Storage and release of Ibuprofen by tailoring the morphology of Hollow Mesoporous Silica materials and their characterization

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Abstract: Different batches of mesoporous silica spheres with modified pore surface were prepared in single step chemical reaction with diverse surface morphologies and pore geometrics using pluronic F127- non-ionic surfactant, and 3-aminopropyltriethoxy silane (TEOS) and ammonia with and without modification. Ibuprofen was used as a model drug to characterize the different batches of prepared mesoporous silica comprehensively. Ibuprofen drug storage capacities as well rate of drug release profiles from the mesoporous silica were studied. Characteristic of each batch of prepared silica were studied by Ultraviolet Spectroscopy, X-ray Diffraction, Scanning Electron Microscopy, Surface area and Pore size Analyzer and Micromeritics Gemini analyzer. From the studies it was shown that drug loading and release profile of ibuprofen from the hollow mesoporous silica are related to the surface area and pore size of mesoporous silica. By modifying the pore size, surface area of the silica and surface topology these values of studied profiles can be changed and better results can be achieved. Although surface area of the mesoporous silica samples was found to be very small which affected loading and releasing property of ibuprofen, the results showed very encouraging indication of mesoporous silica technology application in drug delivery system.

Keywords: Mesoporous silica, Morphology, Modification, Drug release, Ibuprofen.

1. Introduction

In drug delivery systems new applications of mesoporous silica have been explored for the batter control of drug storage and release due to their high surface area, well defined pore structures and tenable pore surface [1-5]. Most of the times amorphous mesoporous silica materials have been focused as a drug carrier since it is non-toxic, highly bio-compatible, adjustable pore diameter, low cost and the wall of the pores containing free silicon group with abundant Si-OH bonds which can take part in the reactions with appropriate drug functional groups[1,5]. These materials acquire modifiable and uniformed pore sizes in the range of 1.5 to 10 nm [4]. The potential applications of mesoporous silica in catalysis, separation, sensing and optical active materials make them very attractive and batter choice for drug carrier in the last decade [1].

Recent there has been increased interest in hollow mesoporous silica materials for utilization as drug carrier in the field of controlled drug release, to meet the need for prolonged and batter formulation of drug administration. Many research scientists have investigated the drug storage and releasing properties of mesoporous silica materials. The obtained results have indicated that the appropriate pore size and pore volume of hollow mesoporous silica spheres make them batter and ensured supports for the hosting and moreover releasing a large variety of drug molecules having specific therapeutic activity in the required area of the biological system. Investigations was also been done for the conventional silica materials which also lead some good results of storage and releasing drug molecules. However the drug carrier property of conventional silica materials was not been relatively high. They also showed some irregular bulk morphology which makes difficult for the scientist to design required drug delivery system. That's why researchers worked to design a system which will recover these disadvantages. One effective strategy is synthesizing hollow mesoporous silica spheres with penetrating pore channels. Some of the research groups found that hollow mesoporous silica spheres are ideal carrier for drug storage and release [1-4, 7-9].

Research on hollow mesoporous silica materials has demonstrated that drug storage and release with hollow mesoporous silica is a good technology for controlled drug delivery system [10]. Controlled release technology has become very important and effective in modern medication and pharmaceuticals [11]. Controlled release formulation has many advantages over the conventional form of dosage forms: appropriately maintaining patient's blood level for the required set of time, minimizing deleterious side effects, prolonging effectiveness, making a rapid increase of bioavailability at short intervals, protecting sensitive drug from the enzymatic and acidic degradation in the gastrointestinal tract and most importantly improving patient's compliance [10-12].

It has been investigated that quite a few factors may convey enormous influence on the drug release profiles from hollow mesoporous silica carriers. One of the most significant aspects is the pore size of the mesoporous silica, or steric hindrance. It is by and large accepted that kinetics of the drug molecules is pronouncedly influenced by the pore size of the mesoporous silica. Some researchers reported that drug delivery rate gradually decreases with the reduction of the pore size [13, 14]. The second key feature is the interaction between the mesoporous silica molecules and the drug to be stored, usually known as host-guest interaction. Here the property of the mesoporous silica spheres and the drug plays a vital role for a stable drug storage system. Munoz et al. originate that drug release from the host can be slow down because of the higher affinity between the drug and the mesoporous silica [15]. The third feature is the aperture geometry of the mesoporous silica. It is establish that smaller pore openings of mesoporous silica with one-dimensional (1D) or three-dimensional (3D) " cage-like" pore structure is of great benefit to slow down the drug release rate. Different morphologies for mesoporous silica can be achieved by using templating method or by the phase transformation approach. This usually involves the size and shape of the mesoporous silica in the micron scale. It gives the scope for the mesoporous silica to show rich morphological behaviour. The main reasons for showing such performance are:

1. Silicate ions indicate as a counter ions forming soft hexagonal liquid crystalline phase.
2. An affluent arrangement of the surfactant system can be rationalized to form various types of mesoporous structures.
3. By changing the composition of the reaction system or the conditions the morphology of the mesoporous structure also change.
4. The rate of the silica condensation reaction is also controllable at the later stage of the reaction.
5. Self organization and the Siloxane bond formation progression can also independently control.

In the end, the pH of the dissolution media could affect the drug delivery profiles as well [14, 16, and 17].

Ibuprofen is one of the eminent non-steroidal anti-inflammatory drugs which is frequently using for the treatment of inflammation, analgesic or rheumatism and this drug furthermore contains one carboxylic acid group that makes the strong bonding with many functional groups via acid-base reaction [1, 18 and 19]. This drug has a short biological half-life which makes the drug strongest contestant for the sustained or controlled release drug delivery system. Therefore, preference was given to ibuprofen as a model drug for the sustained/controlled release system [20]. It also shows good pharmacological activity and the appropriate particle size (1.0 x 0.6 nm) of the drug ensures its straightforward diffusion into or out of the mesoporous channels of as prepared hollow mesoporous silica spheres. Although study with some other drugs like-

vancomycin, gentamycin, cisplatin, aspirin, captopril and naproxen was done for batter drug storage and releasing property by other research groups [14, 19].

2. Experimental

2.1 Materials and Chemicals:

All the reagents were used as they were received from the lab without any further purification: Ibuprofen, ethanol, ammonia, 3-aminopropyltriethoxy silane, Tetraethoxysilane, toluene, Methyltriethoxy silane, 2.5 M HCL solution and Pluronic F127.

2.3 Synthesis Methodology: Mesoporous silica spheres were synthesized according to earlier articles (14-18). A typical procedure followed for different scales are given below:

2.3.1 Small Scale Preparation: 50 ml preparation. A distinctive experiment was performed as follows: 2 gm of pluronic F127 was dissolved in 18 ml of distilled water. Then 32 ml of 2.5 M HCL solution was added and stirred to make it homogeneous. 4.7 ml of TEOS was added to the homogeneous solution and stirred for 24 hour. After stirring for 24 hour samples were placed in desiccators for drying. After seven days, samples were dehydrated under vacuum at 180°C and from the dried samples 0.51gm of hollow mesoporous silica (HMS) was suspended in 50 ml of toluene. 0.0556 mmol of methyl-triethoxy silane was added into the above mixture and refluxed at 80°C for 48 hour under N_2 atmosphere. The white solid filtered off and washed with toluene several times. Then the samples were dried under vacuum at 60°C for 2 days[14-18]. One batch of silica was prepared following this method and it was denoted B_1.

2.3.2 Full Scale Preparation: 100 ml preparation. Same procedure used as 2.3.1 replacing 2 gm pluronic F127, 18 ml of distilled water, 32 ml of 2.5 M HCL solution and 4.7 ml of TEOS by 4 gm pluronic F127, 36 ml of distilled water, 64 ml of 2.5 M HCL solution and 9.4 ml of TEOS. Two batches of silica were prepared following this method and the batches were denoted as B_2 and B_3. From the dried samples 1.12 gm of hollow mesoporous silica (HMS) was suspended in 100 ml of toluene. 0.0544 mmol of methyl-triethoxy silane was added into the above mixture and refluxed at 80°C for 48 hour under N_2 atmosphere. The white solid filtered off and washed[14-18]. One batch of silica was prepared following this method and denoted as B_4.

2.3.3 Synthesis using Ammonia:

180 ml of ethanol, 5 ml ammonia and 52 ml of deionised water was added to round bottomed flask and heated at 60° C. The solution was stirred continuously (at approximately 100 rpm) throughout the reaction. After reaching the temperature, the mixture was left for 2 hours after which time 11 ml of TEOS was added to initiate the precipitation reaction. The reaction was further left for 24 hours. To continue the growth of silica particles, a mixture of water and TEOS (4 ml: 24 ml) was added to the mixture. At the end of the reaction the mixture formed a 'milky' white dispersion. The reaction was terminated and the dispersion was allowed to cool. Silica purified by dialysis in deionised water at pH 8 and kept for 3 days. Three batches were prepared following this method and denoted as B_5, B_6 and B_7.

2.3.4. Drug Uptake Methodology:

0.25 gm of HMSC was added into 10 ml Na-IBU water solution with a concentration of 40 mg/ml at room temperature. Sealing the vials, then the mixture was kept for one day. The IBU loaded drug was separated from the solution by filtration for samples B_1, B_2, B_3 and B_4. Then for each sample 1ml, 2ml and 3ml was taken and made into 100 ml volumetric flask filling the mark with distilled water, and then was analyzed by UV/Vis spectroscopy at a wavelength of 264 nm[14]. Calibration curve of ibuprofen was determined by taking absorbance vs ibuprofen concentration between 0 and 2 mg/ml as parameters.

For the samples B_5, B_6 and B_7 Na-IBU was loaded following the same procedure and kept for two weeks. Drug loaded samples were separated by centrifugation at 4000 r/min. For each sample 1ml, 2ml and 3ml was taken and made into 100 ml volumetric flask filling the mark with distilled water, and then was analyzed by UV/Vis spectroscopy at a wavelength of 264 nm. Calibration curve of ibuprofen was determined by taking absorbance vs ibuprofen concentration between 0 and 2 mg/ml as parameters.

2.3.5 In vitro Drug Release Methodology:

Drug loaded samples were compressed into tablet with a diameter of 10 mm and thickness of 0.5 mm (approximately). The release rate was obtained by soaking the drug charged tablets in 100 ml of water, maintained at a temperature of 310K. At predetermined time intervals (5 min), 3 ml samples were withdrawn and replaced after taking the reading to keep the volume and concentration constant. These samples were filtered (0.20 µm), and analyzed for ibuprofen content at 264 nm using UV-VIS spectrophotometer for the samples B_1, B_2, B_3, B_4 and at 264 λm for the samples B_5, B_6 B_7. All the experiments were performed in triplicate [14-19].

3. Characterization:

3.1. Material Characterization:

3.1.1 Characterization by X-ray Powder Diffraction:

X-ray powder diffraction was recorded for four batches of prepared samples. The diffraction patterns are showed in figure-1 below:

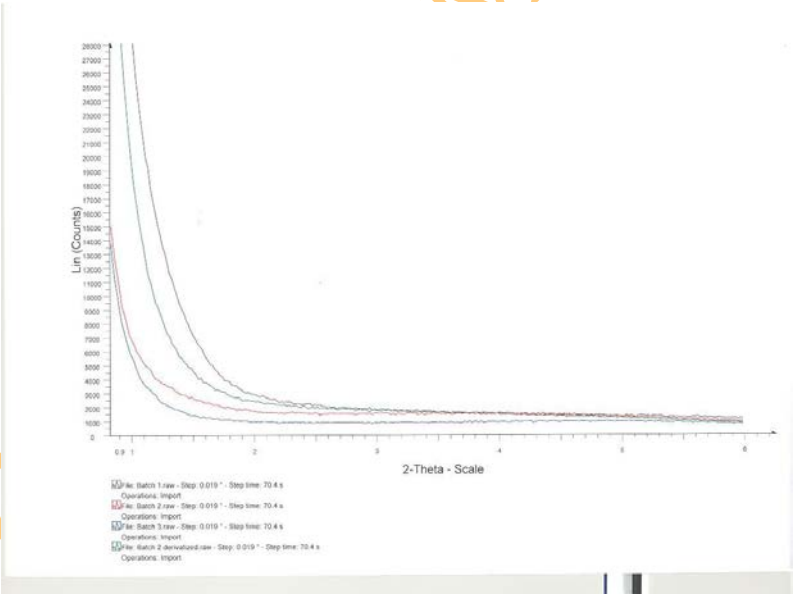

Figure 1: The low angle X-rd patterns at 2-theta scale of as-prepared B_1, B_2, B_3 and B_4 (b_2 derivatized) hollow mesoporous silica.

Fig.1 represents the XRD diffraction patterns of as synthesized and modified samples of mesoporous silica. Four batches (B_1, B_2, B_3 and B_4) of prepared silica were characterized by XRD powder diffraction. There was no diffraction for any of the prepared sample in the figure. 1, which indicates that all the prepared sample are amorphous in nature. Though most of the amorphous mesoporous silica has stability problem but they are recently focused by the researchers due to their bio-compatibility, non-toxicity, adjustable pore size and availability (15, 16). Stability problems of thus mesoporous silica are improved by attaching different

organic groups. Adjustable pore size and suitable pore volume of mesoporous silica materials shows them as a potential support for hosting and further release of a large variety of drug molecules having specific therapeutic effect (14).

3.1.2 Characterization by C-H Analyzer:

Carbon-Hydrogen analyzer was used to measure the percentage of carbon and hydrogen present within the samples. 18.21% of carbon and 3.68% of hydrogen was found in the sample in single state analysis and duplicate analysis stage carbon percentage was 18.13 and hydrogen percentage was 3.58 (fig. 2). A little amount of nitrogen was also found in the sample (approximately 1%). It was due to the instrument error.

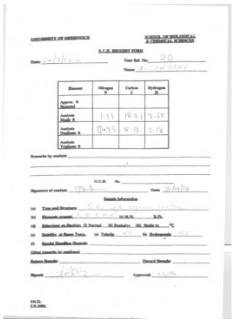

Figure 2: Percentage of Carbon and Hydrogen present within the prepared samples.

3.1.3 Characterization by Micromeritics Gemini surface Area Analyzer:

Micromeritics Gemini surface Area Analyzer was also used to characterize the surface area of prepared samples. The values of the surface area measurement of the samples are given in the table- 1 below:

Sample	Surface Area (m^2/gm)
B_1	1.8
B_2	<1
B_3	<1
B_4	1.8
B_5	26.1
B_6	26.1
B_7	26.1

Table 1: Data of Surface area.

Surface area of the samples B_1, B_2, B_3, B_4 are approximately 1 or below. But surface areas of the samples prepared with ammonia showed better result. In the preparation stage of the silica samples, the surfactants may get stuck with the silica samples which lead to less surface area reading. Further drying was done for all the samples, even after that reading was unchanged.

3.1.4 Characterization by Scanning Electron Microscopy:

Scanning electron microscopy was done for all the prepared samples. SEM image of the prepared samples was taken to analyze the surface morphology of the prepared samples. The broken edges of spheres showed that the samples are hollow. The average size of the spheres were 0.105- 0.120 µ. Fig.3 shows the images of the samples B_1, B_2, B_3 and B_4. There were a few spheres were found for these four prepared batches. Some rough edges can be identified in the images. From the images at fig.4, it can be seen that all the prepared samples for batches B_5, B_6 and B_7 were spherical in shape. For the batches B_5, B_6 and B_7 the number of the hollow spheres is more.

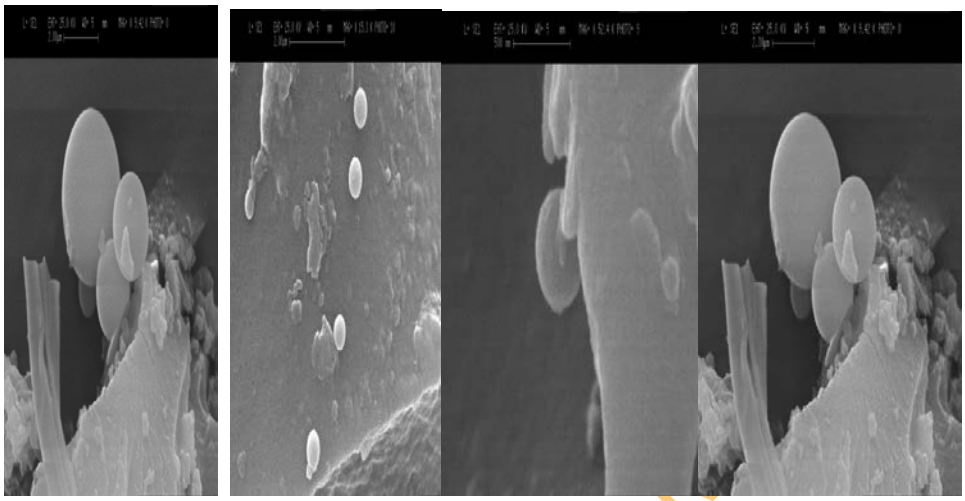

Fig 3: The SEM image of as prepared HMSC; (a) B_1 (b) B_2 (c) B_3 (d) B_4

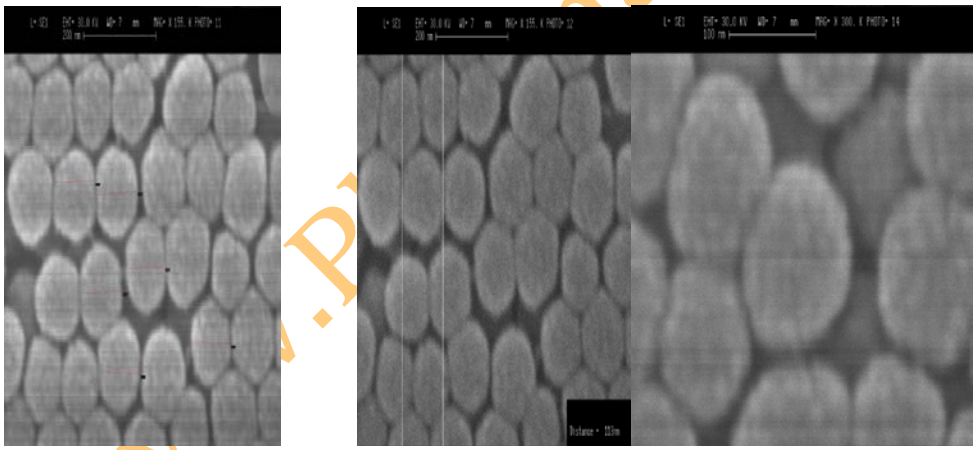

Fig 4: The SEM image of as prepared HMSC; (a) B_5 (b) B_6 (c) B_7 (d) B_7

3.1.5 Characterization by MALVERN Particle Size Analyzer (MASTERSIZER 2000):

MALVERN particle Size analyzer (MASTERSIZER 2000) was used to measure the particle size of the prepared samples. The particle size distribution of the prepared samples is showed in the fig. 5.

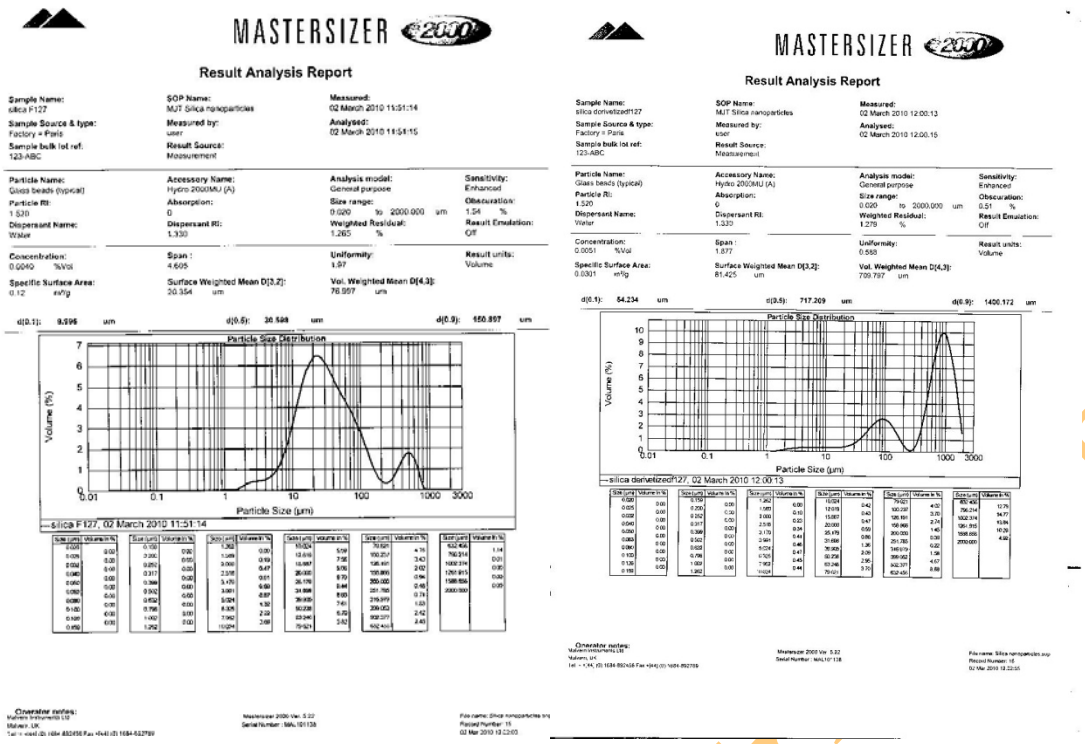

Figure 5: Particle size distribution for the as prepared B_2 and B_4 sample.

3.2 Ibuprofen storage in as prepared Mesoporous Silica Samples:

After loading the Ibuprofen-Na drug in to the as-prepared mesoporous silica samples following the method illustrated at 2.3.4.; 1ml, 2ml and 3ml of sample was taken in to 100ml of volumetric flask and up to the mark was filled with distilled water. For all the batches absorbance was taken using Ultraviolet/Visible (UV/VIS) Spectroscopy at 264 nm.

From these absorbance values amount of IBU-Na adsorbed by per gram of silica was calculated for each batch.

Batch Number	IBU-NA absorbed (mg)
B_1	146
B_2	312
B_3	**34222** (Significant)
B_4	344
B_5	378
B_6	666
B_7	212

Table 2: Amount of IBU-Na adsorbed by per gram of Silica

So, the final amount of IBU-Na per gram of mesoporous silica is 6422 mg and 7770 mg for the batches B_1, B_2, B_3, B_4 and B_5, B_6, B_7. From the results of drug loading, it can analyzed that samples which were prepared following the **2.3.3** method gives better drug loading property. As these samples have more surface area, they are able to hold more drugs than the samples having less surface area. One more reason may be due to the number of spheres silica present in these batches. From the image showed at **fig.6** and **fig.7**, it can be analyzed that batches (B_5, B_6, B_7) prepared following the method illustrated at **2.3.3** contains more sphere silicas than the batches

(B_1, B_2, B_3, B_4) prepared following the method demonstrated at **2.3.2.** Pore diameter of the as prepared silica samples also plays a vital role in drug loading. If the pore diameter of the silica sphere is more than more drugs will be loaded into the samples. In addition, some factors such as mixing and setting time, pH, powder-liquid ratio (F127, water, amount of toluene added), temperature etc. should also bring into account as they have effects on ibuprofen release and uptake. Greater Ibuprofen loading can be achievable by altering these factors as well the surface morphology of the hollow mesoporous silica samples.

3.3 Ibuprofen release from as prepared Drug loaded Mesoporous Silica Samples:

Drug release patterns were also analyzed for all batches of samples. Absorbance was taken for the drug loaded samples following the method illustrated at 2.3.5 at different wavelength by Ultra Violet/ Visible Spectroscopy. The absorbance values of drug release pattern are given below:

Time interval (min)	Absorbance B_1	Absorbance B_2	Absorbance B_3	Absorbance B_4	Absorbance B_5	Absorbance B_6	Absorbance B_7
5	0.005	0.004	0.002	0.006	0.013	0.017	0.013
10	0.007	0.007	0.008	0.008	0.027	0.029	0.025
15	0.012	0.012	0.013	0.011	0.037	0.039	0.034
20	0.022	0.017	0.021	0.015	0.044	0.043	0.038
25	0.026	0.021	0.027	0.018	0.044	0.045	0.038
30	0.035	0.028	0.032	0.025	0.044	0.047	0.038
35	0.046	0.034	0.038	0.032	0.044	0.047	0.038
40	0.051	0.037	0.044	0.039		0.047	
45	0.055	0.037	0.049	0.044		0.047	
50	0.055	0.037	0.049	0.046			
55	0.055	0.037	0.049	0.046			
60	0.055	0.037	0.049	0.046			
65	0.055	0.037	0.049	0.046			

Table 3: Absorbance values for the drug released samples.

The drug release patterns of the samples are given below:

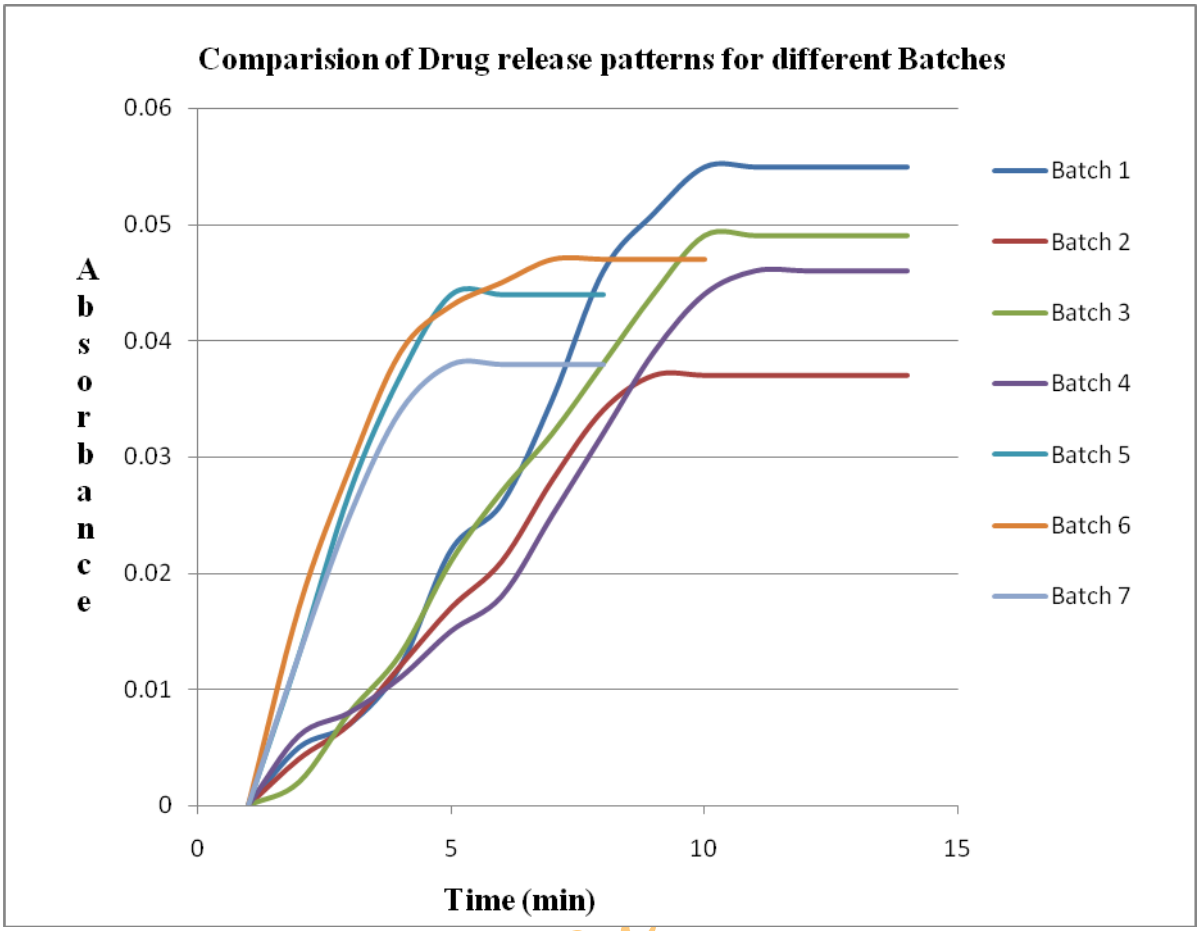

Figure 6: Comparison of the drug release patterns for different batches.

For all the drug released samples a specific time was identified when all drugs was dissolved. This time is denoted by't'. The't' value for all the samples are given below:

Batch number	't' value (min)
B_1	45
B_2	40
B_3	45
B_4	50
B_5	20
B_6	30
B_7	20

Table 3: **'t'** values for different batches.

From this table.11 The't' values for the different batches can be analyzed. For the samples having surface area one or less than one,'t' value range remains between (45-50) minutes. But for the samples having more surface area (26 m^2/gm),'t' value range remains between (20-30) minutes. From these data's it is analyzed that samples having more surface area released all the drugs more quickly than the samples having less surface area. 't' value can also be affected by the structure and pore size of the samples. Bonding between the drug and the samples also plays a vital role measuring the't' value. If the bonding remains stronger than drug release from the sample takes more time in comparison with week bonding between the drug and sample. For the modified batch B_4,'t' value is 5o minute which is greatest. The bonding between the

chemicals and the Ibuprofen drug may be the reason for such delay release of drug. Especially the strong bond among hydrogen and IBU-Na is responsible for the delayed drug release.

From the fig. 6; it was analyzed that the drug release from the as prepared silica samples are continuous. Drug releasing from the samples started immediately after giving the samples into the dissolution medium and increased with time. By changing some conditions during experiment such as, temperature of the dissolution medium, pH of the medium, compression energy to make tablets etc, drug release pattern can be revolutionize. But, these are not done here in discussion because all of them were not brought into account during the experiment due to shorter period of time and same conditions has been repeated for all the experiment

4.1 Conclusion:

Hollow mesoporous silica spheres with different morphologies have been successfully synthesized with simple one-step reaction and post-modification. By using Ibuprofen as a model drug, drug loading and release property of prepared samples were characterized. Modified sample, B_4 gave almost same drug uptake property. But the't' value for the modified sample was long. It took almost 50 minutes to dissolve all the drugs. For all the prepared samples drug releasing property was incessant. With time the percentage of drug release increased. One goal of this project was to synthesize mesoporous silica containing greater surface area. Though the surface area of the prepared samples is smaller, the drug uptake and release patterns showed good behaviour. By changing the affecting factors during experimental e.g. pH, temperature, reacting time etc, better surface area can be achieved. Surfactant washing after initial preparation of silica particles is very important. If surfactants got stuck with the samples than the prepared samples will not give good reading in terms of surface area measurement, drug uptake and release. Drug release process also indicates that silica nano-technology can be used more effectively in control release drug delivery system with further modification of the experimental section and different surface topology of mesoporous silica.

4.2 Future work and Recommendation:

As some results of Ibuprofen drug release and uptake data did not give the desired or expected profile, the following work is required and could be the new revolution of control release drug delivery-

- The mesoporous silica sphere particle size could be reduced to improve the Ibuprofen drug loading and release of control drug delivery system as smaller particles have larger surface area.
- The uptake of IBU-Na drug from high concentration of Ibuprofen solutions could be performed to increase the uptake that would lead to more subsequent release.
- The idea of preparing mesoporous silica with modified pore surface are innovative and the experiment showed well amount of Ibuprofen uptake and release that could be applied and further investigate to improve drug release and uptake.
- The role of other chemical ions such as hydrogen, fluoride ions inside the matrix and their release and uptake associated with Ibuprofen ions could be investigated.
- Only Ibuprofen-Na release and uptake have been investigated in this project but some other related area such as setting time, mixing time, pH and temperature effects or Water-TEOS ratio in various combinations could be experimented and that would give some effects and clear view on drug release and uptake profile.

- Each Ibuprofen release and uptake experiment was done for a very short period of time, which is not enough to achieve a better drug release and uptake profile. Experiment could be done for a longer period of time and more experiment could be done following different methods of uptake and release.

- Some other investigations are needed in some specific areas-

  - Bond strength of mesoporous silica and IBU-Na drug molecule.

  - Hardness of prepared tablets for drug release materials

  - Microbial contamination

  - Pore size of the silica particles (especially for the drug containing molecules)

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