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Self-assembly pattern directed sustained release from porous microspheres of discotic tripeptides†

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Porous microspheres from discotic tripeptides have been investigated as potential candidates for drug delivery vehicles. The C3 symmetric discotic tripeptide adopts supramolecular helical column structure by three fold intermolecular hydrogen bonding interactions as well as face to face π–π stacking interactions. But the C2 symmetric discotic tripeptide adopts supramolecular dimer like structure by six-fold intermolecular hydrogen bonding interactions and face to face π–π stacking interactions. Field emission scanning electron microscopy (FE-SEM) revealed that the C3 symmetric discotic tripeptide exhibits bird nest-like porous microspheres morphology formed by assembly of the individual columns. However the C2 symmetric discotic tripeptide forms round clay pitcher like porous microspheres. These porous microspheres have been used as potential carrier and sustained release of the bacteriostatic antibiotic sulfamethoxazole. The spectroscopic studies as well as the growth inhibition of E. Coli, exhibit that the round clay pitcher like porous microspheres is more efficient than the bird nest-like porous microspheres for sustained release of the drug. The report highlights the importance of self-assembly pattern for the fabrication of advance functional material.

Introduction

Supramolecular microstructures developed via self-assembly of building blocks have received considerable attention because these structures can lead to advance functional materials.1-5 The self-assembly process is governed by various non covalent interactions, including hydrogen-bonding interactions, ion-pair interactions, π–π stacking and hydrophobic interactions.6-8 Normally, this self-assembly process is fully reversible which leads to numerous possible applications of the supramolecular material in the fields of environmental sciences, material sciences, biomedical sciences and chemistry.9-12 The reversibility of the supramolecular systems have allowed to change in their topologies and properties upon exposure to external stimuli such as temperature, light, pH, and redox potential.13-15 Among these diverse self-assembly systems, the amphiphilic microspheres offer potential applications for drug encapsulation, delivery, and sustained release.16

Unwanted side effects and systemic toxicity is a common hazard for using naked drugs.17 So, rapping and pharmaceutical formulation is important.18 But this should work in a synergy and will not generate toxic chemicals by further reaction. An ideal delivery vehicle should deliver the required amount of drug to target site and confirm the sustained release of the encapsulated drug under physiological condition.19 Till date, diverse compounds such as polymers and polymer-based micelles,20 metal-organic frameworks (MOFs),21 covalent organic frameworks (COFs),22 carbon nanotubes,23 metal nanoparticles,24 silica,25 iron oxide nanoparticles,26 or dendrimer nanoparticles have been used for drug formulation and delivery.27 But, due to surface modification most of these reported delivery systems have side effects including intrinsic toxicity or immunogenicity.28 In this regard, peptide-based self-assembled microspheres29 are promising due to their biocompatibility30 and recognition properties.31 Also, due to their hydrophilic-hydrophobic balance for solubilising and targeted delivery of highly hydrophobic anti-tumour32 and antidepressant drugs,33 and statins,34 peptide-based delivery vehicles are very popular. Moreover, the hybrid peptides have stability towards enzymatic degradation.35 Hence, the design and synthesis of new peptide building blocks and delivery vehicles are of great interest. P. K. Das and co-workers have reported vesicles from discotic amphiphile that can encapsulate and deliver doxorubicin inside mammalian cells.36 We are developing microspheres and microvesicles as delivery vehicles, from peptidomimetic compounds.37 Herein, we have designed and synthesized two discotic tripeptides with different symmetry, from commercially available sources. The discotic tripeptide having C3 symmetry adopts supramolecular column structure stabilized by three-fold intermolecular hydrogen bonds.
However, the discotic tripeptide having $C_2$ symmetry forms supramolecular dimer stabilized by six-fold intermolecular hydrogen bonding interactions. The FE-SEM and the Atomic Force Microscopy (AFM) studies revealed that the $C_2$ symmetric discotic tripeptide shows bird nest like porous microspheres morphology but the $C_2$ symmetric discotic tripeptide exhibits round clay pitcher like porous microspheres morphology. The microspheres were loaded with the bacteriostatic antibiotic sulfamethoxazole. The round clay pitcher like porous microspheres of $C_2$ symmetric discotic tripeptide is more efficient than the bird nest-like porous microspheres of $C_2$ symmetric discotic tripeptide, for sustained release of the encapsulated drug.

**Results and discussion**

**Synthesis and characterization**

We have designed and synthesized two discotic tripeptides having $C_1$ symmetry and $C_2$ symmetry (Scheme 1). The assumption was that the compound 1 with $C_1$ symmetry would form a supramolecular columnar structure by three-fold intermolecular hydrogen bonds between amide functionalities, like earlier reports.[60] However, the compound 2 with $C_2$ symmetry may failed to form such columnar structure. Three L-Phe residues should impart hydrophobicity in the compounds and direct donor-acceptor type $\pi$-$\pi$ stacking and further modulate the self-assembly process. The discotic tripeptide 1 was synthesized from benzene-1,3,5-tricarboxylic acid and L-phenylalanine methyl ester using DCC as coupling reagent in 72% yields. The discotic tripeptide 2 was synthesized by coupling of methyl ester of 5-aminoisophthalic acid and Boc-Phe-OH followed by hydrolysis and further coupling with L-phenylalanine methyl ester using DCC as coupling reagent in 44.5% yield (Scheme S1, ESI†). All the synthesized discotic tripeptides and intermediates were purified by column chromatography and fully characterized by $^1$H-NMR, $^{13}$C-NMR and FTIR spectroscopy and mass spectrometry.

![Scheme 1](image1)

**Morphology**

The self-assembly propensity of the discotic tripeptides 1 and 2 were examined by field emission scanning electron microscopy (FE-SEM) and atomic force microscopy (AFM). For FE-SEM studies, a small amount of solution (0.02 M) of the discotic tripeptides 1 and 2 in methanol was placed on a clean glass slide and then dried by slow evaporation at room temperature. The samples were then allowed to dry under vacuum at 30°C for 24 h. The dried samples were coated with gold, and the micrographs were taken in Zeiss DSM 950 scanning electron microscope. The FE-SEM images of the discotic tripeptide 1 exhibit the formation of bird nest-like polydisperse porous microspheres morphology (Fig. 1a). The average diameter of the microspheres is about 1.5 $\mu$m. A careful observation revealed that the bird nest-like porous microspheres are formed by assembly of nanorods (Fig. 1b). The average diameter of the nanorods is ca 130 nm. The size of the pores on the surface of the microspheres is ca 50 nm. We were also able to capture the image of formation of bird nest-like porous microspheres from the nanorods (Fig. S1, ESI†), which shows that the shape and size of the nanorods are very regular. However, the FE-SEM images of the discotic tripeptide 2 shows the formation of round clay pitcher like polydisperse porous microspheres morphology (Fig. 1c). The average diameter of the microspheres is ca 1.2 $\mu$m. The internal diameter of the hollow inside the microspheres is ca 800 nm. The thickness of the microspheres wall is ca 150 nm. Inset of Fig. 1d showing enlarged image of microsphere like round clay pitcher clearly indicates the presence of cavity inside the microspheres and pore on the surface. The size of the pore is ca 50 nm. To know about the topography of the discotic tripeptides 1 and 2, atomic force microscopic studies have been performed. For AFM studies, the solutions (0.02 M) of tripeptides 1 and 2 in methanol were placed on a microscopic glass slide and allowed to dry under vacuum at 30°C for two days and studied by a NT-MDT atomic force microscope.

![Fig. 1](image2)

(a) The FE-SEM images showing bird nest-like porous microspheres morphology of discotic tripeptide 1. (b) The FE-SEM images showing the assembly of nanorods to form the bird nest-like porous microspheres of discotic tripeptide 1. (c) and (d) The FE-SEM images showing round clay pitcher like porous microspheres morphology of discotic tripeptide 2. (d) Inset showing the pores of the microspheres of discotic peptide 2.
The structure of the discotic tripeptides shows the polydisperse microspheres like morphology where the surface of the microspheres is very rough (Fig. S2a, ESI†). ESI Fig. S2b shows the 3D AFM image of the microspheres morphology. However, the AFM image of discotic tripeptide 2 shows the polydisperse microspheres like morphology where the surface of the microspheres is quite smooth (Fig. S2c, ESI†). ESI Fig. S2d shows the 3D AFM image of the microspheres morphology with smooth surface.

**Structure analysis**

For discotic tripeptide 2, mass spectrometry pointing to the existence of both monomer and dimer. Distinct signals for the monomer and a dimer were detected by Q-Tof Micro YA263 high-resolution mass spectrometer (Fig. 2).

![Fig. 2 Mass spectrometry data showing the coexistence of both monomer and dimer of discotic tripeptide 2.](image)

Circular dichorism (CD) spectroscopy in solution state was performed to study the aggregation propensity of the discotic tripeptides 1 and 2. The shape and intensity of the CD spectra differ significantly for discotic tripeptides 1 and 2 in methanol. Discotic tripeptide 1 shows positive cotton effect at 198 nm and negative cotton effects at 208 nm and 228 nm (Fig. 3a), reflecting the formation of helical supramolecular stacks. We conclude that such a strong CD signal originates from a rigid, elongated columnar self-assembly of the compound. The discotic tripeptide 2 has positive band at 200 nm and negative band at 211 and 226 nm with much lower intensity responsible for a dimer structure of shorter stacking (Fig. 3a).

Solid-state FT-IR spectroscopy was performed to study the structure of the discotic tripeptides 1 and 2 in porous microspheres. For discotic tripeptide 1, an intense band at 1743 cm⁻¹ indicates the presence of three ester groups in the compound (Fig. 3b). The peaks at 1641 cm⁻¹ and 1537 cm⁻¹ arise due to formation of H-bonded stacks of the amide C=O groups (Fig. 3b). For discotic tripeptides 2, the band at 1739 cm⁻¹ indicates the presence of two ester groups (Fig. 3b). The peaks at 1660 cm⁻¹ and 1528 cm⁻¹ arise due to the formation of H-bonded amide I and amide II (Fig. 3b). Another informative frequency range is 3500-3200 cm⁻¹, corresponding to the N-H stretching vibration. The discotic tripeptides 1 and 2 show peaks at 3304 cm⁻¹ for hydrogen-bonded NH (Fig. 3b).

The structure of the discotic tripeptides 1 and 2 were also studied by powder X-ray diffraction (PXRD). The PXRD pattern of microspheres of discotic tripeptide 1 shows that the material is crystalline in nature. Sharp reflections were observed in the 5–50° 2θ range (Fig. 3c). Powder X-ray diffraction (PXRD) had reflection at d-spacing of 4.07 Å and 15.98 Å corresponding to the distances between neighbouring aromatic moiety and the laminal spacing, respectively. However, the PXRD pattern of microspheres of discotic tripeptide 2 shows that the material is non-crystalline in nature (Fig. 3d).

![Fig. 3 (a) CD spectra of the discotic tripeptides 1 and 2 in methanol. (b) Solid-state FT-IR spectra of the microspheres obtained from discotic tripeptides 1 and 2. (c) and (d) PXRD pattern of discotic tripeptides 1 and 2, respectively.](image)

![Fig. 4 (a) The schematic presentation, showing self-assembly of discotic tripeptide 1 to columnar stack to nanorods to porous microspheres. (b) The schematic presentation showing self-assembly of discotic tripeptide 2 to dimer to 2D sheet to porous microspheres.](image)
The microspheres from discotic tripeptides are stable and insoluble in water. We have encapsulated a bacteriostatic antibiotic sulfamethoxazole in discotic tripeptides 1 and 2 microspheres. To the 3 mL of 0.50 x 10^{-3} M drug solution in methanol, 5 mg of discotic tripeptides 1 or 2 was added and stirred for 6 h, the solvent was evaporated under vacuum and the drug-loaded microspheres were washed several times with 50 mL water and centrifugation until the drained water after centrifugation exhibited negligible drug fluorescence. The drug-binding property of the microspheres obtained from methanol solution of discotic tripeptides 1 or 2 was studied by absorption and emission spectroscopy as these are quite sensitive techniques to understand any changes in microenvironments. From the absorption spectrum of discotic tripeptide 2 (Fig. 5a), it is clear that with increasing sulfamethoxazole concentration the absorbance at 262 nm gradually increases and the spectrum is red shifted (ca 6 nm). This implies that the microspheres have some interactions with the drug molecules. The result was further supported by the emission spectroscopy. From the Fig. 5b, it is evident that when we increase the concentration of the drug the fluorescence intensity of discotic tripeptide 2 at 347 nm gradually decreases and this spectrum is also shifted by 10 nm. Discotic tripeptide 1 also shows similar results with increasing sulfamethoxazole concentration studied by absorption spectroscopy (Fig. S3, ESI†).

The encapsulation efficiency (%) was quantified by the absorption spectroscopy and calculated as [(amount of drug added - amount of free drug)/ amount of drug added] x 100%. The encapsulation efficiency of the drug loaded discotic tripeptide 1 microspheres was found to be 60% and discotic tripeptide 2 microspheres was 70%. The drug loading content for the formulation was calculated as [weight of the encapsulated drug in the microspheres /weight of the microspheres used] x 100% and was found to be 4.33% for discotic tripeptide 1 and 5.33% for discotic tripeptide 2.

Further FE-SEM experiment was performed to know whether there is any change in size or shape of the microspheres after drug loading. FE-SEM image of the drug-loaded discotic tripeptide 1 clearly indicates the bird nest-like microsphere morphology is retained and there is no average change in size and shape after drug encapsulation (Fig 6a). Only the pores are absent in the drug-loaded microspheres. Fig. 6b shows the FE-SEM image of the drug encapsulated discotic tripeptide 2 microspheres, which clearly indicates the morphology is retained, only the pores of the microspheres are fill up. For reference, FE-SEM study of only sulfamethoxazole drug under the same condition was done. Fig. 6c shows the fiber-like morphology of sulfamethoxazole. The fibers have a diameter ca 100 nm and several micrometers in length.

We have also studied the release of the encapsulated sulfamethoxazole from the nanovesicles. For this purpose, sulfamethoxazole loaded nanovesicles were immersed into 5 mL Tris buffer (at pH 7.4) in a 15 mL centrifuge tube, centrifuged at 2800 rpm for 15 minutes, and examined by absorption spectroscopy at different time intervals. Fig. 7a is the drug release profile which clearly indicates that the microspheres of the discotic tripeptide 2 slowly release the encapsulated drug than the microspheres of the discotic tripeptide 1, with a complete release by 30 h (Fig. S4, ESI).

The sustainable release of encapsulated sulfamethoxazole and in vitro antibacterial activity in water and DMSO (10%) on E. Coli was examined by OD measurement at 600 nm. Fig. 7b shows the growth inhibition profile of E. coli against the sulfamethoxazole solution in 10% DMSO-water. E. Coli is more susceptible in sulfamethoxazole encapsulated microspheres than the naked sulfamethoxazole solution (control) (Fig. 7b). It is clear from the diagram that E. coli is more susceptible to the drug-loaded microspheres of discotic tripeptide 2 than drug-loaded microspheres of discotic tripeptide 1 (Fig. 7b). Fig. 7c(i),(ii) show the growth inhibition zones of E. coli against the drug-loaded microspheres of discotic tripeptide 1 and 2, respectively and Fig 7d shows the same for naked sulfamethoxazole in 10% DMSO-water. Furthermore, Fig. 7e indicates that the discotic tripeptides 1 and 2 do not have any
presented here show the importance of self-assembly pattern for antibacterial activity on the E. coli bacteria.

![Graph](image)

**Fig. 7** (a) Drug release profile of sulfamethoxazole loaded microsphere of discotic tripeptide 1 (red) and sulfamethoxazole loaded microsphere of discotic tripeptide 2 (black) in Tris buffer (pH 7.4) obtained from UV-Vis spectroscopy. (b) The growth inhibition plot of E. Coli with only drug (red), discotic tripeptide 1-drug (blue), discotic tripeptide 2- drug (dark cyan), without any drug (black). The growth inhibition zones of E. Coli bacteria against the (c)(i) encapsulated discotic tripeptide 1-drug, (c)(ii) encapsulated discotic tripeptide 2-drug, (d) sulfamethoxazole (drug), (e)(i) discotic tripeptide 1 and (e)(ii) discotic tripeptide 2 in 10% DMSO-water.

**Conclusions**

In conclusion, this study demonstrates the synthesis and self-assembly of C₂ and C₃ symmetric discotic tripeptides. The C₃ symmetric discotic tripeptide forms supramolecular columnar structure by three fold intermolecular hydrogen bonds. But the C₂ symmetric discotic tripeptide adopts supramolecular dimer by six fold intermolecular hydrogen bonds. FE-SEM images show that the C₂ symmetric discotic tripeptide exhibits bird nest-like porous microspheres morphology formed by the assembly of the columns. However the C₂ symmetric discotic tripeptide forms round clay pitcher like porous microspheres. Further, these microspheres were loaded with the antibiotic sulfamethoxazole. However, the discotic tripeptides are not a growth inhibitor of E. Coli. The spectroscopic studies as well as the growth inhibition of E. Coli exhibit that the round clay pitcher like porous microspheres is more efficient than the bird nest-like porous microspheres for sustained release of the drug. The results presented here show the importance of self-assembly pattern for the fabrication of delivery vehicles.

**Experimental**

**General**

All chemicals were purchased from Sigma chemicals. The discotic peptides were synthesized by conventional solution phase methodology (ESI). All the products were purified by column chromatography using silica (100–200 mesh size) gel as a stationary phase and an n-hexane-ethyl acetate mixture as an eluent. The intermediates and final compounds were fully characterized by 400 MHz ¹H NMR spectroscopy, 100 MHz ¹³C NMR spectroscopy and FTIR spectroscopy and mass spectrometry.

**NMR Experiments**

All NMR studies were carried out on a JEOL 400 MHz spectrometer at 25°C. Compound concentrations were in the range 1–10 mM in CDCl₃ and (CD₃)₂SO.

**FTIR Spectroscopy**

The solid-state FTIR spectrum was obtained with a Perkin Elmer Spectrum RXI spectrophotometer with the KBr disk technique.

**UV/Vis spectroscopy**

UV/Vis absorption spectra were recorded on a UV/Vis spectrophotometer (Hitachi).

**Fluorescence spectroscopy**

Fluorescence spectra were recorded in Cary Eclipse Fluorescence Spectrophotometer. In a typical experiment, compounds were dissolved in methanol. The spectra were recorded by exciting the system at 207nm, 300nm and 258nm.

**Atomic Force Microscopy**

For AFM, images were taken with an NT-MDT instrument (model no. AP-0100), in the semi-contact mode.

**Field Emission Scanning Electron Microscopy**

Morphologies of the reported compounds were investigated using field emission-scanning electron microscope (FE-SEM). A small amount of solution (0.02 M) of the compound was placed on a clean glass slide and then dried by slow evaporation. The sample was then allowed to dry under vacuum at 30°C for 24 h. The materials were gold-coated, and the micrographs were taken in an FE-SEM apparatus (Zeiss DSM 950 scanning electron microscope).

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TOC Graphic

Self-assembly pattern directed sustained release from porous microspheres of discotic tripeptides

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The round clay pitcher-like porous microspheres of $C_2$-symmetric discotic tripeptide is more efficient than the bird nest-like porous microspheres of $C_3$-symmetric discotic tripeptide, for sustained release of the drug.