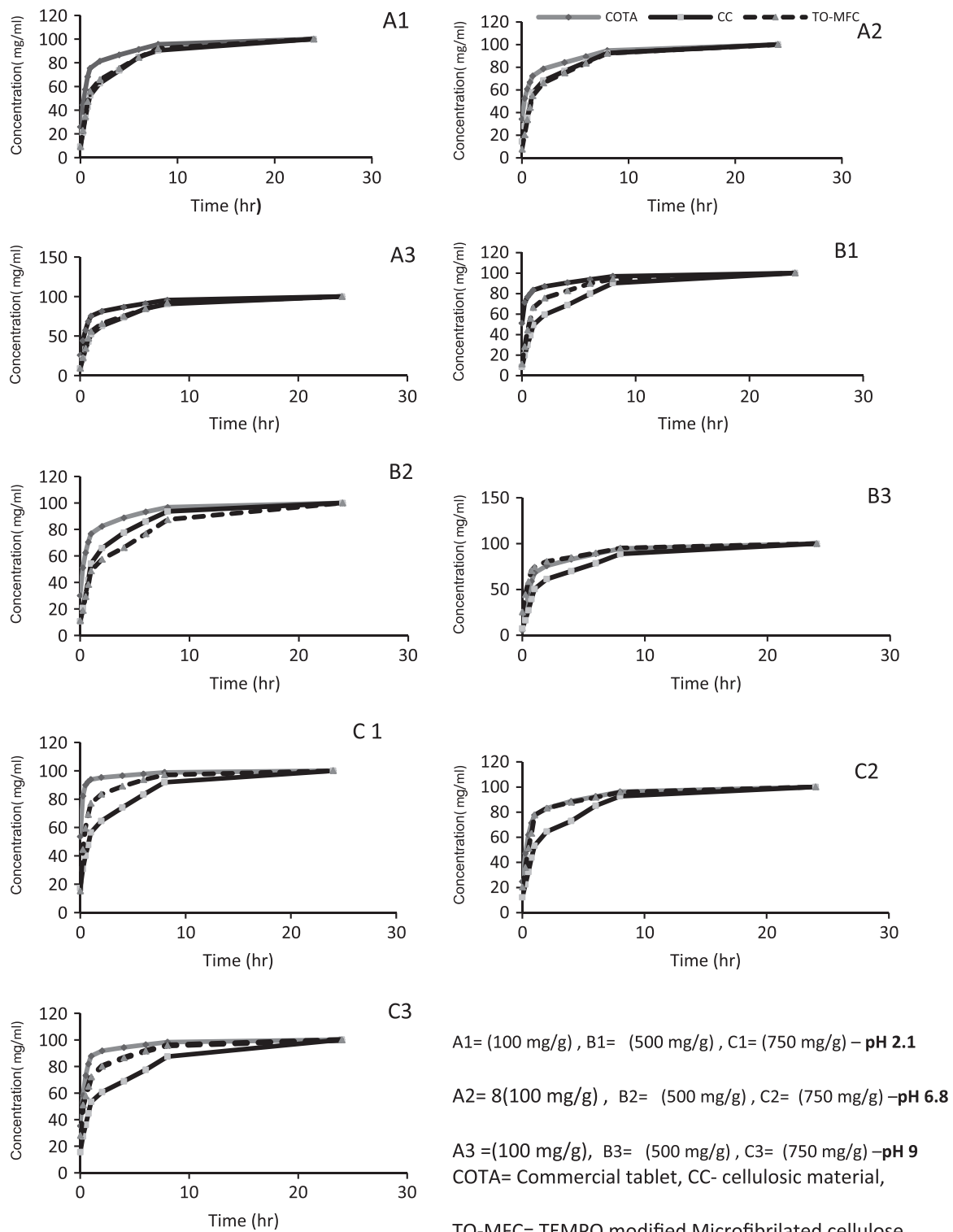
**Fig. 3.** Cumulative release curve of OTC at different time interval for commercial tablet, cellulosic material and TEMPO modified microfibrilated cellulose.

A1= (100 mg/g) , B1=  (500 mg/g) , C1= (750 mg/g) – **pH 2.1**

A2= 8(100 mg/g) ,  B2=   (500 mg/g) , C2=  (750 mg/g) –**pH 6.8**

A3 =(100 mg/g),  B3=   (500 mg/g) , C3=  (750 mg/g) –**pH 9**
COTA= Commercial tablet, CC- cellulosic material,

TO-MFC= TEMPO modified Microfibrilated cellulose

applied on drug released data at different pH. The $R^2$ values were implied to check the suitability of best fit model for releasing phenomenon. The $R^2$ values of the entire model were shown in the Table 3. Higher $R^2$ value of model implicit the better fit model to express the *in vitro* release behavior of oxytetracyclin. Ritger-Peppas equation model showed highest $R^2$ values at all the pH. The system was showing a biphasic model for OTC release as more than 50% of release was occurred within one hour, which describes the burst release phenomenon followed by sustained release [23].

The possible reason for burst release might be the migration of OTC at the surface of networks system during freeze drying process, which directly migrated to the medium of different pH. The phenomenon of burst release is greatly affected by loading amount of OTC, drug solubility and surface area of fibrils. Mostly for water soluble drugs the release occurs only when water penetrates inside the polymeric networks and it get swell to facilitate further release from the system [24].

Further release exponent (n) was calculated from Ritger-Peppas

**Table 2**
Values of $t_{50\%}$ and $t_{90\%}$ for the release of OTC for different loading concentration and pH.

| Sample name | OTC loading (mg/g) | pH value | $t_{50\%}$ (h) | $t_{90\%}$ (h) |
| --- | --- | --- | --- | --- |
| COTA | 100 | 2.1 | 0.3 | 5.0 |
| | | 6.8 | 0.2 | 5.9 |
| | | 9.0 | 0.3 | 4.9 |
| | 500 | 2.1 | 0.01 | 4.3 |
| | | 6.8 | 0.2 | 4.3 |
| | | 9.0 | 0.3 | 6.1 |
| | 750 | 2.1 | 0.06 | 6.2 |
| | | 6.8 | 0.2 | 5.2 |
| | | 9.0 | 0.2 | 1.4 |
| CC | 100 | 2.1 | 0.9 | 7.9 |
| | | 6.8 | 0.7 | 7.4 |
| | | 9.0 | 0.2 | 8 |
| | 500 | 2.1 | 1.3 | 8.3 |
| | | 6.8 | 1.0 | 6.9 |
| | | 9.0 | 1.0 | 9.4 |
| | 750 | 2.1 | 0.8 | 7.7 |
| | | 6.8 | 1.0 | 6.4 |
| | | 9.0 | 0.9 | 10.4 |
| TO-MFC | 100 | 2.1 | 0.8 | 7.5 |
| | | 6.8 | 0.9 | 7.6 |
| | | 9.0 | 0.8 | 7.4 |
| | 500 | 2.1 | 0.6 | 6.7 |
| | | 6.8 | 1.3 | 10.6 |
| | | 9.0 | 0.4 | 6.0 |
| | 750 | 2.1 | 0.3 | 7.6 |
| | | 6.8 | 0.5 | 0.9 |

COTA=commercial tablets, CC=cellulose, TO-MFC=TEMPO modified cellulose.

**Table 3**
Correlation coefficient for various kinetics model applied in the study.

| Sample | Loading | pH value | $R^2$ | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | Zero order | First order | Second order | Ritger-Peppas |
| COTA | 100 | 2.1 | 0.709 | 0.682 | 0.343 | 0.907 |
| | | 6.8 | 0.168 | 0.667 | 0.662 | 0.968 |
| | | 9 | 0.158 | 0.653 | 0.362 | 0.965 |
| | 500 | 2.1 | 0.089 | 0.548 | 0.635 | 0.969 |
| | | 6.8 | 0.022 | 0.475 | 0.337 | 0.880 |
| | | 9 | 0.024 | 0.515 | 0.352 | 0.903 |
| | 750 | 2.1 | 0.695 | 0.526 | 0.621 | 0.908 |
| | | 6.8 | 0.649 | 0.502 | 0.363 | 0.896 |
| | | 9 | 0.210 | 0.492 | 0.377 | 0.970 |
| CC | 100 | 2.1 | 0.673 | 0.621 | 0.331 | 0.891 |
| | | 6.8 | 0.968 | 0.629 | 0.36 | 0.956 |
| | | 9 | 0.345 | 0.611 | 0.36 | 0.951 |
| | 500 | 2.1 | 0.642 | 0.542 | 0.565 | 0.88 |
| | | 6.8 | 0.1317 | 0.48 | 0.338 | 0.882 |
| | | 9 | 0.253 | 0.561 | 0.326 | 0.925 |
| | 750 | 2.1 | 0.709 | 0.533 | 0.621 | 0.915 |
| | | 6.8 | 0.626 | 0.493 | 0.37 | 0.886 |
| | | 9 | 0.644 | 0.606 | 0.401 | 0.949 |
| | 100 | 2.1 | 0.685 | 0.611 | 0.346 | 0.900 |
| TO-MFC | 500 | 6.8 | 0.929 | 0.647 | 0.352 | 0.951 |
| | | 9 | 0.459 | 0.662 | 0.35 | 0.954 |
| | | 2.1 | 0.700 | 0.495 | 0.55 | 0.889 |
| | 750 | 6.8 | 0.154 | 0.590 | 0.396 | 0.942 |
| | | 9 | 0.254 | 0.568 | 0.375 | 0.930 |
| | | 2.1 | 0.612 | 0.477 | 0.56 | 0.88 |
| | | 6.8 | 0.647 | 0.533 | 0.391 | 0.909 |
| | | 9 | 0.662 | 0.542 | 0.391 | 0.914 |

**Table 4**
n value in Ritger-Peppas kinetics.

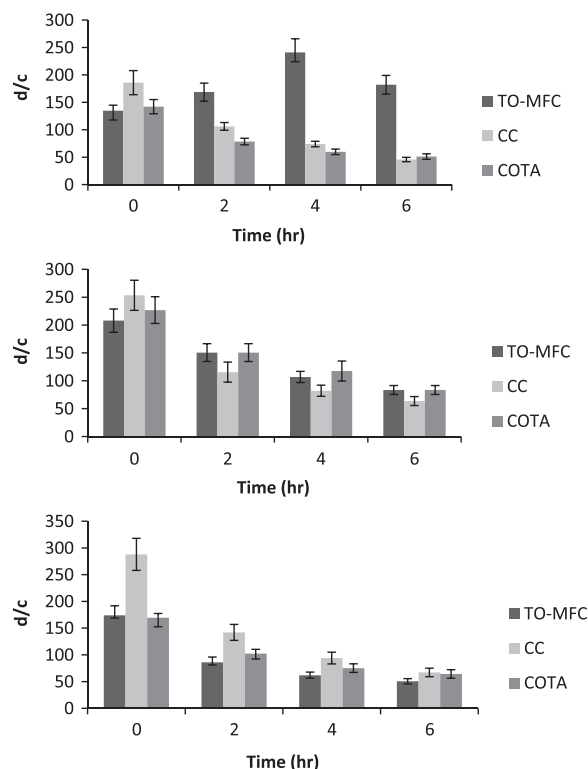| Sample name | OTC loading (mg/g) | pH 2.1 | pH 6.8 | pH 9 |
| --- | --- | --- | --- | --- |
| COTA | 100 | 0.573 | 0.106 | 0.092 |
| | 500 | 0.06 | 0.493 | 0.476 |
| | 750 | 0.507 | 0.484 | 0.465 |
| CC | 100 | 0.553 | 0.179 | 0.213 |
| | 500 | 0.493 | 0.486 | 0.536 |
| | 750 | 0.577 | 0.564 | 0.597 |
| TO-MFC | 100 | 0.534 | 0.195 | 0.191 |
| | 500 | 0.448 | 0.575 | 0.51 |
| | 750 | 0.429 | 0.454 | 0.414 |



**Fig. 4.** Antibacterial activity of drug delivery system of commercial tablet (COTA), cellulosic material (CC) and TEMPO modified microfibrilated cellulose (TO-MFC) [d/c: diameter of zone of inhibition/cumulative release concentration of drug].

model to assess the release behavior from network system. For the case of cylindrical tablets, $0.45 \leq n$ corresponds to a Fickian diffusion mechanism, $0.45 < n < 0.89$ to non-Fickian transport, $n=0.89$ to Case II (relaxational) transport, and $n > 0.89$ to super case II transport [25]. The value of release exponent (n) calculated from Ritger-Peppas model given in Table 4. Higher the n value lowers the release rate, as the diffusion is partially governed by swelling [20]. At acidic pH, mostly n value is less than alkaline pH thereby the release rate is higher at acidic pH. The results showed that the release was mostly anomalous type as the value of $n < 0.45$ in some cases while in some cases $n > 0.5$. The release was initially dealt by diffusion whereas after sometime the swelling of network majorly govern the release from fibril network. The results showed that both the materials are suitable for OTC delivery but the surface modification and some coating material is further needed to avoid the burst release of OTC from the networks. The surface characteristics, OTC loading amount and pH of medium is closely affecting the release behavior of OTC from the fibril surface.

### 3.5. In vitro antibacterial activity of drug delivery system

In addition to the important observation, OTC loaded nanocomposites were tested for its antibacterial efficacy at different pH to see whether they were able to demonstrate antibacterial effect or not (Fig. 4). It is well-known that OTC presents a class of the compound that is sensitive to pH and degrades at higher pH.

Several reports described the degraded products of OTC at different pH possessing no antibacterial activity [26]. Hence, it was logical to investigate the influence of pH (2.1, 6.8 and 9.0) on the antibacterial efficacy of the drug released at different time interval (0, 2, 4 and 6 h). For this purpose, we examined the antibacterial efficacy of OTC released from commercial tablet, CC and TO-MFC composites by well diffusion method. The antibacterial activities for CC and TO-MFC were performed for 750 and 500 μg/ml loading of drug, respectively, as at this concentration maximum release was observed. For the normalization purpose, the ratio of antibacterial efficacy /concentration was taken (Fig. 4) for 0, 2, 4 and 6 h. The obtained results exhibited that OTC maintained the antibacterial efficacy in a broad range of pH (2.1, 6.8 and 9.0). In most of the cases, the immediate antibacterial potential of control was more than other two matrixes but by the end of 6 h the ZOI value for both other matrix get increased as compared to control. Also, the antibacterial activities of three matrixes appear in the similar manner as reported for releasing. Thus, both the synthetic drug delivery system was found able in maintaining the efficacy of OTC as a well known antibiotic.

## 4. Conclusion

Here, we prepared OTC loaded nano-composites based on cellulose and TEMPO oxidized MFCs. The sustained released of OTC at different physiological pH was assessed. These cellulose matrixes efficiently retained the OTC molecule for sustained release and protected bioactivity of the drug at different pH. This new drug delivery system, based on TEMPO oxidized MFCs can be used for various therapeutic applications using different problematic medicines.

## Conflicts of interest

None declared.

## Ethical approval

None.

## Funding source

None.

## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.nhtm.2016.06.001.

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