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Chitosan Modified Mesoporous Silica Nanoparticles as A Versatile Drug Carrier with pH Dependent Properties

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Abstract. Mesoporous silica nanoparticles (MSN) offer so many advantages as drug carrier, including large surface area, controllable pore size and morphology, and ease surface modification. Chitosan modified MSN has been synthesized to obtain drug carrier with pH dependent properties. Chitosan itself has been used in many studies as drug carrier due to its biocompatibility. In the present study, we combined MSN and chitosan in order to take advantage the high surface area and pore volume of MSN, and also the specific characteristics of chitosan at different pH values. The modification enables optimization of drug release at a low pH. The chitosan attachment on the surface of MSN was characterized by using FTIR. The release study of chitosan modified MSN at a variety of pH showed that the modification creates a controlled release profile of drug molecule (curcumin). At a high pH value, the accumulation release was low compared to that at a low level of pH. The release profile of chitosan-modified MSN at different concentrations of chitosan was also studied. The chitosan-MSN showed a controlled release profile.

INTRODUCTION

Drug Delivery System (DDS) that enables a controlled release profile is highly demanded since this feature has successfully improved drug efficacy. Various types of materials have been used, such as polymer, liposome and mesoporous silica particles, as carrier in DDS. Nanoporous silica based materials have been studied extensively in the last decade for various biological applications, including as a carrier in DDS [1]. The high surface area and pore volume, the controllable of pore size and morphology, and also the ease of surface modification have attracted much attention of researchers around the world to study these materials for various applications. Among previous studies, the observation of nanoporous silica based materials as drug carriers is one of the most active research areas.

Curcumin shows a high potent for being the treatment for various types of disease, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, epilepsy,cerebral injury, cardiovascular diseases, cancer, allergy, asthma, bronchitis, colitis, rheumatoid arthritis, renal ischemia, psoriasis, diabetes, obesity,depression, fatigue, and AIDS [2-4]. Yet, the low bioavailability of curcumin hinders the therapeutic effects from curcumin [5]. Many studies have been conducted to seek the effective DDS to enhance the therapeutic effects of curcumin [6].

MSNs have been used to enhance the theraputic effect of curcumin, in which various types of functionalized MSNs have been investigated, i.e., guanidine PEGylated mesoporous silica nanoparticles [7], lipid bilayer-coated curcumin-based MSN [8], curcumin-loaded silica encapsulated porous chitosan [9], mesoporous silica coated curcumin lipid core [10], and curcumin silica composites with double functionalization [11]. However, not many studies have focussed on the synthesis and application of chitosan-MSN for curcumin delivery.

Previously, the use of MSNs to enhance bioavailability of curcumin has been studied [12]. In the present study, a facile method to develop composite of chitosan-MSN is used and the materials are tested for the controlled release

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ofile by conducting release study of curcumin at a different pH solutions. It will examine a ph-dependent controlled release drug delivery system that has been successfully synthesized.

MATERIALS AND METHODS

Chemicals: Triblock poly(ethylene oxide)-block-poly(propylene oxide)-block-poly(ethylene oxide) copolymer $EO_{106}PO_{70}EO_{106}$ (Pluronic F127, MW=13400), copolymer $EO_{20}PO_{70}EO_{20}$ Pluronic 123, tetraethoxysilane (TEOS, 99%), 1,3,5-trimethylbenzene (TMB), 3-minopropyl triethoxysilane (APTES 99%), potassium chloride (KCl), phosphate buffer tablet and Tween 80 were purchased from Aldrich. A fluorocarbon surfactant (FC-4) was purchased from Yick-Vic Chemicals & Pharmaceuticals (HK) Ltd. All chemicals were used as received without any purification.

Synthesis of mesoporous silica nanoparticles (MSNs)

Nano-sized mesoporous silica materials with a cubic mesostructure were synthesized in accordance with previous method developed by Ying et al. [13] with some modifications. Subsequently, 0.5 g of F127 and 1.4 of FC_4 were mixed in the solution of 60 mL of 0.02 M HCl for 24 h before g of TMB was added and stirred continually for 4 (four) h, then 3 g of TEOS was mixed into the solution and was stirred for 24 h at 20°C. T solution was synthesized then removed to an autoclave and heated at *hydrothermal temperature* of 130° C for 24 h for hydrothermal treatment. The product was separated, washed and dried. The surfactant was removed by using calcination. The product was named MSN.

Curcumin loading

An amount of 350 mg of curcumin was dissolved in ethanol then followed by an addition of 175 mg MSN. The mixture was sonicated for one hour then followed by stirring it for 20 h. The amount of adsorbed curcumin was determined using UV-Vis Spectroscopy. The sample was named MSN-Cur (MC).

Chitosan modification

An amount of 0.025 gr of chitosan was dissolved in 25 ml acetic acid (1.5% v/v) and stirred for 4 h. Subsequently, 0.1 g MSN-Cur was also dissolved in 25 ml acetic acid (1.5% v/v). The chitosan solution was mixed with the MSN-Cur solution and stirred for 4 h. The product was separated by centrifugation and then dried. The procedure was repeated for different concentrations of chitosan. The product was named MSN-Cur-Chitosan (MCC).

Curcumin *in vitro* release

The release was performed based on the previous method developed by Jambhrunkar et al. with a slight modification [14]. At first, several solutions with a variety of pH were prepared (pH: 2.5 , 4.5, and 7.4). Then, for the release testing, 0.05 g of MCC was mixed with 10 ml of buffer solution in a dialysis membrane. Th, the membrane was located inside 250 ml of release media at certain pH. At certain interval time, an amount of 1 ml of the solution was llected and immediately replaced with 1 ml of release solution. The sample concentration was determined by using a UV–Vis spectrophotometer at 432 nm. The procedure was repeated for different pH solutions.

Characterization

Fourier-Transform Infrared Spectroscopy has been used to ascertain the functionalization of MSN with chitosan. UV-Vis Spectroscopy was used to determine the concentration of curcumin in the release media.

RESULTS AND DISCUSSION

At first, mesoporous silica nanoparticles were synthesized based on the method developed by Han et al. [13], and the same method to synthesis MSN was used. The material characterizations have been reported [12]. Mesoporous silica nanoparticles (IBN-2) with particle size around 100 nm were successfully synthesized. XRD analysis of MSN shows a typical pattern of porous material with cubic mesostructured. The nitrogen sorption analysis shows that type IV isotherm with a type H2 of hysteresis loop indicates porous materials with a cage-like structure. The pore size was 10 nm [12]. In general, the 3D mesostructured or a cage-like structures/interconnected pores has a better mass transfer for particles within the pores and also more resistant to pore blockage compared to that of the 2D mesostructured [15, 16].

The successful of chitosan modification onto MSN can be confirmed using FTIR. Figure 1 shows the comparison of FTIR spectra for different samples, namely: MSN, Curcumin, Chitosan, MSN-Curcumin (MC) and MSN-Curcumin-Chitosan (MCC). MC and MCC have similar spectra, representing the existence of MSN and Curcumin and also Chitosan in the same samples. The peak at 1095 cm^{-1} represents Si-OH, 1089.71 cm^{-1} indicates Si-O-Si, and 3278.76 cm^{-1} indicates SiO-H. The presence of chitosan can be detected from numerous peaks, such as 1490.87cm^{-1} (–C=O) *protonated amine* and 1643.24cm^{-1} (–C=O) *secondary amide*. Specifically, MCC also has several peaks that represent curcumin, such as 3436cm^{-1} O-H *stretching*, and 1514,02 cm^{-1}C=O and also C=C vibration. The characterizations using FTIR clearly shows the existence of MSN, curcumin and chitosan in the MCC sample [12, 17].

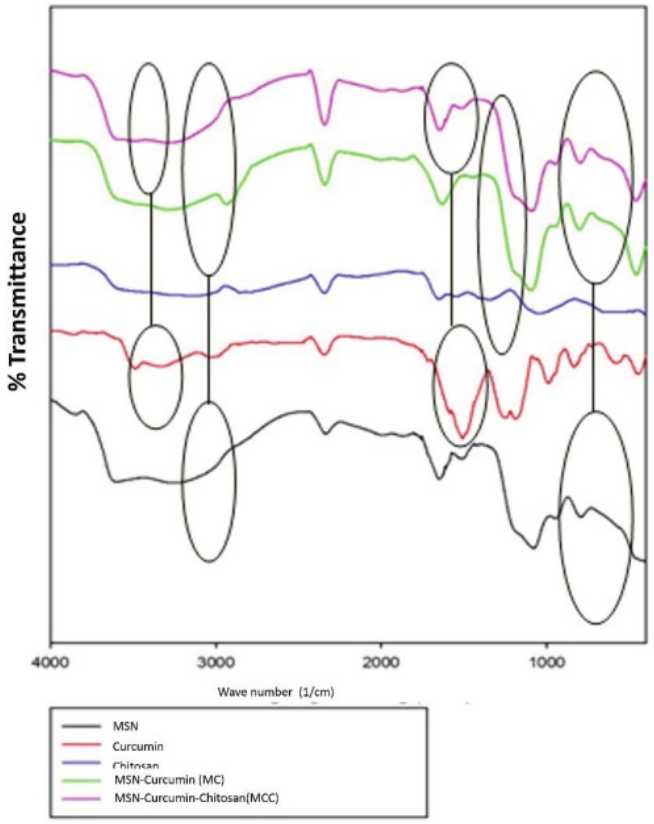

FIGURE 1. The Result of FTIR Analysis.

In the present study, MSN was used as a main carrier for curcumin, while chitosan was required to create surface modification of MSN. This modification supports the controlled release of curcumin from MSN. At first, we studied the optimum concentration of chitosan for MSN surface modification. Different concentrations of chitosan, namely 0.05%, 0.1%, 0.2% and 0.3% were studied. The release profile of curcumin at a variety of pH for various concentrations can be seen in Fig. 2 to Fig. 6. Fig. 2 to Fig. 5 demonstrate the release profile at a variety of pH and different chitosan concentrations, namely: 0.05, 0.1, 0.2 and 0.3, subsequently. Furthermore, Fig. 6 shows the release profile for various chitosan concentrations at pH 2.5.

It revealed an interesting finding in which in all concentrations of chitosan, namely: 0.05%, 0.1%, 0.2% and 0.3%, the effect of chitosan against the release profile at different pH: 2.5, 4.3 and 7.4, was obvious. All samples had similar trend, which is a higher accumulative release profile at the lowest pH: 2.5. As the pH solution increased, the percentage was dropped.

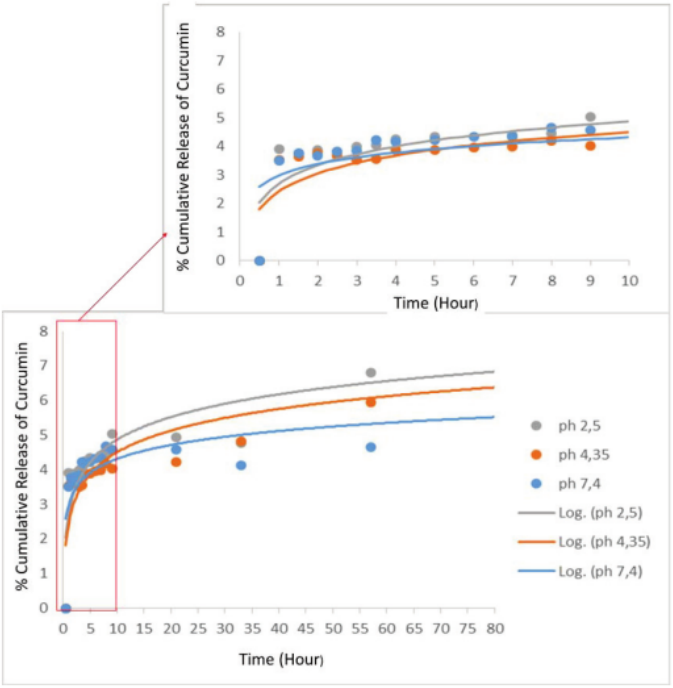

FIGURE 2. *In Vitro* release profile of Curcumin at a variety of pH for 0.05% chitosan concentration.

Most of the curcumin were located within the pores of MSN (IBN-2). The chitosan modification caused pore closure. However, at low pH, the closure is opened. This is mainly due to the characteristics of chitosan. The swelling of Chitosan at a low pH, remove the pore blockage by chitosan, as results more curcumin within the pores can be released. Finally, the higher accumulation of curcumin release can be achieved at a low pH compared to higher pH [18].

By comparing Fig. 2, 3, 4 and 5, the application of MCC with 0.05% chitosan concentration resulted in a higher accumulation release compared to other concentrations of chitosan. At a high concentration of chitosan, there is a possibility that chitosan may cause steric hindrance for curcumin molecules to diffuse within the pores. Thus, it is important to consider the optimum concentration of chitosan.

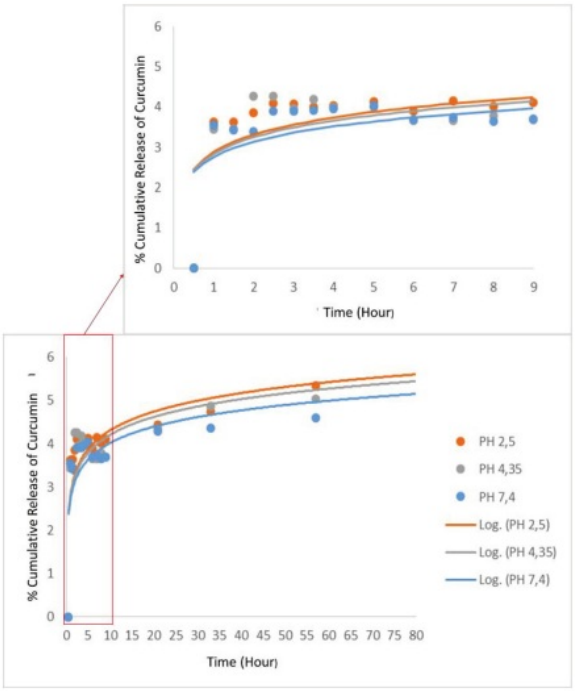

FIGURE 3. *In Vitro* release profile of Curcumin at a variety of pH for 0.1% chitosan concentration.

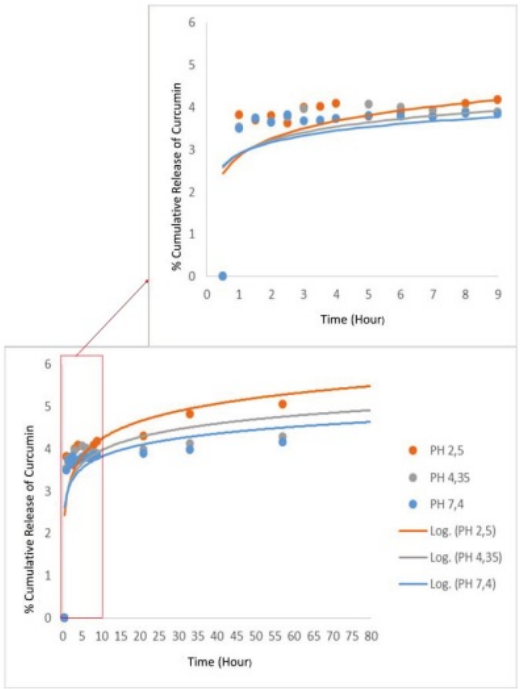

FIGURE 4. *In Vitro* release profile of Curcumin at a variety of pH for 0.2% chitosan concentration

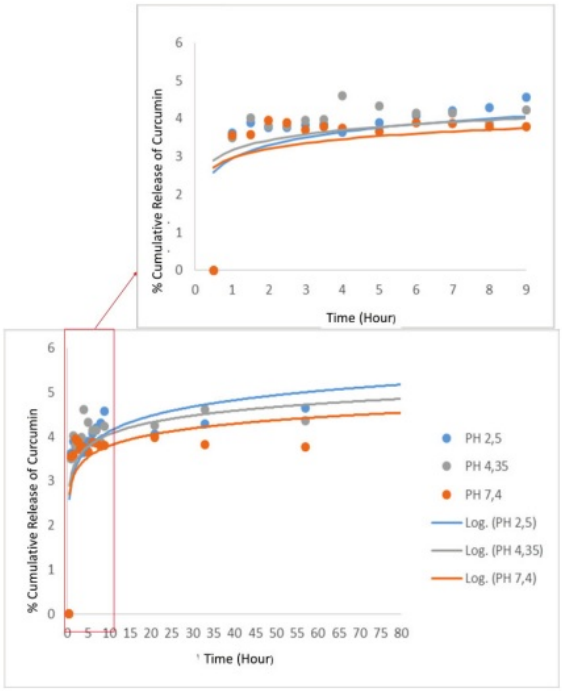

FIGURE 5. *In Vitro* release profile of Curcumin at a variety of pH for 0.3% chitosan concentration.

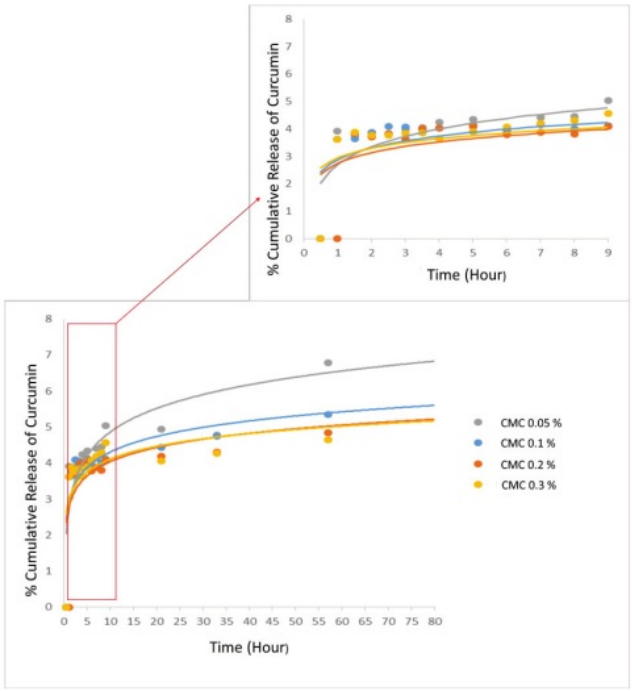

FIGURE 6. *In Vitro* release profile of Curcumin at a variety of pH for 2.5% chitosan concentration.

The existence of pores within MSN is very important to avoid "burst release" and to maintain a "prolonged release". In addition, the nanopores limit interaction between curcumin and reduce the formation of agglomeration. The nanopores also maintain the curcumin in non-crystalline form. These conditions lead to the higher solubility of curcumin [12]. In the present study, MSN with type of IBN-2 was used. This type of MSN has a cubic mesostructured which may enhance the release profile of curcumin [12, 15, 19, 20].

CONCLUSION

Nanocomposites of MSN-Curcumin-Chitosan (MCC) has been successfully synthesized. The produced MCC showed a controlled release profile based on pH value. MCC reached an optimum accumulation of release at a low pH (2.5). It indicates that the release profile of curcumin is affected by the concentration of chitosan developed within the MSN. The results show a promising potency of MCC for drug controlled release. These properties may enhance the therapeutic effect of the medicine and reduce the undesirable side effects.

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