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Trans-stilbene based spherical mesoporous organosilica material for loading and release of hydrophobic curcumin

Yaşar Gök[a], Osman Tayyar Arlı[b], Halil Zeki Gök[c*]

[a,b,c] *Burdur Mehmet Akif Ersoy University, Faculty of Arts and Sciences, Department of Chemistry, Burdur, Türkiye*

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[a]https://orcid.org/0000-0003-3134-7560
[b]https://orcid.org/0000-0001-7619-2668
[c]https://orcid.org/0000-0001-7641-2683

*Correspondence: Halil Zeki Gök
Burdur Mehmet Akif Ersoy University, Faculty of Arts and Sciences, Department of Chemistry, Burdur,Türkiye
e-mail: halilzekigok@gmail.com

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ABSTRACT

In this study, a new mesoporous organosilica carrier system was synthesized in which hydrophobic trans-stilbene is placed on the walls of the drug delivery system. In this way, it is aimed to increase the interaction between hydrophobic curcumin and the silica surface and to load more curcumin into the drug delivery system. Trans-stilbene based mesoporous organosilica (TSMON) material was prepared in the reaction of (E)-1,2-bis(4-(3-(triethoxysilyl)propyl)phenyl) ethylene (1) with tetraethyl orthosilicate in the presence of triblock copolymer cetyltrimethylammonium bromide as a template in NaOH solution. Characterization of synthesized TSMON was done by FT-IR, XRD, BET, SEM and TGA analyses. Curcumin loading into the drug delivery system TSMON was carried out by mixing curcumin and TSMON in the dark for 24 hours. After the measurements made in the UV-Vis spectrophotometer, entrapment efficiency and loading capacity for TSMON were calculated as 22% and 18.2%, respectively. Next, the time dependent release of curcumin from Cur@TSMON at physiological and endosomal pH was studied. After 5 days of UV-Vis measurements, the percentage of curcumin release from Cur@TSMON was around 1% at pH = 5 and 7.4. The low release percentage obtained indicates a strong interaction between TSMON and curcumin penetrating the pores of the TSMON. This strong interaction allowed the drug delivery system TSMON to carry 99% of the payload without leaking at pH = 5 and 7.4 without pore capping agents.

Key Words: Curcumin, drug loading and release, mesoporous organosilica, trans-stilbene

1. INTRODUCTION

Cancer is one of the most important public health problems of today, which often results in death by disrupting human health. Cancer is characterized by cell cycle disruption due to genetic and epigenetic mutations and increased cell proliferation as a result. Numerous cellular pathways that control normal cell proliferation appear to be disrupted in cancer. According to the International Agency for Research on Cancer (IARC), the number of cancer-related deaths was 8.2 million people in 2012 (1), 8.8 million people in 2015 (2) and 9.6 million people in 2018 (3). The ratio of these deaths among the deaths in the relevant years corresponds to a slice of 20%. Again, according to IARC, 20 million new cases are expected to occur by 2025. Statistics show that the cure rate in cancer cases is also quite low. One of the most important reasons underlying this high mortality rate is the accumulation of therapeutic drugs used in cancer treatments in normal healthy tissues and organs other than tumor tissues (1). Today, traditionally, radiotherapy and chemotherapy methods are widely used in cancer treatment.

The types of drugs used in cancer treatment are divided into two groups as hydrophobic drugs and hydrophilic drugs according to their solubility in water. It is necessary to design the nanocarrier

considering the properties of the drug in order to have a high loading rate of the drug to be transported. (1). The majority of anti-cancer drugs used today are hydrophobic. These drugs can pass through the cell membrane by advancing to the cell without dissolving in the aqueous medium they pass through.

Another area that researchers have been working on in recent years is natural products. The fact that some of the natural products have the potential to prevent cancer or to be used in cancer treatment with less side effects causes the attention of researchers to be drawn in this direction. One of the natural products that has been studied extensively in recent years is curcumin (4-7). However, there are some problems that limit the use of curcumin in cancer research. The most important of these is the low solubility of curcumin in water. Due to their low water solubility, drug application concentrations can be very low (8). Therefore, the ability of curcumin to be transported into the cell is extremely important to increase the therapeutic effect of curcumin. In order to increase the application concentrations, it has been reported that the concentrations of hydrophobic drugs in the aqueous medium can be increased up to 1000 times when transported in nanocarriers (9-10). Mesoporous silica nanostructures, which are among the nanocarrier materials, can have pore sizes ranging from 2 nm to 50 nm. In addition, the thermal and mechanical stability of mesoporous silica carriers is quite high compared to other nanocarriers. Because of these features, mesoporous silica nanocarriers emerge as a class with the potential to be used for drug delivery and biomedical applications. (11-12).

Mesoporous silica nanocarriers are differentiated as mesoporous silica nanoparticles (MSN), mesoporous organosilica nanoparticles (MON) or periodic mesoporous silica nanoparticles (PMO) according to the starting materials used during their synthesis. Synthesis of MSN, MON or PMO is generally performed by following the sol-gel method (13-14). Surface area of the silica structure, pore diameter, pore volume, hydrophobicity, size of the drug molecule, and interactions between the drug and the silica structure can be listed as some of the parameters that affect drug loading studies. The same parameters play an active role in drug release studies. Among these parameters, the type of interaction between the drug molecule and the surface of silica is critical for both drug loading and drug release studies (15).

Since curcumin has a hydrophobic chemical structure, the loading rates to the hydrophilic MSN are generally low. In order to solve this problem, it is necessary to increase the number of studies on MON derivatives, where the hydrophobic character can be adjusted by the amount of added organic compound. In this study, a mesoporous organosilica carrier system was synthesized in which hydrophobic trans-stilbene is placed on the walls of the drug delivery system. In this way, it is aimed to increase the interaction between hydrophobic curcumin and the silica surface and to load more curcumin into the drug delivery system.

2. MATERIALS AND METHODS

2.1. Materials and Equipment

(E)-1,2-bis(4-bromophenyl)ethene was obtained by following the method given in the literature (16). Cetyltrimethylammonium bromide (CTAB), 3-chloropropyltriethoxysilane (CPTES), and all other reagents were obtained from commercial suppliers. The procedures in Perrin and Armarego were applied in the steps of drying and purification of solvents (17). For FT-IR measurements of samples, a Shimadzu IRAffinity-1S was used as the recorder by using KBR pellet technique in order to elucidate the synthesized structures. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 MHz spectrometer using $CDCl_3$ (99.9%) to reveal chemical shifts of the protons and carbon in the synthesized organic materials. To confirm the mesoscale periodicity of the silica material, X-ray diffraction (XRD) measurement of mesoporous materials was performed on a PANalytical Empyrean X-ray diffraction meter using Cu-K_α radiation (λ = 0.154056 nm) in the range of 1°–10° and 10°–80° scattering

angle 2θ . The Jeol SEM-7100-EDX instrument was used to record the field emission scanning electron microscope (FESEM) images of samples to clarify the morphology of samples. Thermogravimetric analysis (TGA) measurements were performed on the Seiko SII TG/DTA 7200 instrument in order to see the mass losses due to temperature increase. During the TGA analysis, the flow rate of N_2 gas was 2 mL min^{-1} and the heat rate was 10 °C min^{-1}. N_2 sorption isotherms were recorded on Micrometrics Surface Area and Porosity Tristar II analyzer to calculate the pore diameter, pore volume and total surface area of the silica material. Optima 3000 UV-Vis spectrophotometer was used for measurements in drug loading and release experiments.

2.2. Synthesis

2.2.1. Synthesis of (E)-1,2-bis(4-(3-(triethoxysilyl) propyl)phenyl)ethylene (1)

(E)-1,2-bis(4-bromophenyl)ethene (7.5 g; 22.2 mmol) and 155 mL of dry THF were added into a two-necked flask and stirred under an inert atmosphere until dissolution occurred. After dissolution was complete, its temperature was adjusted to -78 °C. n-BuLi (54 mL; 88.7 mmol) was dropped into the stirring reaction content at -78 °C for approximately 1 hour. After the dripping was finished, it was stirred for 1 more hour at the same temperature. At the end of the period, CPTES (12.7 g; 53.2 mmol), a solution of which was prepared in 25 mL of dry THF, was added to the stirring reaction at -78 °C with the help of a dropping funnel in 1 hour. After addition, the reaction contents were stirred for another 2 hours at the same temperature. After the time, the reaction contents were allowed to warm to room temperature and stirred at room temperature overnight. The reaction contents were filtered and the filtrate was evaporated to dryness under reduced pressure. The remaining residue was extracted with ether-water. The ether phase was dried over anhydrous Na_2SO_4, filtered and the filtrate was evaporated to dryness. The obtained crude yellow oily product was purified by silica gel column chromatography eluting with dichloromethane. Pure product 1 was obtained in red oily form. Yield: 5.8 g (45%). FT-IR (disk) ν = 3065, 3018, 1597, 1391, 1265, 1214, 1162, 1109, 1075, 966, 824, 745 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) *δ*: 0.89 (m, 2H), 1.23 (m, 9H), 1.88 (m, 2H), 3.54 (m, 2H), 3.79 (m, 6H), 7.17 (d, *J* = 4.5 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 2H), 7.61 (d, *J* = 7.8 Hz, 2H) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) *δ*: 11.6 (CH_2), 18.4 (CH_3), 26.7 (CH_2), 47.8 (CH_2), 59.4 (CH_2), 126.4 (CH), 129.4 (CH), 134.3 (CH),135.0 (C), 138.7 (C). MALDI-TOF MS calculated $[M+H]^-$ for $C_{32}H_{52}O_6Si_2$: 588.3 found: 665.8 $[M+2K]^+$.

2.2.2. Preparation of mesoporous organosilica nanoparticles (TSMON)

CTAB (0.702 g; 1.93 mmol) and H_2O (338 g) were placed in a two-necked 100 mL flask and mixed at room temperature. The temperature of the mixture was brought to 80 °C by adding NaOH (2 M; 2.4 mL) and it was stirred at this temperature until it became clear. Then, a solution of 1 (0.58 g; 1 mmol) in 2.5 mL of acetone and TEOS (3.75 g; 18 mmol) were added to the reaction medium simultaneously with syringes. After addition, it was stirred for another 2 hours at 80 °C. At the end of the period, the temperature was taken to 90 °C and the mixing was stopped and the reaction content was left motionless at this temperature for 48 hours. At the end of the period, the reaction contents were filtered and the solid was washed with water. It was dried in an oven at 80 °C for 24 hours. In order to remove the surfactant CTAB from the pores of the obtained material, the solid part was taken into a 500 mL flask. After that, 384 mL of ethyl alcohol and 8.7 g of HCl were added and mixed at 80 °C for 24 hours. At the end of the period, the reaction contents were filtered. The solid was washed with water and dried in an oven at 80 °C for 24 hours. ~1.4 g of solid was obtained.

2.3. Drug loading and release

2.3.1. Curcumin loaded TSMON (Cur@TSMON)

In order to load curcumin into TSMON, 25 mL of curcumin stock solution (4 mg curcumin/mL ethyl alcohol) was taken, 100 mg of TSMON was added into it, and it was dispersed with the help of a sonicator. The sonicated solution was stirred in the dark at room temperature for 24 hours. At the end of

the period, the mixture was centrifuged.

The supernatant was kept for the encapsulation efficiency calculations. TSMON was separated from the drug loading solution and washed with 20 mL of ethanol and centrifuged. The supernatant was added to the previous collected one. The drug-loaded nanoparticles were dried under vacuum. Entrapment efficiency and drug loading capacity were calculated using Equations 1 and 2 after reading the absorbance of loading and washing solutions in UV-Vis spectrophotometer at λ = 420 nm (18-19).

$$Entrapment\ efficiency\ (\%) = \frac{mass\ of\ loaded\ curcumin(mg)}{initial\ mass\ of\ curcumin(mg)} x100 \quad (1)$$

$$Loading\ capacity\ (\%) = \frac{mass\ of\ the\ loaded\ curcumin\ in\ TSMON(mg)}{mass\ of\ TSMON\ (mg)} x100 \quad (2)$$

2.3.2. Drug release (Cur@TSMON)

Drug release studies from the drug-loaded Cur@TSMON structure were performed according to the methods given in the literature (20). Cur@TSMON (1 mg for pH = 7.4 and 1.1 mg for pH = 5) constructs disperse in 10 mL of PBS (pH = 7.4 and pH = 5) buffer containing 10% (v/v) Tween-80 was mixed at 37 °C and 100 rpm. After taking samples from the solution at scheduled time intervals and centrifuging at 12.000 rpm for 15 minutes, the absorption of the supernatant part was read at 420 nm in the UV-Vis spectrophotometer. After reading, the supernatant was added back to the drug release medium and mixing was continued. The amount of drug released over time was determined by placing the absorption value read on the standard calibration curve.

The drug release profiles of mesostructures were determined by graphing the data obtained depending on time.

3. RESULT AND DISCUSSION

3.1. Synthesis and characterization

The synthesis scheme of the trans stilbene based mesoporous organosilica drug delivery system TSMON is given in scheme 1. The starting product (E) -1,2-bis(4-bromophenyl)ethene was synthesized following the method given in the literature (16). Organic bridged bissilyl compound 1 was obtained from the reaction of the (E)-1,2-bis(4-bromophenyl) ethene with 3-chloropropyltriethoxysilane (CPTES) in the presence of n-BuLi in dry THF at -78°C in an inert atmosphere. The structure of the obtained compound was elucidated by various spectroscopic techniques. In the FT-IR spectrum taken using the ATR technique, the tension vibration bands belonging to the -C-H group in the aliphatic chain participating in the structure appeared below 3000 cm^{-1}, indicating that the CPTES group was successfully bonded to the E-alkene structure. ^{1}H and ^{13}C NMR spectra of compound 1 were recorded in $CDCl_3$ solvent. The signals appearing at d = 0.89, 1.23, 1.88, 3.54 and 3.79 ppm in the ^{1}H NMR spectrum obtained are in harmony with the expected signals for the protons in the $-CH_2$ and $-CH_3$ groups in the structure of CPTES and support the proposed structure for compound 1. Again, in the ^{13}C NMR spectrum, it was seen that the carbon atoms in the -

Scheme 1. Synthesis of mesoporous organosilica drug delivery material **TSMON**

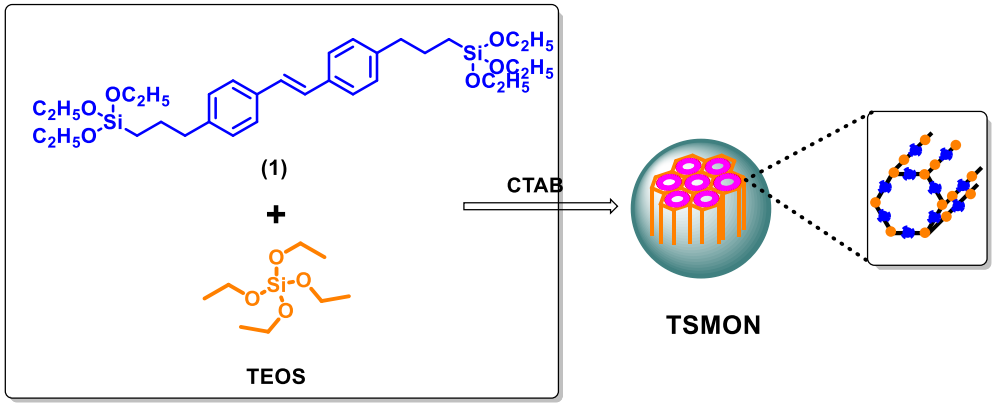


Figure 1. FT-IR spectrum of **curcumin**, **TSMON** and **Cur@TSMON**

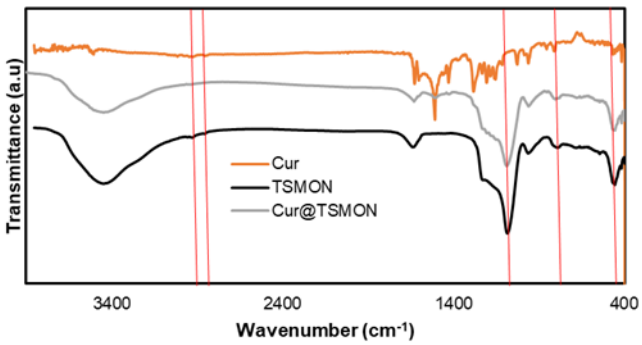
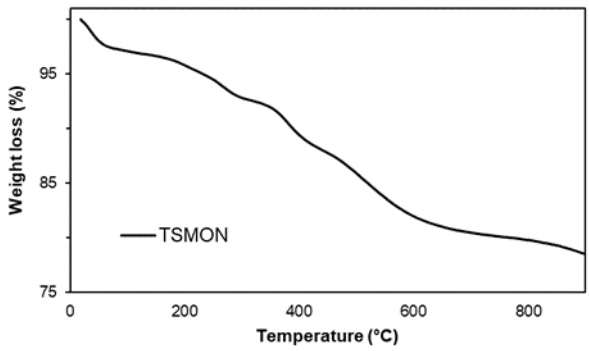


Figure 2. TGA curve of **TSMON**



CH_2 and -CH_3 groups in the aliphatic chain resonate in different regions at d = 11.6 (CH_3), 26.7 (CH_2), 47.8 (CH_2), 59.4 (CH_2) ppm, which is consistent with the proposed structure. The observation of the molecular ion peak at m/z = 665.81 $[M+2K]^+$ in the mass spectra of the synthesized 1 obtained by MALDI-TOF technique supports the proposed structure.

Mesoporous organosilica (TSMON) material was prepared in the reaction of 1 with tetraethyl orthosilicate (TEOS) in the presence of triblock copolymer cetyltrimethylammonium bromide (CTAB) as a template in basic solution. As the first step, FT-IR spectroscopy was applied to characterize TSMON nanoparticles. Observation of the main three characteristic peaks at 1.080, 817, and 455 cm^{-1}, corresponded to the antisymmetric, symmetric Si-O stretching and deformation mode of SiO_4 tetrahedral in the silica framework confirmed the successful synthesis of TSMON (Figure 1). These observed values are in agreement with the literature (21). The presence of the additional bands at around 2926 and 2845 cm^{-1} for -CH_2 group, and 3064 cm^{-1} for aromatic ring in the spectrum of TSMON can be taken as clear evidence that organic bridged silyl derivative 1 was successfully incorporated to the silica wall of mesoporous material by condensation of 1 and TEOS.

The TGA curve for TSMON is shown in Figure 2. The ~3% mass loss observed in the TGA curve below 150 °C is due to the physically attached solvents trapped in the pores in the channels of the TSMON. The ~19% mass loss observed between 150 °C and 800 °C corresponds to the degradable organic parts contained in TSMON. Low angle powder X-ray diffraction analysis was carried out to understand whether a mesoscale periodicity occurs in the TSMON structure. The obtained low angle powder X -ray diffraction pattern is shown in Figure 3. The occurrence of a very strong signal at 2θ = 2.1° and two low-intensity signals at 2θ = 3.6 and 4.2° in the low angle XRD dust pattern clearly shows that a mesoscale periodicity has occurred for TSMON. Scanning electron microscope (SEM) analysis was performed to examine the morphological features of the obtained mesostructured organosilica TSMON and is shown in Figure 4. The image shows that TMSON has a relatively uniform, spherical and monodisperse, with the particle size around 110 nm (Figure 4).

Figure 3. Low angle X-ray diffraction (XRD) pattern of **TSMON**

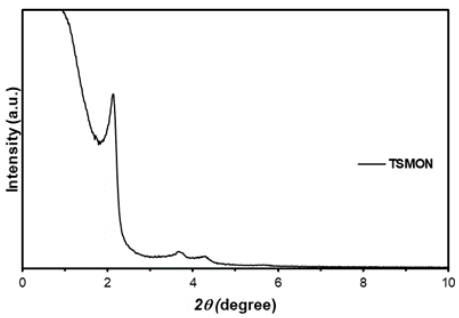


Figure 4. Scanning electron microscope images (SEM) of **TSMON**

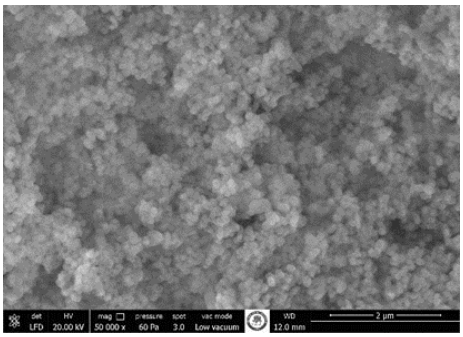
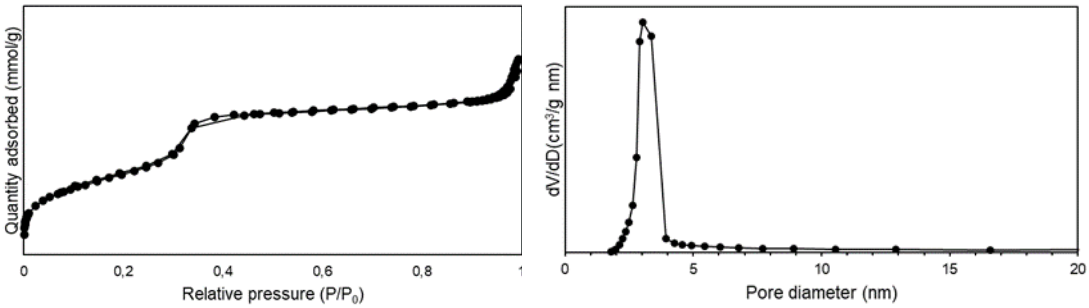


Figure 5. N_2 adsorption-desorption isotherm of **TSMON** (at left) and pore size distribution of **TSMON** (at right)



Absorption-desorption isotherms and pore size distribution curves for TSMON are given in Figure 5. The pore size distribution was calculated from the adsorption curve by using Barrett-Joyner-Halenda (BJH) method. The adsorption-desorption isotherm obtained for TSMON corresponds to the type IV isotherm with an H1 hysteresis loop according to the IUPAC classification (22). The pores of the TSMON mesoporous organosilica structure with this type of isotherm were filled in the range of p/p° = 0.2-0.3 relative pressure value during the adsorption phase. This type of curve indicates that the material is uniformly mesoporous. The BET surface area and the average pore size (DBJH) of the TSMON mesoporous silica structure were calculated as 660 m^2/g and 3.8 nm, respectively.

Curcumin loading efficiency

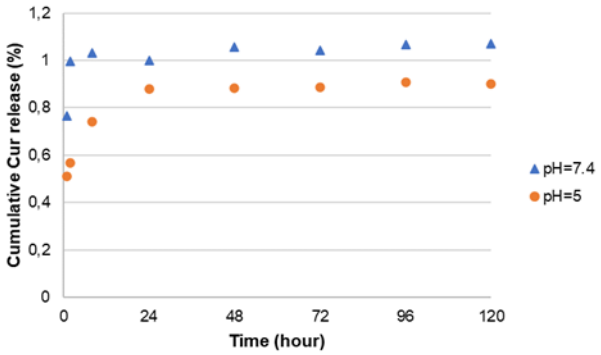
Curcumin, a natural product with hydrophobic properties, was used to determine the loading capacity of drug delivery system TSMON through physical interactions. For this, TSMON was added into curcumin stock solution and dispersed with the help of a sonicator. The sonicated solution was stirred for 24 hours at room temperature in the dark. At the end of the period, the mixture was centrifuged to separate the loading solution and the drug loaded nanoparticles (Cur@TSMON). Curcumin loaded nanoparticles were washed 2 times with ethanol and centrifuged again, and the washing solutions were combined with the loading solutions. In order to determine the amount of curcumin remaining in the washing and loading solutions, absorption readings of these solutions were performed at λ= 420 nm in the UV-Vis spectrophotometer. Using the values obtained after the measurement, the entrapment efficiency (%EE) and loading capacity (%LC) of the TSMON were calculated with the help of equations 1 and 2. For TSMON, the percentage of drug loading was calculated as 22% using equation 1 and the loading capacity was calculated as 18.2% with the help of equation 2.

Successful loading of curcumin into the TSMON carrier system was confirmed by FT-IR analysis. The recorded FT-IR spectra of Curcumin and Cur@TSMON are given in Figure 1. Free curcumin has many characteristic vibrations in the FT-IR spectrum. For example, C-O vibration is observed at 1626 cm^{-1}, C=O vibration of conjugated ketone is observed at 1592 cm^{-1} and phenol group at 1502 cm^{-1}. The stretching vibration of the -OH group in the phenol hydroxy group is observed around 3500 cm^{-1}. When the FT-IR spectrum of Cur@TSMON is examined, a decrease in the intensity of the signals belonging to all characteristic vibrations of curcumin is observed. The fact that the vibration at 1592 cm^{-1}, which is one of the characteristic vibrations of curcumin, can still be observed in the FT-IR spectrum of Cur@TSMON confirms that curcumin can be physically loaded into TSMON.

Curcumin release profile

In order to determine the release behavior and amount of curcumin from Cur@TSMON, a release study was performed at physiological pH = 7.4 and endosomal pH = 5 The time-dependent variation of the amount of curcumin in the solution was followed. For this, Cur@TSMON was taken in the amounts specified in the method section and dispersed in 10 mL of PBS (pH = 7.4 and 5) containing 10% tween-80 by volume and mixed at 37 °C at 100 rpm. Samples were taken from the mixture at regular intervals,

Figure 6. Curcumin release profile from **TSMON** at different pH values



centrifuged at 12,000 rpm for 15 minutes, and the absorption of the supernatant was read in a UV-Vis spectrophotometer at a wavelength of 420 nm. Absorption values were plotted on the standard calibration curve and the resulting cumulative release rates were plotted against time. The resulting graphic is given in Figure 6.

As seen in Figure 6, the cumulative amount of curcumin released from Cur@TSMON after 5 days at pH = 5 and 7.4 was around 1%. Maximum release values were reached in the release graph for both pH values in the first 24 hours, and there was no increase in release values for the next 4 days following the first day. The release of only 1% of the loaded drug amount means that the strong intermolecular interaction between curcumin and TSMON is still preserved at the pHs studied. This shows that the drug transport system TSMON, without using pore closing agents, can transport 99% of its cargo without leaking at pH = 5 and 7.4.

In cancer treatment, it is very important that drug delivery systems carry the payload to the target without leaking. Premature leakage of the cargo makes the treatment impossible. It can be considered as a very important result that only 1% of the curcumin carried by the TSMON leaks after 5 days without using pore closing agents. In case of excessive drug leakage, this problem can be eliminated with pore closing agents. However, the use of pore-closing agents increases the number of synthesis steps, thus the time and ultimately the cost. Considering these aspects, the TSMON drug delivery system can be considered more economical than its counterparts.

4. CONCLUSION

Within the scope of this study, a new drug delivery system TSMON, which is in the class of mesoporous organosilica nanomaterials, was synthesized. Using the co-condensation method, hydrophobic trans-stilbene was added to the mesoporous silica structure and thus a drug carrier system with more hydrophobic character was obtained compared to conventional MSN with hydrophilic character. Thanks to the hydrophobic character of the drug delivery system, the amount of curcumin loaded into TSMON was determined as 22%. Drug release studies at physiological and endosomal pH values have shown that only 1% of the curcumin loaded in TSMON can be released. The low release amount indicates that the physical interaction caused by the structural compatibility between curcumin and the drug delivery system is still effective at the pHs studied. It is very important in achieving the desired success in cancer treatment that the drug-loaded carrier system carries the payload without leaking, as well as being able to leave it at the desired place and at the desired time. We continue to work to ensure that the Cur@TSMON system obtained in this study can release curcumin wherever and whenever it is desired.

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Conflicts of Interest: The authors declared that there is no conflict of interest.

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REFERENCES

1. Sun T., Zhang Y. S., Pang B., Hyun D. C., Yang M., & Xia Y. Engineered nanoparticles for drug delivery in cancer therapy. Angewandte Chemie - International Edition, 53(46), (2014), 12320–12364.
2. Nasery M. M., Abadi B., Poormoghadam D., Zarrabi A., Keyhanvar P., Khanbabaei H., Ashrafizadeh M., Mohammadinejad R., Tavakol S., & Sethi G. Curcumin delivery mediated by bio-based nanoparticles: A review. Molecules, 25(3), (2020), 1–28.
3. Ferlay J., Colombet M., Soerjomataram I., Mathers C., Parkin D.M., Piñeros M., Znaor A., Bray F. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. International Journal of Breast Cancer. 144(8), (2019), 1941-1953.
4. Nelson K. M., Dahlin J. L., Bisson J., Graham J., Pauli G. F., & Walters M. A. The Essential Medicinal Chemistry of Curcumin Journal of Medicinal Chemistry, 60(5), (2017) 1620–1637.
5. Hatcher H., Planalp R., Cho J., Torti F.M., Torti S.V. Curcumin: from ancient medicine to current clinical trials. Cellular and Molecular Life Sciences. 65, (2008), 1631–1652.
6. Jin R., Xia Y., Chen Q., Li W., Chen D., Ye H., et al. Da0324, an inhibitor of nuclear factor-kappaB activation, demonstrates selective antitumor activity on human gastric cancer cells. Drug Design, Development and Therapy, 10, (2016), 979–995.
7. Kilicay E., Karahaliloglu Z., Hazer B., Tekin I.O., Denkbas E.B. Concanavaline A conjugated bacterial polyester-based PHBHHx nanoparticles loaded with curcumin for breast cancer therapy. Journal of Microencapsulation, 33, (2016), 1–12.
8. Park W., Amin A.R., Chen Z.G., Shin D.M. New perspectives of curcumin in cancer prevention. Cancer Prevention Research, 6, (2013), 387–400.
9. Huh K. M., Lee S. C., Cho Y. W., Lee J., Jeong J. H., & Park K. Hydrotropic polymer micelle system for delivery of paclitaxel. Journal of Controlled Release, 101(1-3 SPEC. ISS.), (2005), 59–68.
10. Lim E., Kim T., Paik S., Haam S., Huh Y., & Lee K. Nanomaterials for Theranostics : Recent Advances and Future Challenges. Chemical Reviews, 115, (2015), 327-394.
11. He Y., Shao L., Usman I., Hu Y., Pan A., Liang S., & Xu H. A pH-responsive dissociable mesoporous silica-based nanoplatform enabling efficient dual-drug co-delivery and rapid clearance for cancer therapy. Biomaterials Science, 21:8 (12), (2020), 3418-3429.
12. Giri S., Trewyn B.G., Lin V.S. Mesoporous silica nanomaterial-based biotechnological and biomedical delivery systems. 2, (2007), 99-111.
13. Croissant J. G., Fatieiev Y., Julfakyan K., Lu J., Emwas A. H., Anjum D. H., Omar H., Tamanoi F., Zink J. I., & Khashab N. M. Biodegradable Oxamide-Phenylene-Based Mesoporous Organosilica Nanoparticles with Unprecedented Drug Payloads for Delivery in Cells. Chemistry - A European Journal, 22(42), (2016), 14806–14811.
14. Croissant J. G., Fatieiev Y., Almalik A., & Khashab N. M. Mesoporous Silica and Organosilica Nanoparticles: Physical Chemistry, Biosafety, Delivery Strategies, and Biomedical Applications. Advanced Healthcare Materials, 7(4), (2018), 1700831
15. Bharti C., Gulati N., Nagaic, U., & Pal A. Mesoporous silica nanoparticles in target drug delivery system: A review. International Journal of Pharmaceutical Investigation, 5(3), (2015) 124.
16. Gök Y., Kılıçarslan S., Gök H.Z., Karayiğit İ.Ü. Enantioselective Ethylation of Various Aldehydes Catalyzed by Readily Accessible Chiral Diols. Chirality, 28, (2016), 593-598.
17. Perrin DD, Armarego WFL (1989): Purification of Laboratory Chemicals. In: Second ed., Pergamon Press, Oxford.
18. Chen C., Sun W., Wang X., Wang Y., & Wang P. Rational design of curcumin loaded multifunctional mesoporous silica nanoparticles to enhance the cytotoxicity for targeted and controlled drug release. Materials Science and Engineering C, 85, (2018), 88–96.
19. Sun X., Wang N., Yang L. Y., Ouyang X. K., & Huang F. Folic acid and pei modified mesoporous silica for targeted delivery of curcumin, Pharmaceutics, 11(9), (2019), 11090430.
20. Palanikumar L., Kim H. Y., Oh J. Y., Thomas A. P., Choi E. S., Jeena M. T., Joo S. H., & Ryu J. H. Noncovalent surface locking of mesoporous silica nanoparticles for exceptionally high hydrophobic drug loading and enhanced colloidal stability. Biomacromolecules, 16(9), (2015), 2701–2714.
21. Nasab N. A., Kumleh H. H., Beygzadeh M., Teimourian S., & Kazemzad M. Delivery of curcumin by a pH-responsive chitosan mesoporous silica nanoparticles for cancer treatment. Artificial Cells. Nanomedicine and Biotechnology, 46(1), (2018), 75–81. https://doi.org/10.1080/21691401.2017.1290648
22. Sing K. S. W. Reporting physisorption data for gas/solid systems with special reference to the determination of surface area and porosity. Pure Appl. Chem., 57, (1985), 603.