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Synthesis, Characterization and Drug Release Capability of New Cost Effective Mesoporous Silica Nano Particle for Ibuprofen Drug Delivery

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Abstract

New mesoporous silica nanoparticle (MSNs) with high surface area and pore volume has been synthesized successfully using TritonX-100 as main and Tween 60 as co-template (at various concentrations). Ibuprofen a water insoluble model drug was loaded into the synthesized silica nanoparticle and studied for sustained release capability. All the as synthesized and drug loaded nanoparticle were characterized using physicochemical techniques such as FTIR, Difuse reflectance UV spectroscopy(UV-DRS), Brunauer Emmett Teller (BET) technique, Differential Scanning Calorimetri (DSC),Thermo gravimetric analysis(TGA), powder XRD and scanning electron microscopy(SEM) for the morphology and drug loading. From the results it was noted that all the silica nanoparticle synthesized by sol-gel method were mesoporous with high surface area and pore volume (1024.3, 1056.2 and 1083.6 m^2 g^{-1} and 0.9229, 0.9904 and 0.8468 for TW6-$1_{rt,}$ TW6-2_{rt} and TW6-3_{rt} respectively) and have the capability of up taking 32 % ibuprofen model drug further they shows initial burst release for 50h followed by sustained maintenance of dose even after 150h.

Keywords*: meso silica, ibuprofen, drug release, Tween 60, TritonX-100*

1. Introduction

Mesoporous material (MCM-41) is introduced as an alternative to microporous materials in the year 1992 by Mobil Corporation scientist [1, 2]. Following up these lots of materials with meso structures were synthesized like SBA family, MSU (MSUs) family [3], FSMs family [4] and KIT [5] were invented by various groups. They made attracted by scientist by their exclusive properties such as ordered and easily tunable pore structure, pore volume and surface morphology, and find applications in various applications such as catalysis, adsorption, separation, purification science and as a template for synthesizing other mesoporous material such as mesoporous carbon [6-10]. Further they also find their attraction over the pharmaceutical scientist after the tremanadous study reported by Velet regi et al in the year 2001, utilizes the MCM-41 for the sustained release of ibuprofen [11]. Porous silica matrixs saoutstanding properties elicit by silicas such as biocompatibility, biodegradability and easy surface multi-functionalization, high specific surface area and pore volume to accommodate large quantity of guest molecule, tunable pore structures and excellent physicochemical stability [8-11]. Polymeric drug delivery systems such as liposomes, polymeric micelles, and nano hydrogels were used in successful controlled delivery but they

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also suffered in one or more physicochemical aspects, like stability and durability these makes to them to release the payloads unexpectedly in a burst release manner [9]. MSNs not only proved themselves as effective carriers for controlled drug delivery [12-17] but also they were effectively used in bio-signal probing tools [18-20] and as biomarker supporter [21] as imaging and sensing tool.

In these sense many MSNs have been developed and studied for drug delivery still none of them were find their application commercially due to utilization of brominated, fluorinated SDAs, which released after synthesizing the MSNs, the template remain in the silica after calcining MSNs also cause systemic toxicity as well as environmental pollutions, further cost of the silica source and SDAs these all together pushed as to find economic SDA and silica source without using this hazardous materials. As part of this we already reported a method to synthesis mesosilica (MSNs) using some pharmaceutically approved surfactants such as triton-100 as main SDA and tween 20 as contemplate for obtaining pore structure [22]. Success on the reported materials in pore forming, here in we reported the synthesis and drug release properties of new MSNs materials by changing the co-template from tween 20 used in our earlier report to tween 60 (with increased carbon chain length). Further to their environmentally friendly nature the SDA used here are very cheap while comparing with other common surfactants studied for MSN's synthesis.

In the present study we also selected the ibuprofen a non steroidal anti inflammatory drug widely used for relieve pain. Ibuprofen has only 2 h as biological half-life, this shorter biological half-life makes it a suitable drug for sustained or controlled drug delivery system development. Therefore, ibuprofen has been commonly employed as a model drug in the development of sustained/controlled releases further to this its structural feature makes it easy to accommodate into the MSNs with respect to our earlier report.

2. Experimental

2.1. Materials

Surfactants such as polyethylene glycol *p*-(1,1,3,3-tetramethylbutyl)-phenyl ether (TritonX-100), Polyethylene glycol sorbitan monostearate (Tween 60) were used as non polluting structural directing agent (SDA), Tetraethyl orthosilicate (TEOS) is as silica source, Ibuprofen reference standard (ibu) and sodium fluoride were obtained from Sigma Aldrich (Gmbh, Germany). Hexane, sodium chloride, disodium hydrogen phosphate, potassium dihydrogen *ortho* phosphate and HCl were obtained from Acros chemicals. All chemicals were used as received without further purification.

2.2. Synthesis of silica carrier

We adopted the same procedure which reported in our earlier report with little modification in use of secondary template. In our earlier report we used Tween 20 as secondary template here in we used Tween 60 (a larger molecule with lengthier carbon chain in structure) content. In a typical procedure 6.4 g of TritonX-100 and various amounts of Tween 60 were added to 300 g of DI water with constant stirring at 35–40 °C until to get a clear solution of the mixture. To this solution about 16.8 g of TEOS was added in drop wise. This mixture was stirred for another 3 h to get sol component. 0.083 g of sodium fluoride was then added to the sol mixture to obtain the gel component; this gel was then aged at room temperature for 24 h. In another procedure the gel components were aged solvothermally at 100 °C in a static hot air oven for 24 h. The solid product settled down were recovered by vacuum filtration, washed repeatedly with water and dried overnight at 50 °C. The templates remain in the

materials were removed by calcining at 450 °C for 5 h at a heating rate of 1 °C/min. The synthesized materials are designated as TW6-1_{rt}, TW6-2_{rt} TW6- 3_{rt}, TW6-1_{st}, TW6-2_{st},and TW6- 3_{st} where TW6 is to represents Tween 60 and 1, 2 and 3 indicate the concentrations of Tween 60 used (0.0009, 0.0018, 0.0027 mol) and subscript rt and st aging temperature of the respective silicas (room temperature and solvothermal).

2.3. Loading of DX

Ibuprofen loading was done by following the procedure given by Valet Regi eta al., using ibuprofen in 1:1. Then the filtrate is tested for ibuprofen loading UV-visible spectrophotometer at 264 nm. The collected drug-loaded MSN's were dried overnight at RT then pressed into 0.3 g disks (13 × 3 mm^2 in size) using uniaxial pressure (5.0 MPa) for drug release experiments [3].

2.4. Characterization

Here we used a SCINCO thermogravimeter N-1000 to measure the weight loss of the synthesized silica nanoparticles before and after ibu loading. A sample weighing *ca*. 10 mg was loaded into an alumina sample pan in a TG unit and the temperature was programmed to reach 800 °C at a heating rate of 10 °C/min in nitrogen atmosphere. The TG degradation pure DX was also taken for comparison. Nicolet 6700 FT-IR spectrometer was used for recording infrared (FT-IR) spectra of the samples room temperature by KBr pelleting technique. Each sample was scanned 20 times over the range 4000–400 cm^{-1}. Scanning electron microscopy (SEM) Jeol-JSM 5600 (Japan) used to study the morphology of the MSNs synthesized. Usual procedure which reported in our earlier paper was followed for acquiring SEM images. Powder X-ray diffraction patterns were recorded using a Rigaku Miniflex diffractometer using Cu Kα radiation and operated at 40 kV and 30mA (l = 1.54 Å). The diffraction data were recorded in the 2θ range 0.7–10° with a 0.1° step size and a 1 s step time. The nitrogen adsorption–desorption isotherms were measured at 77 K by using a Belsorp mini II (Japan) volumetric adsorption analyzer. Prior to each adsorption measurement the samples were evacuated at 373 K. The specific surface area, S_{BET}, was determined from the linear part of the BET equation. The pore size and pore volume of the particle were taken from the BET results.

In vitro drug release studies

The release of the drug from the loaded samples were studied by soaking each prepared tablets (T6-1D, T6-2D and T6-3D) in 100 ml phosphate buffer solution separately (pH 7.4) at 37 °C; the dissolution fluid was stirred at 100 rpm using a controlled mechanical stirrer. 1 ml aliquots of the samples were withdrawn at fixed sampling times and the same quantity was replaced immediately [3]. The withdrawn sample was then filtered through a 0.1 μm filter and suitably diluted before quantifying.

3. Results and discussions

3.1. Characterization

From the results of nitrogen adsorption and desorption experiment it was shown that particles prepared sol-gel procedure with a fixed concentration of TritonX-100 and 0.0009 (TW6-1_{rt}), 0.0018 (TW6-2_{rt}), 0.0027 mol (TW6- 3_{rt}) of Tween 60 had higher but nearly equal surface area (1024.3, 1056.2 and 1083.6 m^2 g^{-1} for TW6-$1_{rt,}$ TW6-2_{rt} and TW6-3_{rt} respectively) (Table 1) and pore volume (0.9229, 0.9904 and 0.8468 for TW6-$1_{rt,}$ TW6-2_{rt} and

TW6-3_{rt} respectively) than the hydrothermal synthesized silica hence, these were selected for further drug-loading and release study. As can be seen from their characteristic type IV isotherms (Figure 1(a)) for typical mesoporous materials, with a hysteresis loop in the partial pressure (p/p_0) range 0.2–0.8, which is typical for pore filling of standard mesoporous systems further they have little microporous charectaer too while seeing the isotherm in the first part the isotherm raised steeply until 200 V_a/cm^3(STP) g^{-1} which shows the presence of micro pore in them, presence of these micro pore were also benefit in case of delayed release formulation because microspore will allow the drug as well as solvent molecule enter, escape from the pores very slowly. Nitrogen desorption and adsorption experiments for ibu (T60-1D, T60-2D and T60-3D) loaded particles were also carried out; these shows that there is a decrease in the surface area and pore volume after drug-loading but surprisingly there was little but negligible increase pore diameter was observed it may be due to adherence of small amount of drug molecule in the entrance of pore (Figure 1(b) and Table 1). Table 1 BET results of as synthesized and drug loaded silica nanoparticle.

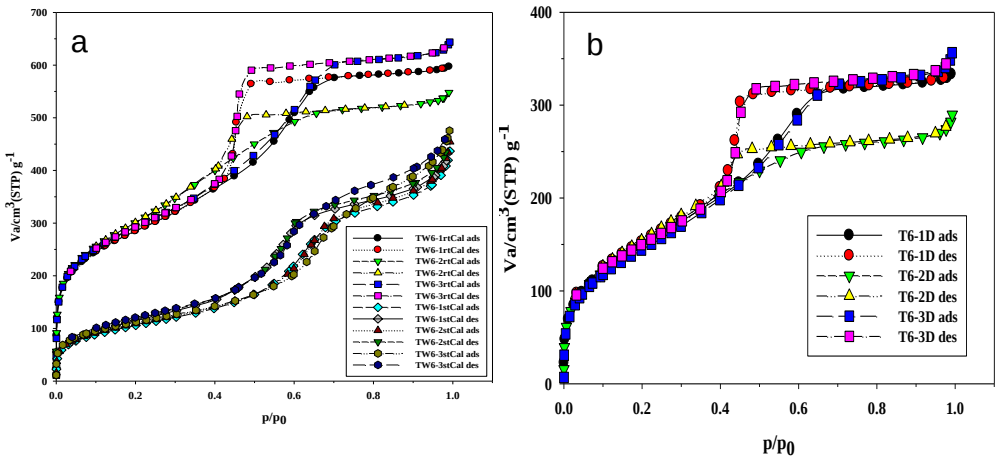

Fig.1. N_2 adsorption-desorption isotherms of silica particle (a) before ibu laoding, (b) after ibu loading (selected particles)

Table 1. BET data of pure and drug loaded particle.

Samples	BET Surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})	Average pore diameter (nm)
TW6-1_{rt}	1024.3	0.9229	3.6038
TW6-2_{rt}	1056.2	0.9904	3.7509
TW6-3_{rt}	1083.6	0.8468	3.1257
TW6-1_{st}	383.69	0.6603	6.8839
TW6-2_{st}	395.97	0.6842	6.9122
TW6-3_{st}	402.58	0.7274	7.2272
T60-1D	560.14	0.5153	3.6795
T60-2D	570.24	0.4396	3.0837
T60-3D	542.06	0.5455	4.0253

The XRD patterns of selected silica nanoparticles after removal of their templates through calcinations gave a strong reflection in the 2θ range 1–1.6° corresponding to mesoporous structure (figure not shown).

The TGA of as synthesized silica was also given in Figure 2(a). Which shows an initial 5% weight loss due to evaporation of water confined in the pore, a major weight loss was noted around 400 °C in all case of silica which indicate the loss of template from the pore of silica. From this observation the calcinations temperature was fixed as 450 °C. Further the TGA of calcined silicas were also given in Figure 2(b) which show only small weigh loss at around 100 °C, which may be due to loss of moisture captured during the storage of silica.

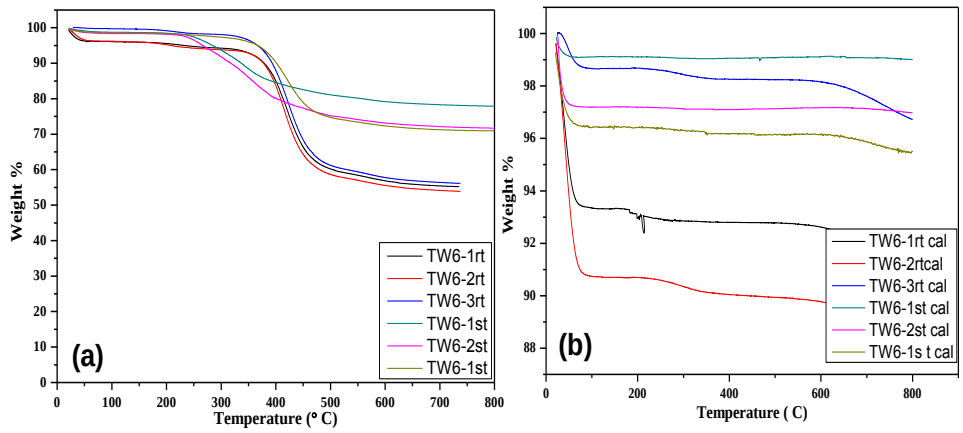

Figure 2. TGA of silica particle (a) before and (b) after calcinations.

Scanning electron micrographs of selected silica nanoparticles (TW6-$1_{rt,}$ TW6-2_{rt} and TW6-3_{rt}) showed spherical particle morphology (Figure 3) and the SEM images of drug-loaded particles showed irregular and agglomerated particles (Figure 3(d, e, f)).

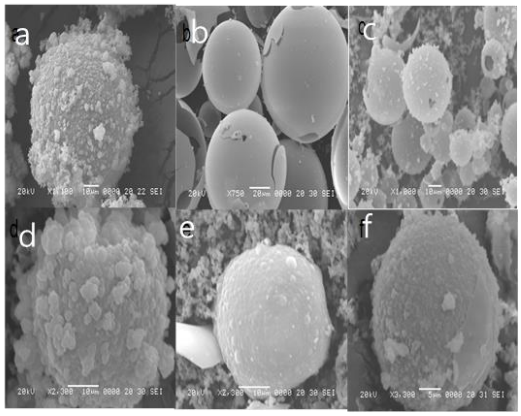

Figure 3. SEM images of calcined silica particle (a) TW6-1rt, (b) TW6-2rt , (c) TW6-3rt, and drug loaded particle (d) T6-1D, (e) T6-2D) and (f) T6-3D

λ-max of the pure drug as well as ibu loaded nanoparticle were taken by solid state Diffuse reflectance UV spectroscopy (DRS-UV). The drug-loaded silica shows similar absorbance

spectrum with solid ibuprofen in the peak around 254 nm when compared to the (Figure 4) this shifts may be due the hydrogen bond interaction –COOH group of ibu with defective –SiOH group of silica nanoparticle. In general the drug ibuprofen in liquid media like hexane or in buffer gave two λ-maxes one is at around 222 nm second is at around λ-max 264 nm. In here the drug is in solid form and method of analysis is diffuse reflectance in solid phase hence the two peaks were merged together to give a single peaks in pure drug. Due to dilution over solid silica matrix (maximum of 33 % loading in silica) the drug loaded particle shows two λ-max as like the liquid samples.

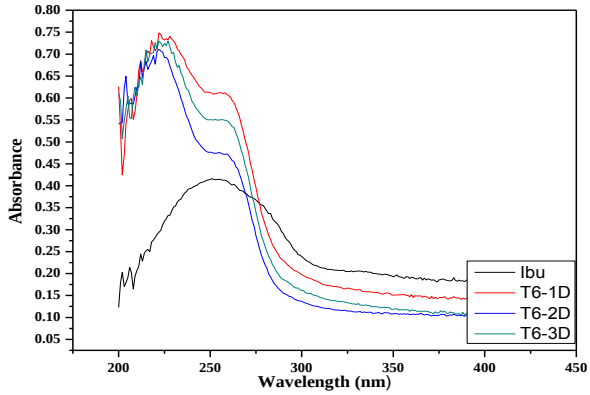

Figure 4. DRS-UV spectra of pure drug (ibu) and drug loaded silicas

Figure 5 depicts the FT-IR spectra of pure drug and drug-loaded nanoparticles. The spectra (a) in the figure is for pure ibu; spectra (b) represents the ibu loaded silica in this figure the bands at around 1720 cm^{-1} is prove the presence of carboxyl group vibration, and the vibration bands from 2950–2850 cm^{-1} is proves the presence of C–H stretching vibrations of ibu. These bands provide the information of ibuprofen loading into the silica. Remaining bands from 795 and 465 cm^{-1} were attributed to Si–O–Si, and the band at 964 cm^{-1} is for Si–OH.

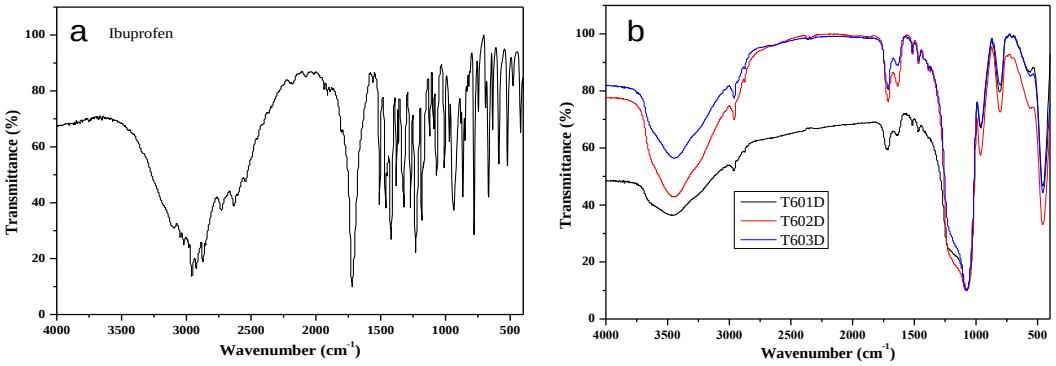

Figure 5. FT-IR spectra of (a) pure drug, (b) T6-1D, T6-2D and T6-3D

Figure 6 depicts the DSC traces of physical mixture ibuprofen with silica (Figure 6(a)) and silica loaded silica (Figure 6(b)). In the traces of physical mixture the ibuprofen melting was noted at around 70 °C. In case of drug loaded particle the same was little shifted to higher temperature of around 110 °C. In drug confined silica particle the drug was dispersed in

amorphous phase further the amount of drug confined is also very small while comparing to silica mass this may be the reason for the shifts of melting temperature towards high.

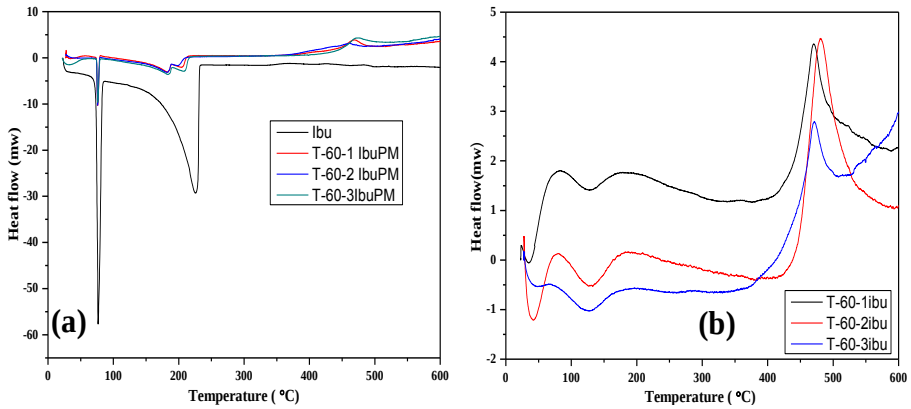

Figure 6. DSC traces of (a) pure drug and physical mixture of silica and drug (b) drug loaded particle (T6-1D, T6-2D and T6-3D)

3.2. Drug inclusion in the particles

Silica nanoparticles with high surface area and good pore volume (TW6-$1_{rt,}$ TW6-2_{rt} and TW6-3_{rt}) were chosen prior to the loading studies. To maximize the loading efficiency of the particles they were soaked in the drug solution at ice temperature for 3 h, then at room temperature for three days. The ratio of particle to ibu in the solutions is 1: 1. The active molecules were then allowed to diffuse into channel pores of the particle, then a careful surface washing was done to remove any surface adhered active molecule. From the reports of Valet Regi et al we have also chosen hexane as solvent for drug loading.

The drug loaded particles were subjected to TG to know the uptake of ibu onto the silica (Figure 7); the results revealed that the initial weight loss of around 2–5% is due to physisorbed water, which is followed by weight loss due to ibu from above 100–350 °C. The pattern is similar to TG reported by other authors Fig. 3. And the percentage loading was 20, 26 and 28 for T6-1D, T6-2D and T6-3D respectively. The percentage loading was also confirmed by estimation of the amount of drug remaining in solution by UV spectroscopic analysis using the slope of the standard graph of the drug in the same. The results obtained by UV methods was found about 23, 32.5 and 30.8 % ibu uptake by T6-1D, T6-2D and T6-3D respectively. The little difference observed in TGA is due to the remained carbonized matter by the degradation ibu inside the pore of the material. The drug loading was also observed in BET by the decrease in pore volume of the selected silica nanoparticle. Even though the surface area was high in T6-3D the loading was decreased this may be due reduced pore volume while compared to other further it proves that the independency of drug loading towards surface area.

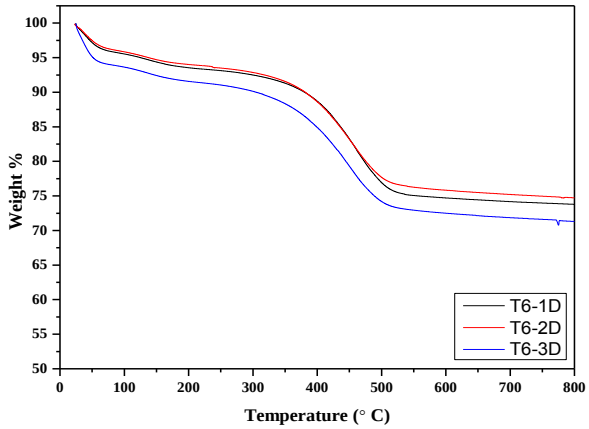

Figure 7. TGA of drug loaded silica particle

3.3. Dissolution studies

From Figure 8 it is interesting to note that initial burst release patterns were observed for all selected silica nanoparticle. For time periods of up to 50 h, the release profiles for both the drug-loaded silica nanoparticles show almost similar release profiles in case of burst release with different % release (65, 72 and 85% for T6. As can be seen in Fig.9 (inset) a burst release of ibu was observed in the first 10 h was around 30% from T6-1D, T6-2D and T6-3D which usually expected from a sustained release formulation. In all the case of selected silica particle after attain a maximum level of release the dose maintenance was begin (nearly 50 h in all case) to release the drug for a longer period, all of them are obeying the first order release mechanism as shown in previous studies on drug-loaded silica nanoparticles [5]. These release profiles and drug-loading efficiencies are of great interest for pharmaceutical application in order to improve the delivery of drugs for longer and sustained action as well as to reduce the risk of dose dumping due to multiple doses.

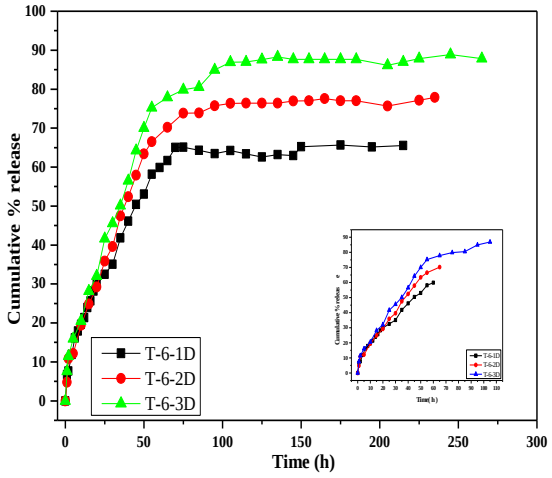

Figure 8. Cumulative drug release profile of drug loaded silicas in phosphate buffer (pH-7.4)

4. Conclusions

In our present study we successfully synthesized new silica nanoparticles with pharmaceutically approved, biocompatible and non-polluting surfactants to produce meso silica with a high surface area and pore volume for the loading of model drug ibuprofen a nonsteroidal anti-inflammatory drug. The results obtained showed that drug could be easily loaded with great efficiency at the maximum of 33% in case of T60-3D into the prepared silica nano particles. While the drug release pattern shows a long time and released pattern up to maximum of 90% for about 200 h in a sustained manner for all the room temperature aged synthesized particles. Based on the results we have obtained, we concluded that the prepared silica nanoparticle using TritonX-100 and Tween 60 could also be act as an ideal drug delivery carrier for various active pharmaceutical substances in sustained or delayed release formulations.

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References

[1] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli and J. S. Beck, Nature, vol. 359, no. 710, **(1992)**, http://dx.doi.org/10.1038/359710a0.
[2] S. N. Jun and R. Ryoo, J. Catal., vol. 195, no. 237, **(2000)**, http://dx.doi.org/10.1006/jcat.2000.2999.
[3] A. R. Silva, K. Wilson, A. C. Whitwood, *et al.*, Eur. J. Inorg. Chem., vol. 1275, **(2006)**, http://dx.doi.org/10.1002/ejic.200500979.
[4] J. S. Jang, B. Lim, J. Lee, *et al.*, Chem. Commun., vol. 83, **(2001)**, http://dx.doi.org/10.1039/B006197M.
[5] M. Vallet-Regi, A. Ramila, R. P. del Real and J. Perez-Pariente, Chem. Mater., vol. 13, no. 308, **(2001)**, http://dx.doi.org/10.1021/cm0011559.
[6] Y. L. Cheng, B. G. Trewyn, D. M. Jeftinija, K. Jeftinija, X. Shu, S. Jeftinija and V. S. Y. Lin, J. Am. Chem. Soc., vol. 125, no. 4451, **(2003)**, http://dx.doi.org/10.1021/ja028650l.
[7] Q. Fu, G. V. R. Rao, L. K. Ista, Y. Wu, B. P. Andrzejewski, L. A. Sklar, T. L. Ward and G. P. Lo´ pez, Adv. Mater., vol. 15, no. 1262, **(2003)**, http://dx.doi.org/10.1002/adma.200305165**.**
[8] A. Ramilia, B. Munoz, J. Perez-Pariente and M. Vallet-Regı, J. Sol-Gel Sci. Technol., vol. 26, no. 1199, **(2003)**, http://dx.doi.org/10.1023/A:1020764319963.
[9] F. Qua, G. Zhu, H. Lin, W. Zhang, J. Sun, S. Li and S. Qiu, J. Solid State Chem., vol. 179, no. 2027, **(2006)**, http://dx.doi.org/10.1016/j.jssc.2006.04.002.
[10] B. Munoz, A. Ramila, J. Perez-Pariente, I. Dıaz and M. Vallet-Regı, Chem. Mater., vol. 15, no. 500, **(2003)**, http://dx.doi.org/10.1021/cm021217q.
[11] L. Gao, J. Sun, L. Zhang, J. Wang and B. Ren, Mater. Chem. Phys., vol. 135, no. 786, **(2012)**, http://dx.doi.org/10.1016/j.matchemphys.2012.05.059.
[12] R. Morterab, S. Fiorilli, E. Garroneb, E. Vernéa and B. Onida, J. Chem. Eng., vol. 156, no. 184, **(2010)**, http://dx.doi.org/10.1016/j.cej.2009.10.018.
[13] J. Andersson, J. Rosenholm, S. Areva and M. Linden, Chem. Mater., vol. 16, no. 4160, **(2004)**, http://dx.doi.org/10.1021/cm0401490.
[14] P. Horcajada, A. Ramila, J. Perez-Pariente and M. Vallet-Regı, Micropor. Mesopor. Mater., vol. 68, no. 105, **(2004)**, http://dx.doi.org/10.1016/j.micromeso.2003.12.012.
[15] W. Zhao, J. Gu, L. Zhang, H. Chen and J. Shi, J. Am. Chem. Soc., vol. 8916, no. 127, **(2005)**, http://dx.doi.org/10.1021/ja051113r.
[16] S. Giri, B. G. Trewyn, M. P. Stellmaker and V. S. -Y. Lin, Angew. Chem. Int. Ed., vol. 44, no. 5038, **(2005)**, http://dx.doi.org/10.1002/anie.200501819.
[17] Q. Tang, Y. Xu, D. Wu and Y. Sun, Chem. Lett., vol. 35, no. 474, **(2006)**, http://dx.doi.org/10.1246/cl.2006.474.
[18] F. Highton, "The Pharmaceutics of Ibuprofen", in: Ibuprofen. A Critical Bibliographic Review, Edited K.D. Rainsford, Taylor & Francis, London, **(1999)**, pp. 53.

[19] Q. He, Z. Zhang, Y. Gao, J. Shi and Y. Li, Small., vol. 5, no. 2722, **(2009)**, http://dx.doi.org/10.1002/smll.200900923.
[20] A. M. Alkilany, P. K. Nagaria, C. R. Hexel, T. J. Shaw, C. J. Murphy and M. D. Wyatt, Small., vol. 5, no. 701, **(2009)**, http://dx.doi.org/10.1002/smll.200801546.
[21] K. W. Yip, E. Ito, X. Mao, P. Y. Au, D. W. Hedley, J. D. Mocanu, C. Bastianutto, A. Schimmer and F. F. Liu, Mol. Cancer Ther., vol. 5, no. 2234, **(2006)**, http://dx.doi.org/10.1158/1535-7163.MCT-06-0134.
[22] M. Ganesh, P. Hemalatha, M. M. Peng, K. Rajasekar and H. T. Jang, J. Ind. Eng. Chem., vol. 18, no. 684, **(2012)**, http://dx.doi.org/10.1016/j.jiec.2011.11.121.

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