New mesostructured origami silica matrix: a nano-platform for highly retentive and pH-controlled delivery system

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Abstract
In the present study, stabilizer caged fluorescent rhodamine B mesoporous silica particles with special shapes were prepared. The prepared particles have a pore volume of 1.92 cm³/g and a pore diameter of 12 nm. The abundant hydroxyl functional groups of mesoporous silica are responsible for the superior loading capacity of target molecular specie. The appearance of bands due to –COOH, –CH₃, –CH₂, –NH etc. indicated that the fluorescent rhodamine B could be engaged with the stabilizer inside the mesoporous channels. The performance of mesostructured origami silica matrix was evaluated by in vitro release experiments. From the in vitro release results, this material is suggested to have appropriate features for almost no release at pH = 1.2 and very slow release at neutral pH value. The same material could be best employed at pH 4.5 and at high pH values. It is concluded that mesostructured origami silica matrix is a smart nano-platform and can be utilized for high retention of cargo molecules.

1. Introduction
Scientists of different research fields are highly motivated to resolve human health issues against serious and fatal diseases. In this regard, scientists and researchers have shown their keen interest in analeptic platform based on nano-medicine that can successfully and energetically change the pharmacokinetics and bio-dispersal/bio-dissemination of pharmacologically active agents such as drugs and fluorescent materials [1–3]. To improve analeptic nano-platforms, their intrinsic limitations can be addressed by nanotechnology. Practically, limitations of analeptic nano-platforms,
such as low stability, high toxicity, fast excretion and non-specificity, can be improved under control environment. Delivery of drug or fluorescent material via these nano-channels becomes difficult to control and handle complicated biological systems. Several captious issues, including stability issues in blood circulation, insufficient drug adequacy, unwanted side effects and cost issues, are the challenges in scientific applications of analeptic nano-platforms [4]. To cope with these issues, different kinds of analeptic agents, such as organic and inorganic nano-platforms, are being widely used to construct stimuli-responsive nano-channels to improve analeptic efficacy and to acclimatize pharmacokinetics [5]. Among these nano-channels, silica-based analeptic channels reveal advantageous characteristics such as highly controlled shape and size, remarkable biocompatibility, low toxicity, biosafety, stability in clinical applications [6–8].

Manipulation of cargos, including drug delivery system for therapeutic treatments, must be highly controlled and targeted. Engineering/manipulating strategies manoeuvring drug delivery carriers like silica nanoparticles have become an important requisite for many therapeutic treatments to target at bacterial infections of tumours due to instability, undesirable side effects and toxicity [9]. To reduce the risk of undesirable side effects and systematic toxicity, engineering of cargos containing drug release system must be controlled and targeted in a localized environment. If the drug release system is controllable, then it can easily effectuate a cancer tumour or bacterial infections with good efficacy [10]. An important factor for drug carrier particles to reach actual targets and release drug is based on high concentration of drug loading [11]. Well-ordered and uniform silica particles with different morphologies, such as discoids, gyroids, fibres or spheres, especially having hexagonal packed platforms are gaining much importance for accommodating drugs or fluorescent dyes [12]. Due to their novel shapes, silica particles are thought to be much suitable for the retention of fluorescent molecules, dye or other molecular species of interest. In the real sense, thin films and other different morphological shapes such as discoids, gyroids, fibres, and twisted shapes are the technological necessities [13]. The mechanism of thin film formation is the introduction of surface into solutions at the early stages of polymerization process. The nano-windows/nano-channels of these films can be aligned to accommodate the guest molecules. The synthesis of such type of silica can maintain high concentration of drugs within the particles with high retentions and good unloading of drug at the target point. In situ loaded guest molecular species’ synthesis of silica particles showed significantly higher loading of guest molecular species compared to post-loaded guest molecular species traditionally synthesized silica particles [9].

This technique prepared highly ordered micelles close packing, so that guest molecular species does not leak. Maximum content/concentration of guest molecular species can be loaded/re-trained in this synthetic technique. The release of guest molecular species at targeted point is more predictable and sustainable in this type of technique than that of typical traditional content – gradient-driven loading techniques. This sort of loading and unloading/release of guest molecular species (fluorescent rhodamine B) can make visual persuading/visual tracking of the guest molecular species unloading from the edge of micelles advancing inside. This type of visual tracking cannot be fulfilled by typical tradition synthesis techniques. Therefore, the essence of the above discussion is that in situ loaded silica composites/particles with special morphology will definitely and positively contain remarkably higher concentration of cargo molecule as compared to typical traditionally synthesized nano-composites. This is the main advantage of this synthesis technique.

Lu wu et al., prepared multi-shelled mesoporous silica through a self-assembly of two surfactants (CTAB and sodium dodecyl benzene sulphonate). The dual-template strategy showed high drug (doxorubicin hydrochloride) loading efficiency and the pH-controlled responsive release behaviour [14]. Carlo M. Carbonaro et al., proposed a possible solution of leaching using template-based sealing scheme by incorporating a dye (Rhodamine 6G) in mesoporous silica [15]. Similarly, Kim et al. concluded that curcumin-loaded silica matrix, having micellar dispersion strategy, proved to be a best hybrid-silica pH-controlled drug delivery system [16]. Jessica C. Tom et al., prepared mesoporous silica films functionalized with localized charge-switchable polymer (a dual responsive polymer) and suggested a best carrier for cationic and anionic species [17]. Cameron A. Stewar reported a new drug-template synthesis of silica particles having ideal loading and release profile [9]. Naik and Sokolov prepared origami-type mesoporous micron-sized silica particles. These origami silica particles showed high loading of fluorescent guest molecules with ultra-brightness. Their release in organic media was also investigated and the possible solution to control the release was also discussed [12]. Kala parthi also synthesized the origami-type mesoporous micron-sized silica particles and studied the phenomenon of ultra-brightness of host rhodamine 6G dye. The matrix showed a high loading (50 mM) of physically encapsulated rhodamine 6G inside nanoporous silica without noticeable dimerization [18].

The present study aims to express the synthesis of a bio-inspired alternative system for in situ rhodamine B molecules loading in origami mesoporous silica particles and then to investigate its in vitro release profile in different pH media. This was not studied earlier to the best of our literature survey.
2. Experimental

2.1. Materials/chemicals

The following chemicals were used as received: Tetraethylorthosilicate (TEOS) (99%, Merck), Sodium Hydroxide (99.80%, Merck), Hydrochloric Acid (BDH, 35%), Sodium bicarbonate (∼ 99%, Daejung), Cetyltrimethyl ammonium bromide (CTAB) (99%, Sigma-Aldrich), Ethanol (Merck, 98%), Methylated spirit (purity (v/v) 99%, Fischer scientific), Acetic acid (∼ 99%, Merck), Acetone (98%, Merck), formamide solution (Merck), Rhodamine B (> 97%, Merck).

2.2. Synthesis procedure of mesoporous silica (fibres, discoids, gyroids and thin films)

Mesoporous silica particles, with different morphologies, were synthesized by modifying the technique to synthesize origami-type particles [12]. Mesoporous silica particles (a combination of discoids, fibres, gyroids, etc.,) were synthesized by acid-catalyzed hydrolysis of TEOS. In this strategy, TEOS is an organic silica source (a precursor), formamide is a pH stabilizer and CTAB is a template. Typically, in a high-density polypropylene (HD-PP) beaker, 0.32 g of CTAB was dissolved in 16 mL of deionized water followed by the addition of 4 mL of formamide. After that, 3 mL of concentrated HCl (37%) was added under vigorous stirring. The sol/mixture was stirred at 600 rpm for 10 min. After stirring, the mixture was allowed to stand for 3 h under static condition at room temperature. The sol was divided into two portions. In one part, having nearly 15 mL of sol, 0.5 mL of TEOS was added to the sol and stirred for a minute to dissolve the TEOS under ambient conditions. The resulting sol was then left to stand under quiescent conditions for 3 days. The resultant product was filtered using a Buckner funnel. The product was then washed with copious amount of distilled water (at least 1 L) and oven dried at 70°C for 150 min. After drying, the material was then calcined in air using a Muffle furnace at 550°C for 6 h at a heating rate of 10°C min⁻¹.

2.3. Synthesis of fluorescent rhodamine B dye-modified mesoporous silica (fibres, discoids, gyroids, thin films etc.)

In the second part of the above-synthesized sol, the 15 mL of sol was mixed with 15 mL of 0.005 M solution of rhodamine B dye under stirring for 5 min. Then an aliquot of 1 mL of TEOS was also added to a reaction vessel under stirring. The resulting sol was then left to stand under quiescent conditions for 3 days. The resultant product was filtered using the Buckner funnel. The product was washed with copious amount of distilled water (at least 1 L) and oven dried at 70°C for 90 min.

Scheme 1. Interaction pathways of host molecules and silanol groups of mesoporous silica.

2.4. Rhodamine B dye release experiment from mesoporous silica particles

A calculated amount of 0.05 g of as synthesized rhodamine B dye-doped mesoporous silica particles was mixed with 200 mL of water (as aqueous media) and 200 mL of methylated spirit (as organic media), respectively and left incubated at room temperature under vigorous shaking for 36 h. Rhodamine B dye release profile, in aqueous (acidic and alkaline) and organic media for the different regular release times, was analysed using a Carry 60 UV/Visible dual beam spectrophotometer [19].

2.5. Characterization

FTIR (Fourier transform infrared spectroscopy) was performed using Alpha Bruker ATR in the range of 400–1000 cm⁻¹. SEM (scan electron microscopy) – EDS (energy dispersive spectrometry) was performed using JED-2300 (JEOL instrument) Analysis Station. To analyse the textural properties, Brunauer Emmett and Teller (BET) analysis was performed through instrument Quantachrome Nona Win2.

3. Results and discussion

3.1. Formation mechanism of mesostructured origami silica matrix and proposed mechanism of adsorption or interaction of guest molecular species

Since the preliminary development, a wide variety of synthetic strategies have been forwarded. Exploitation of reaction conditions (especially pH value), structure directing surfactant molecules and the types of precursor/silica monomers control the overall synthesis of the target material [20]. These factors are responsible for the type of interaction (hydrogen bonding or electrostatic) between the structure directing surfactant (S) and silica precursor (I). The type of surfactant, along with pH of the reaction mixture, directs electrostatic interactions. As in our case, utilizing cationic surfactant under acidic conditions (pH < 2), which is below the isoelectric point of the Si-OH, necessitates the counter-ion (X⁻) to reconcile the surfactant (S⁺) – silica (I⁺) interaction [20] (Figure 1).

The well-known cationic surfactant CTAB generally shapes the spherical micelles in such a way that its polar...
cationic (hydrophilic) head groups are on the outer surface, while its non-polar (hydrophobic) tails drive to the interior surface to minimize their connection with water. Above certain ionic strength and concentration limit, these micelles changed from sphere shape to rod shape [21].

The micelles are involved commonly in drug delivery, so it is important to understand in-depth interactions of guest molecular species with micellar media. Beneficial interactions between guest molecular species and micelles are a central requirement for proficient drug delivery. On the other hand, tailoring the extent of association mainly depends on the nature of functional groups on the guest molecular species and the nature/type of micelles [22]. It is good to explain the stern layer and the palisade layer to understand easily. In micelle, the stern layer is generally the layer around the core of a micelle consisting of ionic head groups which are tightly bound to counterions of opposite charge. The palisade layer of micelle is generally the area between non-polar end/hydrophobic core of micelle and the stern layer having few carbon atoms of the chain of surfactant originating from the polar ionic head group [23]. To tune the partitioning aptitude of the guest molecular species in the micelles can be efficient in the targeted release of the guest molecular species at the site of action. However, as reported, the aqueous phase can penetrate into the micelle designed by surfactant molecules up to four carbon atoms of the chain from the head group [24]. In Figure 2, rhodamine B molecules are distributed near the surface of micelle and to a certain extent can be partitioned inside the palisade layer of the micelles.

The first step is the formation of micelles of surfactant (CTAB). CTAB micelles aggregate and shape into micellar rods [25]. This type of morphology facilitates the loading of guest molecular species into the micellar compartment as compared to the typical traditionally synthesized spherical micelle [26]. In the present report, coating with silica to form mesoporous silica particles involved the polymerization/hydrolysis of tetraethyl orthosilicate (TEOS) under acidic conditions. Silica (TEOS)-coated micellar rods further bend and fold to fabricate various origami shapes [27].

The interaction strength between guest molecules and the silica surface is always uneven and depends on the active adsorption points [28]. In the case of molecular compounds (like acidic drugs) that possess carboxylic acid groups (–COOH), such as rhodamine-B and ibuprofen, , the interaction of silanol groups of mesoporous silica was proposed to occur by two main pathways, as depicted in Scheme 1 (where Rh stands for the remaining part of rhodamine B) [29].

The first one is through hydrogen bonding and the second one is through ligand-exchange mechanism. Generally, adsorption of molecular species, containing hydroxyl groups, is favoured by the first pathway, as it demands the less amount of activation energy [19,28]. A quaternary amine group, a carboxyl group and nitrogen atom with lone-pair electrons, is present in rhodamine B molecule. The Carboxyl group remains in unprotonated form at near neutral pH value conditions. Rhodamine B remains in cationic form as dominant below pH 3 but changes into its zwitterionic form when the pH rises above 8 [30,31].

3.2. BET analysis

The most important physical characteristics that regulate the efficiency of the scaffold to be an ideal release system are its textural properties (pore diameter, surface area, pore structure, pore volume) particle size and particle morphology [20]. Keeping in mind, the molecular species (cargo) to be carried and delivered, modification of these physical characteristics can significantly affect the loading and/or release profile.

From typical N₂ adsorption–desorption isotherm, a type IV isotherm, which is a typical fingerprint of mesoporous silica, is observed (Figure 3) [32]. Four distinct stages are observed as follows: (i) a gradual increase in N₂ uptake (the first linear section) at a low relative pressure is due to the sorption on the surface of the
mesopores or meso – channels and outward surface of particles related to monolayer–multilayer adsorption phenomena. A non-zero slope in the low relative pressure range of 0.04–0.25 directs about substantial surface area of both external and mesoporous or the mesoporous only [33]. These features also reflect the existence of micropores in our material [34]. An important region, at relative pressure P/Po near about 0.3–0.4, is related to volume filling of mesopores, (ii) a slight pace at intermediate relative pressure attributes to capillary condensation phenomena within the pores or inter-particle voids, (iii) a plateau or elevation with a slight inclination at a relative high pressure (P/Po = 0.4–0.7) related to multilayer adsorption on the external surface of the adsorbent, (iv) a sharp rise in N2 uptake relates to filling up all other available pores when pressure reached to its saturation value (near P/Po = 1.0) [35,36]. From BET plot (multi-point), the calculated BET surface area is 283.54 m²/g. Calculations from BJH adsorption method are summarizes as follows: pore volume is 0.08 cm³/g and pore diameter is 3.48 nm (Figure 4). Calcined mesoporous silica (without template and rhodamine B) showed high pore volume (1.92 cm³/g) and pore size (12 nm) (Figure 5). The extensive decrease in pore diameter indicates a successful pore filling by the guest molecular species [15,37]. Complete profile of BET analysis and BJH pore size distribution for material indicates the existence of a broad pore size distribution.
of mesopores (50 nm > pore size > 2 nm) and micropores (pores size < 2 nm). This unique combination of micropores (in minor) and mesopores (in major) makes this material outstanding for the adsorption of multi-sized guest molecular species.

### 3.3. FTIR results

FTIR spectral analysis was done to estimate the successful preparation of carrier mesoporous silica material and to confirm the incorporation of rhodamine B molecules along with the template CTAB (Figure 6). The characteristic bands were found at 1053 cm\(^{-1}\), corresponding to asymmetric stretching vibration and 798 cm\(^{-1}\) corresponding to symmetric stretching of Si-O-Si (siloxane band) of mesoporous silica material. Peak at 970 cm\(^{-1}\) is attributed to the stretching vibration of free/surface Si-OH (silanol group) directing higher surface area of material [38]. Bands at 1211 and 1710 cm\(^{-1}\) indicated the presence of carboxylic group (as C–O stretch and C = O stretch, respectively) of rhodamine B molecule [39,40]. The bands at 1385 cm\(^{-1}\) and 1486
may be attributed to the symmetric bond deformation and asymmetric bond deformation vibrations of methyl (CH3), respectively [41]. The absorption peaks at 2945 and 2773 cm⁻¹ are indicative for CH₂ group of CTAB surfactant present in the mesoporous channels [42,43]. There are also some peaks around 1460 and 2900 cm⁻¹ assigned to the C–H stretching that might be corresponded to aromatic rings of loaded rhodamine B [44]. The central region from 1800 to 2400 cm⁻¹ is also an indicative of the organic residues (loaded rhodamine b dye with surfactant) present in the mesoporous material [45].

3.4. SEM and EDX analysis

Morphology characterized by scanning electron microscopy (SEM) revealed the well-formed spheres, fibres, discoids, gyroids, thin films and some twisted fibre like shapes (Figure 7). Silica (TEOS)-coated micellar rods further bend and fold to fabricate various origami shapes [27]. Formation of rhodamine B-modified thin films and other origami shapes is due to folding and bending phenomena of thin/fine stripes of nano-porous film developed on the air-water interface. High resilience to rhodamine B release is justified if take in our mind the synthesis mechanism of these zoo of shapes. These micro-containers may also serve as high loading cargo molecules. From the EDX spectra of calcined (unmodified) and rhodamine B-modified mesoporous silica particles, the higher weight percentage of Carbon (24.75%) confirmed the presence of rhodamine B and template CTAB in mesoporous silica material (Figures 8 and 9).

3.5. In vitro pH-stimuli responsive rhodamine B release profile

Retention of dye in the pores can be ascribed by two important interactions:

(i) surfactant–dye interactions (ii) dye-silanol group interactions.

This may possibly as a result of three processes [46] (i) adsorption of molecules of dye on the micelle surface (exterior) or (ii) penetration of dye molecules in the palisade layer of the micelle or (iii) entrapment of dye in the core of micelle. In the beginning, the rapid release rate most likely corresponds to the guest molecular species present near exterior region of the mesoporous channels diffusing out and released into the medium, a slow increase depicted by a plateau region. The guest molecular species inside the mesopores are surrounded or engaged by the CTAB molecules. CTAB commonly plays a dual role a stabilizer and a structure.
directing agent. Here, CTAB molecules function as stabilizing cages and slow down the diffusion rates of cargo molecules entrapped inside the mesoporous channels [47].

The meso-channels of the fabricated discoids comprise a cylindrical geometry [48]. The rhodamine B dye molecules are well distributed inside each cylinder along with surfactant molecules. These surfactant molecules are utilized as the templating molecular species and also as dispersing agents inside the channel. The separation or dispersion prevents the rhodamine dye molecules from dimerization to preserve its fluorescent property [18,49]. The surfactant molecules utilized for the development of the mesoporous structure perform a dual role: one as a splitter and the other as a sealing agent or locking agent against leaching of the guest rhodamine B molecules.
The variation in the rhodamine B release might be attributed to “dye-silanol groups’ interactions” [16]. One should understand that deprotonated forms of rhodamine B are involved in the release profile at the investigated low and high pH values (as pKa = 3.7). The Carboxyl group remains in unprotonated form at near neutral pH values’ conditions. Rhodamine B remains in cationic form as dominant below pH = 3 but changes into its zwitterionic form when the pH rises above 8 [30,31].

Secondly, the value of isoelectric point for amorphous silica (Si-OH) in aqueous media is 2–3 [50]. It is suggested from the calculations of computational branch that Si-OH (Q^3) silanol groups on the mesoporous silica surface have a pKa value of 4.5, while Si(OH)\(_2\) (Q^2) silanol groups have a pKa value around 8.5 [51]. Therefore, in the 1.2–7.4 pH interval deprotonation of Si-OH (Q^3) silanol groups takes place, while Si(OH)\(_2\) (Q^2) silanol groups remains is the same. When pH value approaches to 7.4, nearly all Si-OH (Q^3) silanol groups become deprotonated.

At very low pH near 1.2, there is a possible dominant dipole/dipole interaction or hydrogen bonding among rhodamine B molecules and silanol (Si-OH) groups. These interactions are strong enough to bind the rhodamine B molecules with mesoporous silica that results no release even in highly acidic conditions.

At moderate or neutral pH value, deprotonation of Si-OH (Q^3) silanol groups takes place only that imparts negative charge on it (while Si(OH)\(_2\) (Q^2) silanol groups remains the same). At this pH value, some of rhodamine B (cationic form) changes into zwitterionic form [31]. Due to these changes, a very low release of dye molecule was observed. Following transformation of some silanol Si-OH into negatively charged Si-O\(^-\) groups, a chance of ion–dipole interaction (between Si-O\(^-\) groups and rhodamine B molecule –COOH group) is also expected. At pH values above 9, all silanol groups become deprotonated and all rhodamine B molecules now transform into zwitterionic form [52]. The change into zwitterionic form may produce dimmers due to the interaction between positively charged carboxyl group and negatively charged xanthene group of another molecule of rhodamine B. These
transformations lead to a slight reduction in electrostatic interaction (hydrogen bonding), which results as a release of dye molecules from the parent material (Figure 10).

From the *in vitro* rhodamine B release profile, this material is suggested to have appropriate features for slow release in gastric fluids (pH = 1.2) and at neutral pH, which recommends a constant release of drug over some specific time to avoid from the system of repeated administration. This material could be also utilized at pH = 4.5 and at higher pH value as a fast release system due to burst release in the earlier stage to achieve fast and utmost relief (Figure 11).

![Figure 10](image1.png)

*Figure 10.* In vitro release profile of rhodamine B at different pH values.

![Figure 11](image2.png)

*Figure 11.* (a) Fluorescent Rhodamine B-modified mesoporous silica material, Rhoadamine B release; (b) In neutral pH values. (c) In pH near 1.2, (d) In higher pH values above 8, (e) In slight acidic (acetate buffer solution)
4. Conclusion and future perspective

4.1. Conclusion

Mesoporous silica particles with different shapes (fibres, discoids, spheres, gyroids, etc.) were successfully fabricated by a simple one-step strategy. The in situ loaded fluorescent rhodamine B synthesis of silica particles was characterized and employed for in vitro release experiment. At pH = 4.5 and at higher pH values, this system showed a fast release due to the deprotonation of (partial or complete) silanol groups and the transformation of rhodamine B into zwitterionic form. While at pH = 1.2, a very low release was observed, which was attributed to dominant dipole/dipole interaction or hydrogen bonding between rhodamine B molecules and silanol (Si-OH) groups. High retention of cargo molecule was also attributed to special shapes of the host material. So, it is concluded that mesostructured origami silica matrix is a smart nano-platform and could be utilized for high retention of cargo molecules with controlled pH responsive release.

4.2. Future perspective

Scientists can make maximum benefit of the in situ guest molecules with loaded silica self-assembly of particles, having a special morphology to support carrier materials in the field of therapeutics. Anticancer drugs can be increasingly loaded onto the carriers to reach the target point for controlled release. Tuning and arrangement of components of the anticancer drug delivery system can be made through a force in a sustainable and predictable fashion. Therefore, these silica mesoporous particles may be considered an ideal reservoir for drug release medium. Work or research is still continued to improve better incorporation of drugs and coatings of materials. This improvement in drug-carrier cargo actually enhances the therapeutic treatments in the world.

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