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Microwave-assisted synthesis of curcumin-encapsulated silica-chitosan composite for drug release study

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The synthesis of curcumin-encapsulated silica-chitosan composite in a domestic microwave oven has been reported. The composite was synthesized through sol-gel route. Chitosan, a bio-compatible polymer, was used as capping agent while TEOS was used as silica precursor. The optimized composite samples were characterized by scanning electron microscopy (SEM), Fourier transform infrared spectroscopy (FTIR), thermo-gravimetric analysis (TGA) and X-ray diffraction (XRD) analysis. The feasibility of the drug release was monitored by setting up *in vitro* drug release experiments. The latter were performed in phosphate buffer saline (PBS) at pH 7.4 and room temperature (30ºC). Sustained curcumin release was found which took place up to 76% in regular manner in 90 h. The curcumin release kinetics was calculated using Higuchi, Korsmeyer – Peppas, zero order and first order models of drug release kinetics by fitting the values of curcumin release data in their respective equations. The Higuchi model of drug release was found best suited for the curcumin release from the composite among all the models studied for drug release.

Keywords: Curcumin, Silica, Chitosan, Composite, TEOS, Sol-gel

INTRODUCTION

Derivations of medicines from plants has been an important part of health care since ancient time and is playing a crucial role in present too [1, 2]. Curcumin is a prominent naturally occurring multitherapeutic agent [3]. Curcumin is obtained by the extraction of the rhizome of *Curcuma longa* which is commonly known as turmeric, a herbaceous plant of zingiberaceae family [4]. The rhizome is crushed to a fine powder of turmeric. Turmeric is yellow colored common kitchen spice which has been used for a long time for medicinal purpose as well. Turmeric contains only ~2% curcumin which is extracted in the form of curcuminoid along with bis-desmethoxycurcumin (BDMC) and desmethoxycurcumin (DMC). Curcumin is supposed to be a most vital fraction of turmeric and responsible for most of the biological functions associated with it. Curcumin is well of terpene and contains them predominantly in mono and sesqui form [5]. Curcumin is natural polyphenol which is hydrophobic in nature, hence shows poor solubility in water but charming one in other organic solvents like ethanol, methanol, acetone and dimethyl sulfoxide [6]. The phenol and diketone moieties of curcumin make it rich of antioxidant character. Curcumin shows charming anti-inflammatory, wound healing, antimicrobial and antiproliferative properties and hence is widely studied for the healing of different types cancers [7]. In spite of different valuable features associated with curcumin, its area of clinical applications is limited due to its hydrophobicity which restricts its easy bioavailability moreover, quick degradability and rapid metabolism also limit up its applications [7-9].

Bioavailability of naturally obtained drugs is needed to be enhanced to promote their oral consumption. Since last few decades, designing of drug delivery systems to carry such types of hydrophobic or lipophilic drugs like curcumin are drawing huge attention as it successfully carries the drugs to targeted area and enhances their bioavailability by providing sustained release [10]. Among various types of drug delivery systems, those based on mesoporous silica (MS) are being introduced as potential drug carriers due to their promising aptitude for drug delivery [11]. As the MS-based materials are rich in pore volume and surface area, therefore, they provide more significant hand for carrying a higher quantity of drug. Earlier research has affirmed that MS is able to increase the solubility of insoluble drugs like hydrophobic medicines used to treat the cancer, moreover they neglect the consumption of hazardous organic solvents and are more stable in thermal and chemical respect [12]. MS-based drug delivery systems show highly hydrophilic behavior, novel nonreactive attitude towards chemicals and excellent

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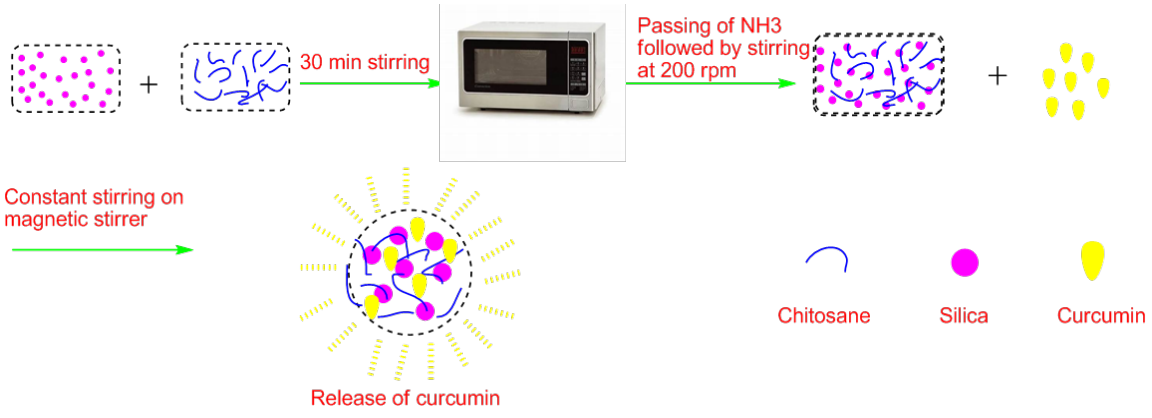
biocompatibility which makes them a suitable material for both *in vitro* and *in vivo* drug delivery systems [12]. There are a number of interactions formed between mesoporous surface of silica and drug moiety like electrostatic interaction, ionic bonding, hydrogen bonding, etc. which facilitate the hold of silica over drug moiety [13]. On discussing the mesoporous silica with respect to drug delivery system, a big deal of virtues is associated with it. We may utilize these in developing a significant curcumin delivery system using which various drawbacks associated with curcumin delivery like its bioavailability may be improved. A number of researchers worked to develop curcumin release systems using mesoporous silica as drug carrier [14, 15].

Kuang *et al.* built up a curcumin delivery system based on mesoporous silica for the treatment of cancer by photodynamic therapy (DPT) in which curcumin was being used as photosensitizer. The silica worked perfectly in mediating the curcumin in the DPT by carrying it up and made intracellular release [13]. Kotcherlakota *et al*. designed an amine functionalized series (S2, S4 and S6) based on mesoporous silica for curcumin release. MSU-2, KIT-6 and MCM-41, highly porous silica materials, were being used as model. Among all curcumin containing samples, the S4 was found to be more significant against cancer cells feasibility [16]. Mullassery *et al.* synthesized the composite of mesoporous silica using acrylamide β-cyclodextrin grafted 3-aminopropyltriethoxysilane bentonite (AMCD-g-APSB) for *in vitro* drug release study [17]. Nasab *et al.* prepared mesoporous silica-based drug carrier system to enhance the biocompatibility and bioavailability of curcumin. The curcumin was being capped by chitosan and the system worked perfectly as a shield to carry the drug successfully [18].

Due to success and positive results associated with drug carrier systems, a hydrophobic drug like curcumin might be encapsulated into hydrophilic polymer hydrogel or polymeric micelles for controlled release of the drug at targeted area [19]. The role of polymer is very crucial for the synthesis of MB-based system. Chitosan was found significant for the purpose due to its biocompatibility and biodegradability [20].

Chitosan is a cationic polysaccharide which can be obtained by deacetylated chitin. Chitosan is a well-known polysaccharide which is also one of the trusty applicants among biopolymers due to its wide area of applications like good antibacterial and antifungal properties and high metal binding capacity [21]. Moreover, it has power over a range of biological properties, like antimicrobial, antioxidant, anti-inflammatory, anti-cholesterol, cytocompatible and analgesic [22] which make it crucial for various applications, most relevant in pharmaceutical and medical fields like drug delivery and wound dressing [23]. Chitin is obtained from various kinds of living organisms, mostly from the cell wall of yeast and fungi. Chitosan has biodegradability, biocompatibility, non-toxic and mucoadhesive nature which enlarge its applications area aspects [24]. Chitosan is an only polymer with cationic character keeping it distinguishable from others. As chitosan is a polyaminoglycoside, the cationic character of chitosan is associated with its amino groups. This feature permits the modulation of its physicochemical properties through covalent links to other residues and responsible for its tendency to conjugate with different medicinal agentsm hence it plays a crucial role in drug delivery systems. In the present work, focusing on stable presentation of curcumin *via* delivery platform, we synthesized the curcumin-encapsulated silica-chitosan composite hydrogel to facilitate and regulate the curcumin delivery. Chitosan worked as pH responser polymer shell on silica surface [25, 26].



Scheme 1. Schematic representation of the synthesis of curcumin-encapsulated silica-chitosan composite.

EXPERIMENTAL

Materials and reagents

Tetraethoxysilane (TEOS 98%) was being used as silica precursor and was purchased from Merck, Mumbai, India. Chitosan, a natural polymer, was supplied from Otto chem. private Ltd. India; ethanol, curcumin and PBS buffer were provided from Merck. All chemicals were being used as supplied without further purification. LG Microwave (MH 2548QPS model), was used as energy source to conduct the respective chemical reactions. The solution's pH was evaluated with the help of digital pH meter from Globe instruments. All the quantitative analyses for the determination of curcumin released were carried out on Systronics double beam UV-VIS spectrophotometer.

Synthesis of silica-chitosan composite and encapsulation of curcumin

The synthesis of silica/chitosan composite with chitosan was based on the sol-gel method as reported previously [24]. Firstly, a 1% w/v solution of chitosan was prepared by dissolving 500 mg of chitosan in 50 ml of citric acid followed by 10 h continuous stirring to prepare a homogenous solution. Separately in a flask, 1 ml of TEOS was dissolved in 1 mL of ethanol and that solution was added dropwise to the already prepared solution of chitosan with constant stirring. After 30 min of stirring, the mixture solution was heated in a microwave for 30 sec at 20 microwave power (180 W). The solution was kept to cool down to room temperature for the introduction of ammonia current for small extent and then the flask was kept again on magnetic stirrer at 200 rpm. After around 10 h of stirring, the solution started thickening. Meanwhile, the solution of curcumin was also prepared in ethanol and was added slowly. After around 1 h a transparent gel was formed that was dried and washed up by ethanol.

Characterization of silica-chitosan composite

The curcumin-embedded silica-chitosan composite as synthesized, was characterized with the help of appropriate analytical techniques: Fourier transform infrared (FTIR) spectroscopy was employed to recognize the different functional groups in the composite sample, working in the range from 500 cm^{-1} to 4000 cm^{-1}, on a Thermo-Scientific (Nicole 6700); X-ray diffraction (XRD) technique was used to record the pore structure from 5^o to 40^o 2θ angle, carried out on Bruker D 8 advance instrument (Shimadzu, Japan). The thermal treatment of the samples was carried out in a differential scanning calorimeter (Mettler Toledo DSC1) by heating up to 800ºC at 10 K min^{-1} heating rate to analyze its behavior towards thermal treatment; the morphology and the structure of the synthesized composite was established by scanning electron microscopy (SEM) carried out on a Leo 435 VP model.

In vitro release study of curcumin from silica-chitosan composite

Drug release study was performed based on previously reported work with slight modifications [27]. The amount of curcumin-loaded composite sample containing 10 mg of curcumin was weighed and dispersed into 100 mL solution of phosphate buffer saline (PBS) of pH 7.4 containing 25% ethanol. The release medium as prepared was placed on a thermostatic shaker (100 rpm) at room temperature. At regular and definite time intervals, 3 mL release medium was withdrawn and replaced with same amount of fresh PBS buffer solution. The withdrawn solution was centrifuged for 5 min at 5000 rpm, then the measurement of the amount of curcumin released was done by UV–VIS spectrophotometer at λ_{max} = 425. First the instrument was calibrated by curcumin then the amount of released curcumin was analyzed with the help of a calibration curve [28-31]. The amount of curcumin released was quantified by using eq. 1 given below:

$$\text{Release } \% = \frac{\text{Amount of curcumin released}}{\text{Total amount of curcumin present}} \times 100.. \quad (1)$$

Kinetics of release

Release kinetics of drug from the composite and its mechanism was analyzed using different types of models such as Higuchi, zero order and first order models by fitting the drug release data in the equations given below [32, 33].

Higuchi model

In the Higuchi model, the graph is plotted between drug release and $t^{1/2}$. This model shows the graph representing the constant release of drug in a rational period of time which generally corresponds to inactive matrix and straight line is formed in the graph [34]. Higuchi model is represented by the equation (2):

$$M_t/M_\infty = K_H t^{1/2} \quad (2)$$

where M_t/M_∞ represents the fractional of released drug in t time while K_H is Higuchi constant.

Korsmeyer-Peppas model of drug release

It is also called a power law model which describes the release of drug from the polymeric system. This model is able to explain the release mechanism of drug in a simultaneous manner like water diffusion in the matrix, dissolution of matrix and swelling of matrix. The model is represented by equation (3):

$$M_t/M_\infty = kt^n \quad (3)$$

where M_t/M_∞ symbolizes the fractional of released drug in t time, K is Korsmeyer constant and n is release exponent.

Zero-order reaction

This type of kinetic study attributes to the constant release of the given drug; hence the drug release is only a function of time and is independent of drug concentration. Zero-order kinetic model is important in explaining the mechanism of different types of drugs like the drugs administrated to maintain the blood pressure and pain control drugs. The equation for calculating zero-order release kinetics is represented as equation (4):

$$M_t/M_\infty = k_0 t \quad (4)$$

where M_t/M_∞ symbolizes the fractional of released drug in t time while K_0 is zero-order constant.

First-order reaction

This model was developed to present the release of water-soluble drug. This model states that the release of drug at time‘t’ is only dependent of drug concentration. The first-order release kinetics model is represented by equation (5):

$$M_t/M_\infty = 1\text{-}\exp(-k_1 t) \quad (5)$$

where M_t/M_∞ symbolizes the fractional of drug released at time t, K_1 is first-order constant.

RESULTS AND DISCUSSION

Synthesis of curcumin-encapsulated silica-chitosan composite

Scheme 1 represents the systematic plan of silica-chitosan composite synthesis and curcumin encapsulation, in diagrammatic form. Mixture of TEOS and ethanol was added slowly and drop wise manner to the pre dissolved chitosan solution with constant stirring forming a homogenous solution. Then the solution was microwaved for 30 seconds followed by passing of ammonia current with constant stirring at 200 rpm. When the hydrogel started to be formed, curcumin solution was introduced to it.

Characterization of the samples

SEM

Figure 1 represents the SEM image of the curcumin loaded silica-chitosan composite. The external view of composite shows slightly porous and roughly arranged solid surface. The particles in the composite appear to be present in agglomerated form which is suggested due to the viscous nature of chitosan to entrap curcumin and silica in to the composite [34].

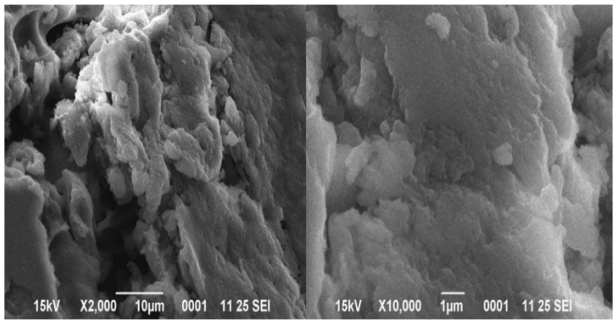


Figure 1. SEM image of the surface of curcumin-encapsulated silica-chitosan composite.

Thermal analysis

The result of thermal treatment of curcumin loaded silica-chitosan composite was studied by its TGA curve, shown in Figure 2. The TGA curve of silica-chitosan composite shows two weight loss steps. First one starts from 50 °C which leads to very slow and gradual decrease in weight till 300 °C while the second one starts at 350 °C. The TGA curve of the composite clarifies that there is negligible loss in weight till 200°C which demonstrates the thermally stable behavior of the composite. This also confirms that the curcumin present in the composite did not lose its properties during the experiments [35].

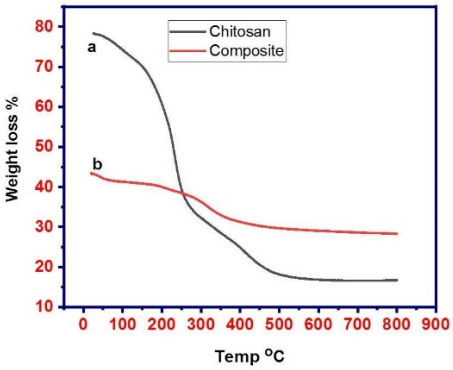


Figure 2. Thermogravimetric analysis of chitosan (a) and composite (b).

X-ray diffraction

The XRD outline of synthesized composite and chitosan is represented in Figure 3. As the XRD analysis pattern of curcumin is certain and already reported in literature, the behavior of curcumin was found to prove a highly crystalline nature [36]. The XRD diffractograms of chitosan, silica and synthesized composite are represented in Figure 3 revealing the semi-crystalline nature of chitosan and composite while the crystalline one of silica [37]. However, after the encapsulation of crystalline curcumin into chitosan-silica composite, no finely resolved crystalline peak was found in the XRD pattern of the composite suggesting that curcumin is well dispersed into the semi-crystalline chitosan matrix of composite [36].

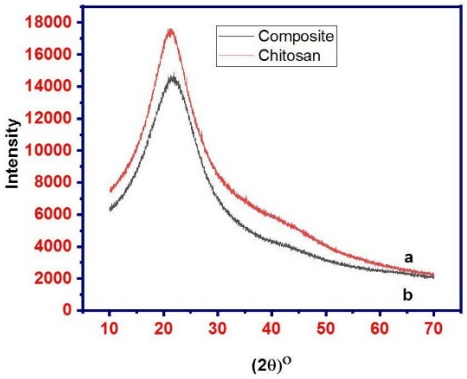


Figure 3. X-ray diffraction analysis graphs of chitosan (a) and composite (b).

FTIR spectra

The FTIR spectra of curcumin-loaded silica-chitosan composite are represented in Figure 4. The spectrum of curcumin shows the characteristic bands of −OH stretching at 3250 cm^{-1}, C=C and C=O mixed vibrations at 1630 cm^{-1}, C−O and C−C mixed vibrations at 1510 cm^{-1}, olefin C−H bending vibration at 1430 cm^{-1}, C−O−C stretching vibration at 1030 $cm^{-1}$and C−C−H aromatic bending vibration at 850 cm^{-1} [38]. In the spectrum of chitosan, the band at 3400 cm^{-1} is due to N-H stretching of amine group while the one at 1690 $cm^{-1}$is due to C=O stretching of carbonyl group of amide. The band at 1050 cm^{-1} represents the C-O stretching of secondary hydroxyl group [27]. In the spectrum of composite, there is slight shifting of some bands with the appearance of few new ones like the band at 1160 cm^{-1} representing the Si-O-Si stretching of silica in the composite. The height of the band at 3400 cm^{-1} slightly decreases due to the lower probability of hydrogen bonding due to a lesser number of hydroxyl groups present on the composite as compared with chitosan. The band at 1690 cm^{-1} in chitosan is shifted to a higher frequency value at 1750 cm^{-1} in the composite and the appearance of few new ones like a band present at 1160 cm^{-1} represents the Si-O-Si stretching of silica in the composite. The height of the band at 3400 cm^{-1} slightly decreases due to the lower probability of hydrogen bonding due to a lesser number of hydroxyl groups present on the composite as compared with chitosan. The band at 1690 cm^{-1} in chitosan is shifted to higher frequency value at 1750 cm^{-1} in the composite [27].

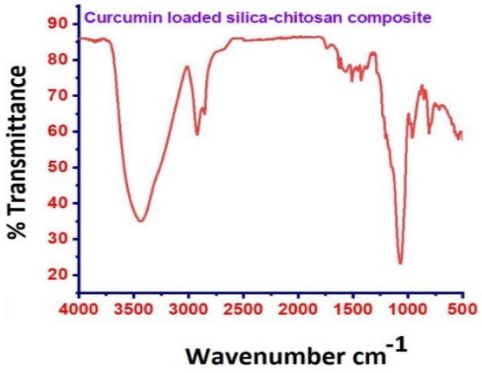


Figure 4. FTIR spectrum of curcumin-loaded silica.

In vitro curcumin release experiments

The *in vitro* experiments for curcumin release from the silica-chitosan composite were carried out at pH 7.4. Figure 5 shows that the curcumin release from the encapsulated silica-chitosan composite took place in a controlled way. In the first 10 hours just 30% of curcumin was released from the composite, which increased in a steady manner up to 52% after 24 hours. This regulation and maintenance of release was supported by the crucial role of amine groups of chitosan [39]. A sustained and gradual release was being observed up to 90 hours when 76% of drug was released. After that the rate of curcumin release was so slow that it was not noticeable.

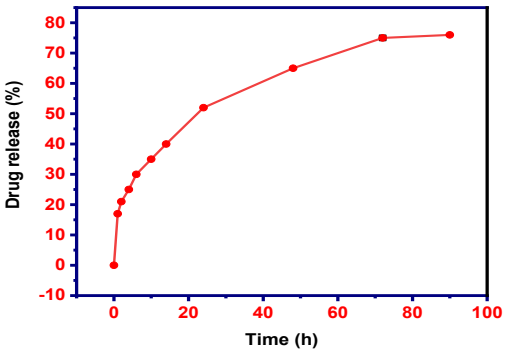


Figure 5. *In vitro* release of curcumin (%) with time from curcumin-encapsulated silica-chitosan composite in PBS (pH 7.4) at 30 °C.

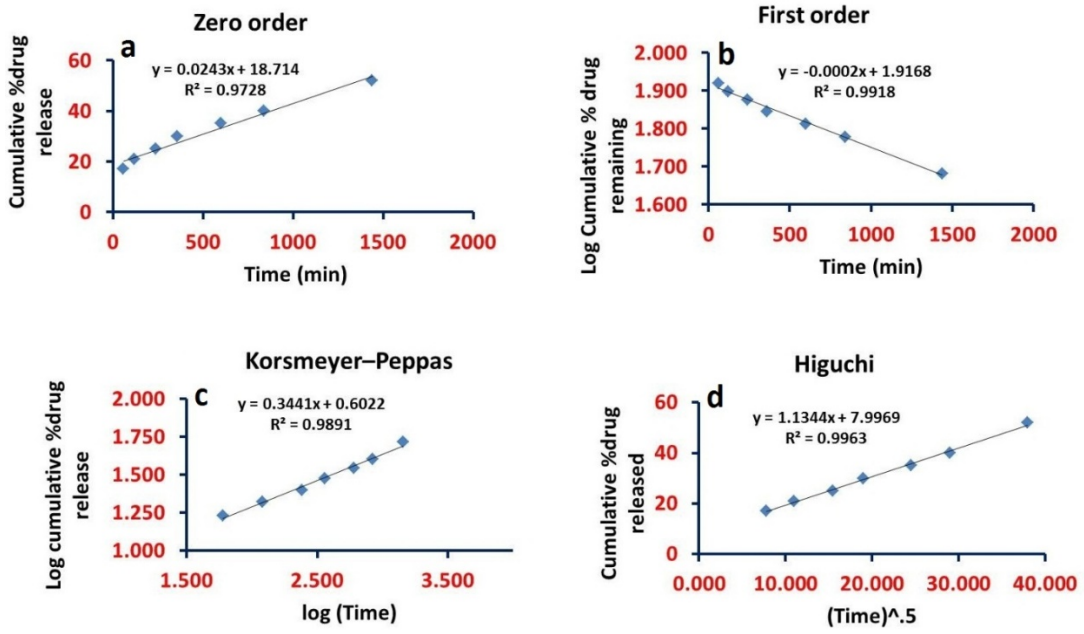


Figure 6. Kinetic study of curcumin release by zero order, first order, Korsmeyer-Peppas and Higuchi models of drug release.

Table 1. Kinetic models study and their various parameters.

S.N.	Kinetic Models	Plot	Parameters
1.	Kinetic equation for zero order	$M_t/M_\infty = k_0 t$	K_0 =0.024, R^2 = 0.972
2.	Kinetic equation for first order	$M_t/M_\infty = 1 - e^{(-k_1 t)}$	K_1 = 0, R^2 = 0.991
3.	Kinetic equation of Korsmeyer-Peppas	$M_t/M_\infty = kt^n$	K= 2.688 × 10^{-2}, R^2 = 0.989
4.	Kinetic equation for Higuchi model	$M_t/M_\infty = kt^{1/2}$	K_H = 0.996, R^2 = 0.996

Kinetic study of drug release

Figure 6 plots represent the kinetics of drug release through different models. In order to find out the kinetics of curcumin release from the curcumin-encapsulated silica-chitosan composite, we evaluated the regression coefficient for different kinetic models by fitting the *in vitro* drug release data of curcumin in the following four mathematical models, i.e., zero order, first order, Korsmeyer-Peppas and Higuchi models of drug release. The values of R^2 signify that the Higuchi model for drug release best fits curcumin release kinetic data. The kinetic drug release parameters (correlation coefficient (R^2) and rate constant) were calculated from Figure 6 and are shown in Table 1.

CONCLUSION

The successful synthesis of curcumin-encapsulated silica-chitosan composite by using sol-gel method and microwave radiation as energy source was reported. The structure, morphology and presence of different functional groups in the synthesized composite was ascertained by SEM and FTIR analytical techniques while the thermal behavior and crystal orientation were enlightened by TGA and XRD techniques. Curcumin is a versatile polyphenol which is applicable in a number of medical applications like antioxidant, antimicrobial, and anti-cancer agent. The bioavailability of curcumin was approached to enhance by its encapsulation into silica-chitosan composite. Silica-based drug delivery systems, being good carriers, provided an easy room to carry the sufficient amount of curcumin with additional qualities of chitosan in regulating the sustained release of drug. *In-vitro* drug release study experiments were performed in PBS (pH 7.4) at room temperature (30°C). Drug release took place in continuous manner and maximum up to 76% curcumin was released in 90 h. The kinetics of the release was also evaluated by using Higuchi, Korsmeyer-Peppas, zero order and

first order models of drug release kinetics by fitting the curcumin release data in their respective equations. The value of regression coefficient suggested that Higuchi model (R^2 value = 0.996) is best fitted for the release of curcumin from curcumin-encapsulated silica-chitosan composite.

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Conflict of Interest: *All authors have no conflict of interest.*

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