Peptide-Based Soft Materials as Potential Drug Delivery Vehicles

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Abstract: Emerging concepts in the construction of nanostructures hold immense potential in the areas of drug delivery and targeting. Such nanoscopic assemblies/structures, similar to natural proteins and self-associating systems, may lead to the formation of programmable soft structures with expanded drug delivery options and the capability to circumvent first-pass metabolism. This article aims to illustrate key recent developments and innovative bioinspired design paradigms pertaining to peptide-containing self-assembled tubular and vesicular soft structures. Soft structures are composed of components that self-assemble to reveal diverse morphologies stabilized by weak, noncovalent interactions. Morphological properties of such structures and their ability to encapsulate drugs, biologicals and bioactive small molecules, with the promise of targeted delivery, are discussed.

Key Words: Soft structures, peptide, proteins, drug delivery.

INTRODUCTION

Encapsulation of environment-sensitive medicinally active agents for safe delivery to the target site is an integral research theme and is an investigational aspect of all drug discovery initiatives and some emerging new paradigms such as nanomedicine [1-7]. A nanoscopic approach, akin to conventional delivery methods, shields a chemotherapeutic agent from various destabilizing and degrading milieu in formulations and *in vivo*, until its arrival and release at a desired location. This helps to maintain optimal concentrations of a given drug, thus improving its bioavailability. However, if a vehicle can be crafted with a design strategy containing a tissue-specific address label, it will further enhance the potential of a drug delivery approach. Drug delivery vehicles should normally support facile transport of conventional chemotherapeutics, natural products and biologics, across a variety of membranes and barriers without significantly compromising the rate of approach and release of a drug in the vicinity of the target site(s).

The carriers devised should be biocompatible, devoid of inherent biological activity, cross-reactivity and cytotoxicity. These should possess optimal bioavailability and effective targeting abilities, in order to explore the full potential of the above approach. In case of *in situ* generated delivery platforms, it becomes important to introduce other desirable features in the design paradigms including a closely governed and predictable self-association mechanism providing controlled shapes, sizes and morphologies of delivery vehicles. Several investigational studies merit detailed analysis to expand the repertoire of soft delivery vehicles into nanoscopic structures regime [8-11].

Malmsten has recently presented an illustrative account of soft drug delivery systems having chosen selected examples of conventional as well as novel approaches involving carbon nanotubes and polyelectrolyte capsules constructed *via* layer-by-layer nanoassembly processes [12]. Nanoscale carriers may encapsulate, covalently attach, or chemiadsorb a bioactive drug for transport and it is surmised that this size scale may even offer certain advantages during administration *via* intravenous and subcutaneous routes and circumvent issues related to solubility and dispersability. It is beyond doubt that all emerging unconventional modalities will require close scrutiny pertaining to physicochemical parameterization and possible short- and long-term biological effect and toxicity, however, the characterization of suitable combinations will have to be closely monitored [13-14].

This review will specifically focus on *peptide-based soft structures*, which may offer benefits in terms of tailored design and scope for chemical decoration for selective tissue targeting. These soft structures possess the advantage of being made up of natural components thus reducing the possibility of toxicity. Ideally, soft structures comprise of components that self-assemble to reveal diverse morphologies stabilized by weak, noncovalent interactions. The use of such materials is advantageous as they can rapidly assemble at room temperature and disintegrate in response to relevant stimuli. This review also incorporates studies of various stimuli that help trigger disruption of soft structures close to the target site, thus permitting rapid release of bioactive molecules without affecting the integrity of their molecular structures. However, this brief account is meant to simply illustrate newer strategies and paradigms in soft matter design. The possibility of drug delivery using nanostructured materials has been subject of a recent review [15].

The diversity of peptide-based design of functional supramolecular structures emanates from the basic difference engendered in the side-chain of constituent amino acids that ranges from simple alkyl groups to a host of acidic, basic, hydrophilic, aromatic and heterocyclic groups [16-19]. These functionalities confer wide-ranging physicochemical properties with the help of a variety of conventional noncovalent interactions such as hydrogen bonds, hydrophobic interactions, and salt bridges, and a number of other specific interactions such as π-π stacking, cation-π and charge-dipole interactions [20-25].

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1. PEPTIDE-BASED OPEN ENDED SOFT STRUCTURES

a. Peptide-Amphiphile (PA) Constructs

Peptide-based materials encompass a myriad of soft matter ranging from tubular amphiphiles to spherical vesicular structures, where hydrophilic peptide headgroups having a preference for certain secondary structures and connected with appropriate hydrophobic tail(s) undergo self-association to result in hybrid peptide-amphiphile materials with a multitude of possible conformations and structures [26-27]. A recent account by Kokkoli and workers describes applications of such amphiphilic materials as suitable models to study the phenomenon of bioadhesion and their potential as scaffolds for tissue engineering, regenerative medicine, and targeted drug delivery [28].

This class of compounds exhibit multivalency [29] and also reveal the possibility of achieving defined topologies dependent on amino acid selection and alkyl tail modification [30, 31]. A facile coupling of these compounds with micelles and liposomes expand their utility in delivery applications (Fig. **1**).

New studies suggest that phospholipid addition to PA nanofibers modulate their chemical properties and mechanical strength and make them even more suitable for tissue regeneration and as delivery vehicles [32]. The attachment of polyethylene glycol head groups of different molecular weights has also been projected to "mask" targeting functionalities and to tune the residence time of delivery [33].

Fields and coworkers have recently described an interesting design of triple-helical "peptide-amphiphile" (α1(IV) 1263-1277) and its incorporation into liposomes of varying compositions, which bind the CD44/chondroitin sulfate proteoglycan receptor of metastatic melanoma and fibroblast cell lines [34]. A dose-dependent delivery of the rhodamine fluorophore could be achieved and it was proposed that such a system may serve as a vehicle for doxorubicin delivery with 'tunable' drug load characteristics. In addition, it was proposed that such triple helical peptide-amphiphile constructs could be optimized to target $\alpha 1\beta 1$, $\alpha 2\beta 1$, $\alpha 3\beta 1$, or $\alpha 11\beta 1$ integrins or collagen-binding microbial surface components having the capability to recognize adhesive matrix molecules, and thus offer a flexible design paradigm for composite drug delivery vehicles.

The delivery of doxorubicin with the help of self-assembling PA nanofibers at physiological pH was elaborated by Morelli and colleagues. Sequestration of pyrene and doxorubicin within the confines of these soft structures occurred, which was confirmed by a combination of techniques such as small angle neutron scattering and atomic force microscopy [35].

Another recent study reported novel PA nanofiber scaffolds containing which introduced various functional motifs and a self-assembling peptide RADA16 [36]. The biological function of these specialized motifs relates to the promotion of cell adhesion, differentiation and bone marrow homing activities. Success of such hybrid motifs was evident for two such scaffolds, functionalized with bone marrow homing motifs, which significantly enhanced the survival of neural stem cells and promoted differentiation towards cells expressing neuronal and glial markers in adult mouse neural stem cells. This study suggested that designer peptide scaffolds, in the absence of additional external growth factors, could influence neural stem cell differentiation towards desired phenotypes.

Davis and coworkers employed self-assembling peptide nanofibers to create a microenvironment in the myocardium that supported vascular cell recruitment - a strategy important for the construction of injectable cardiac tissue regeneration modalities. Self-assembled peptide microenvironments recruited smooth muscle cells, suggesting the potential of neovascularization without an inflammatory response [37]. It was proposed that injectable peptide microenvironments may provide protected regions for endothelial cell survival and organization, leading to the initiation of cardiomyocyte recruitment or maturation. As an added benefit, chemically tethered growth factors could be released in a controllable fashion, for optimal regulation of this regenerative process.

A similar cell culture study demonstrated selective differentiation of neural progenitor cells into neurons when encapsulated with carefully designed self-assembling PA nanofibers. A pentapeptide epitope, isolucine-lysine-valine-ala-

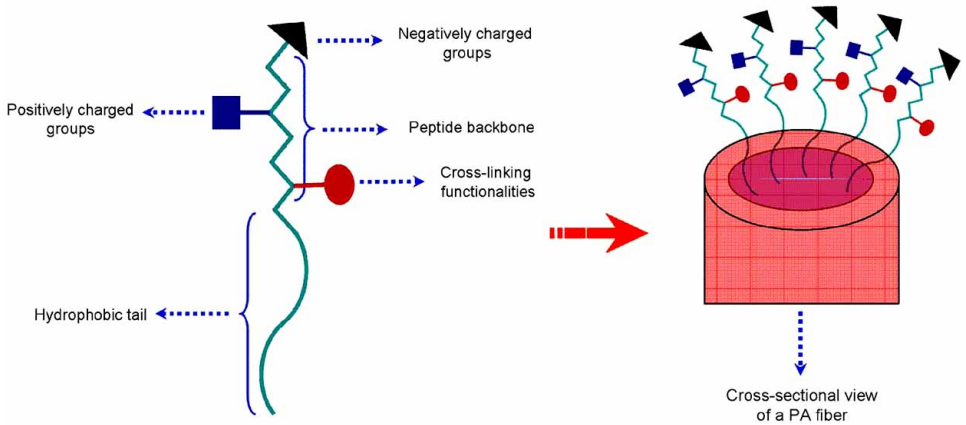

Fig. (1). Schematic representation showing design of a peptide-amphiphile construct leading to the formation of fibers and tubular structures (adapted from ref. [31]).

nine-valine, was part of the PA sequence, and is known to aid neurite sprouting and growth [38]. Scanning electron micrographs revealed formation of 3D PA networks, with high aspect ratio and surface areas, and resulted in gel-like solid formation. Interestingly, a nonbioactive control sequence failed to facilitate differentiation despite maintaining cell viability thus allowing authors to conclude that physical entrapment of the bioactive epitope PA nanofibers was crucial for differentiation cell culture studies.

Other related studies address modification of PA nanofibers with different epitopes [39], transport of basic fibroblast growth factor for angiogenesis [40], and the use of such nanoscale materials in neural regeneration, neuroprotection, and targeted delivery of brain-specific drugs across the blood-brain barrier [41,42].

b. Peptide-Lipid Hybrid Soft Structures

Cubosomal phases consist of bicontinuous lipid bilayers, with intercommunicating aqueous channels in a thermodynamically stable state [43]. The embedded intercommunicating water nanochannels are critical for the structural stability of cuboidal lipid bilayers and for the stabilization of anchored biomolecules. A recent study has described their importance in dictating nanomaterial properties of such phases [44]. The ability of cubic phases to incorporate and control release of drugs and their biocompatibility makes them useful as potential drug delivery systems [45]. It is established that the drug release from the confines of the cubic phases is diffusion-controlled and depends also on the observed phase transformations [46].

An extension of this concept is demonstrated for the development of proteocubosomes where protein-directed three dimensional patterning of lipid cubic lattice affords a novel structural order of lipid/water interfaces, thus creating 'open-nanochannel hierarchical fluid vehicles' [47-48]. Structural detailing of these scaffolds by freeze-fracture electron microscopy revealed that proteocubosomes are nanoporous and compartmentalized, thereby offering considerable scope in nanofluidics, as protein drug delivery vehicles, and protein-encapsulating fluid nanomaterials, to name a few (Fig. **2**). However, some drawbacks such as shorter release duration and high viscosity of these constructs, require design features that would make such systems more compatible with oral and parenteral drug delivery applications.

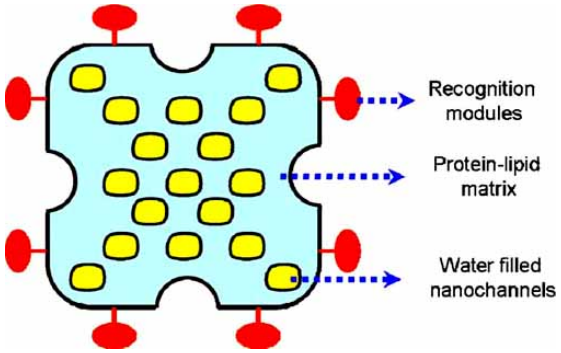

Fig. (2). Schematic representation of a proteocubosome showing water-filled nanochannels dispersed in a protein-lipid phase (adapted from ref. [47]).

c. Self-Assembling Cell-Penetrating Peptides (CPP)

CPPs belong to a class of basic amino acid-rich polypeptides, which possess amphipathic character and exhibit different secondary structural features. These peptides are able to mediate energy- and receptor-independent transport and delivery of bioactive cargo *via* endocytosis as one of the preferred mechanisms for cellular internalization. Cationic CPPs translocate across the plasma membrane to achieve delivery of drugs as well as other bioactives such as peptides, proteins and oligonucleotides, and improve the bioavailability of hydrophilic macromolecules [49-51].

CPP self-assembly relies on achieving particular orientations conducive and supportive of maximum amphipathicity [52]. For example, a naturally occurring CPP, human calcitonin fragment (9-32)-branched (hCT-br) self-assembles to exhibit helically organized fibrils as confirmed by turbidimetry and electron microscopic analysis [53-55]. In one study with hCT-br and sweet arrow peptide CPPs, containing a nuclear localization signal, facile uptake in HeLa cells was evident through an interaction with the extracellular matrix followed by lipid raft-mediated endocytosis [56]. Such experiments reveal potential of CPP constructs as viable modalities for intracellular drug delivery.

Delehanty, Mattoussi and coworkers recently demonstrated an interesting approach towards self-assembled HIV-1 Tat derived CPP-polyhistidine hybrid with luminescent quantum dots *via* specific metal affinity interactions. These bioconjugates exhibited transmembrane delivery and efficient concentration-dependent intracellular labeling of eukaryotic cell lines [57].

CPP-based delivery approach has been extended to small interfering RNA [58]. Departing from the conventional design involving a covalent linkage between CPP and bioactive cargo, Restle and colleagues followed a non-covalent approach by employing a novel carrier peptide MPGα that afforded rapid complexation with nucleic acid. As a result, 90% inhibition of luciferase gene activity was achieved and this study also addressed issues concerning cellular uptake mechanism, which suggested evidence of an endocytic pathway.

d. Short Peptide-Based Fibrous Structures

Simple peptides capable of exhibiting self-assembled linear or branched structures represent an exciting class of biocompatible soft materials [59-65]. The possibilities of using open-ended peptide structures for delivery applications are emerging and as described above, they could be further assisted by CPP conjugation for facilitated cellular delivery, while preserving the integrity of vehicles in the physiological environment [66-68].

In this context, amyloid fibrils offer considerable scope for self-organization of protein(peptide)-only structures that could be further used for a variety of nanobiotechnological applications including, molecular bioelectronics, drug delivery and nanomedicine [22,69-72]. The physical basis of amyloid fiber formation and its ensuing stability includes concepts such as specific hydrogen bonding, favorable electrostatic interactions, π–π stacking, and hydrophobic interac-

tions. Interestingly, recent experiments suggest that amyloid peptide fibers exhibit high structural malleability resembling plastic materials and mimicking several properties associated with synthetic polymers [72]. In another study, filamentous aggregates from insulin were shown to possess high mechanical strength and stiffness comparable to silk [73]. It was suggested that these observations not only assist in understanding the role of amyloid fragments in disease progression, but also have ramifications for using these fibers in nanotechnological applications.

With this background, one can envisage that amyloid-like fibrils that are "*devoid of associated toxicity*" may serve as new-generation materials for containment, transport and drug delivery. Akin to proteocubosomes [43], they are also characterized as water-filled nanotubes thus providing a compatible environment for entrapment of polar bioactives [74]. Reches and Gazit have earlier demonstrated that aqueous inner confines of dipeptide nanotubes can be used to achieve templated synthesis of nanowires [75].

2. PEPTIDE-BASED VESICULAR SOFT STRUCTURES

The 'bottom-up' approach of viral capsid formation represents an excellent natural design of a vesicle evolved to encapsulate genomic cargo for safe containment and targeted delivery to the host cells. Spontaneous formation of monodisperse spherical viral capsids, multivalency of recognition elements on viral membrane surface for highly-specific interaction, and survival under drastic conditions, provides sufficient incentive for the design of vesicular superstructures [76]. From the standpoints of capsid mimicry and synthetic ease, the design and formation of polymerosomes have gathered considerable attention where self-assembly of block copolymer amphiphiles leads to soft shell-like structures [77, 78]. These synthetic vesicles have parallels with viral capsids with a possibility of further extending the design to enhance stability, directed interaction with desired tissues, followed by stimuli-responsive disassembly [79-83].

This section of the review will deal with the self-assembly of building blocks containing peptides as an integral component, leading to the formation of soft vesicular morphologies.

a. Vesicular Assemblies from Polypeptide Composite Materials

A generally employed structural motif consists of a synthetic amphiphilic polypeptide-containing block copolymer designed to generate self-assembled vesicular structures that are driven by unique folding pathways and stable conformations. Such vesicles are scalable in nanometric dimensions, can be prepared in bulk quantities and offer amino acid side chains that be modified to attach recognition elements for targeted delivery. This may be followed by the release of encapsulated cargo in response to an external stimulus such as variation in pH [84,85].

Deming and coworkers recently elaborated an excellent example of ingenious design of cationic polypeptide vesicles from $Arg_{60}Leu_{20}$ ($R_{60}L_{20}$) where polyarginine motif played dual roles in facilitating vesicular structure formation and in aiding intracellular delivery by acting as a protein-transduction domain (Fig. **3**) [86]. Micrometer-sized vesicles were formed from $R_{60}L_{20}$, which were able to encapsulate dextran-fluorescent dye conjugate without losing encapsulated cargo during the phase-transport experiments. Moreover, internalization in epithelial and endothelial cell lines and lack of cytotoxicity further proved the promising transport characteristics of this approach for drug delivery and other related applications.

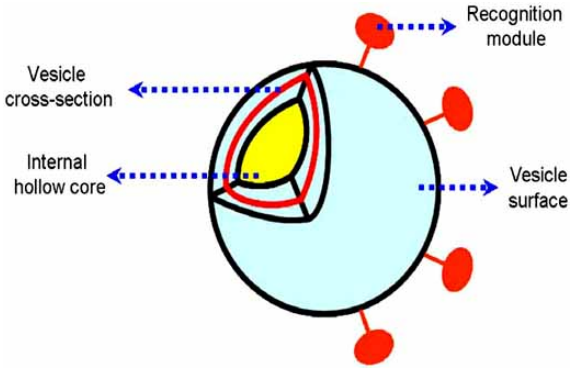

Fig. (3). Schematic representation of a polypeptide vesicle with cross-sectional view of the hollow core and possible decoration with recognition modules. (adapted from ref. [86]).

Polyethylene glycol-modified homopolymers of poly-L-lysine and poly-L-ornithine have also been employed for vesicular self-assembly [87]. With a favorable cytotoxicity profile, these polymeric vesicles were evaluated as drug carriers for doxorubicin and chloroquine, and as gene transfer agents in a human tumor cell line.

Another recent example presented nanostructural details of $poly(glutamic\ acid)_{15}$-$poly(lysine)_{15}$ diblock copolymers, which formed micelles and vesicles [88]. Given the composition of amino acid side chains, these vesicles were responsive to pH variations where the achievable structures exhibited rod-like conformations in hydrophobic domains, and eventually afforded hollow spherical structures. Controlled perturbations due to pH and/or ionic strength, dissolution in water and predictable self-assembly were highlighted as parameters suitable for biomedical applications.

b. Vesicular Assemblies from Short Peptide Constructs

The requirement of long peptide sequences is not absolutely necessary to construct hollow soft vesicular cages. In fact, spontaneous self-assembly of short peptides also offers expedient entry into the construction of vesicular morphologies. It is therefore expected that along the lines of polypeptide-based vesicles, these soft structures may also encapsulate drugs and other bioactive molecules and possibly deliver them to a desired location.

Clathrin coat proteins exhibit self-assembly of three-legged building blocks (triskelion) leading to the formation of cage-like structures for intracellular transport of a variety of bioactive molecules [89, 90]. With this inspiration, we have recently reported design and synthesis of a C_3-symmetric ditryptophan dipeptide triskelion that undergoes rapid self-association to give vesicular structures, at neutral pH, as confirmed by scanning electron microscopy (SEM)

and other related techniques (Fig. **4**) [91]. It was proposed that indole side chains of ditryptophan arms may interdigitate *via* π-π interaction [22], thus resulting in the formation of hollow polyhedra, a mechanism analogous to the clathrin pit formation.

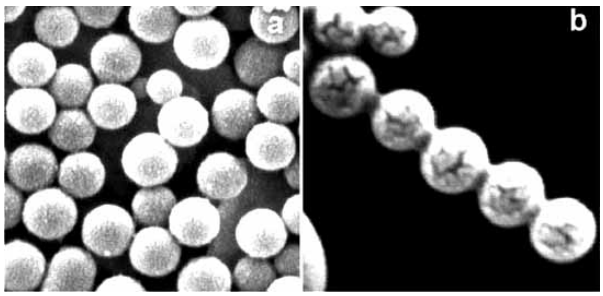

Fig. (4). Vesicles from triskelion ditryptophan peptide conjugate. (a) SEM micrographs show uniformly distributed cage-like structures; (b) Beads-on-a-string type of attachment and ultrastructure of the vesicle surface (reprinted from ref. [91] with permission from the publishers).

These vesicles were found to be excellent encapsulants for a fluorescent dye, rhodamine B, and responded to the stimulus of pH variation. At an acidic pH, of 5.5, the disruption of vesicular structures occurred thereby leaking the entrapped dye from the hollow core (Fig. **5**). These observations suggest that triskelion nanocages can be generated from short peptide sequences and they may have optimal enclathration properties with a simple release mechanism, making them suitable candidates for the delivery of drugs and cytotoxic agents.

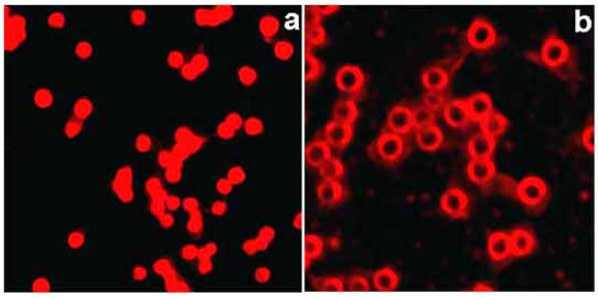

Fig. (5). Fluorescent micrographs of entrapment and release of rhodamine B from nanocages. (a) Images after 24 h incubation reveal uniform circular structures; (b) Image of peptide nanocages upon controlled acidification at pH 5.5. (reprinted from ref. [91] with permission from the publishers).

A similar C_3-symmetric rigid scaffold has been exploited by Matsuura and coworkers with longer octapeptide construct, which formed hollow nanospheres in aqueous acidic solutions. Importantly, corresponding octapeptide only revealed the formation of antiparallel β-sheets suggesting a crucial role of C_3-symmetric linkers in supporting the formation of soft vesicular structures [92]. The possible roles of such self-assembling peptide vesicles can be expanded by suitable chemical modification, and it was envisaged that these viral-sized spheres could act as gene carriers and as nanosized reactors.

Using a different approach, we recently demonstrated that a simple tetrapeptide sequence Pro-Trp-Trp-Pro, from an antimicrobial peptide indolicidin, forms micron-sized vesicles in the solution phase [93]. Morphology of these peptide-only spherical structures was confirmed by microscopic techniques where they displayed a high degree of homogeneity and were found to be thermally stable. Symmetrical linker was obviously lacking from the design, but the genesis of soft spherical structures emanated from an inherent curvature in the molecule. On the basis of MM+ studies, it was proposed that π-π stacking of the tryptophan side-chain plays a crucial role in the self-assembly process, which is further supported by the backbone interactions.

In an interesting departure from the previous example of Trp-rich dipeptide triskelion, these vesicles were found to be sensitive towards monovalent cations, acting perhaps *via* cation-π interaction that competes and interferes with the soft structure stabilizing π-π interactions [22-25] (Fig. **6**). As these vesicles respond to naturally occurring monovalent cations such as K^+ and Na^+, it is envisioned that such stimuli-responsive vesicular structures may be useful for the entrapment and intracellular transport of bioactive substances.

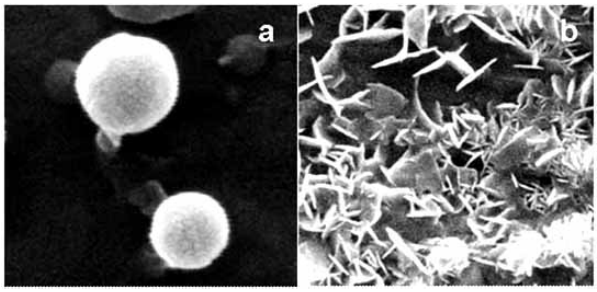

Fig. (6). Soft vesicles from PWWP tetrapeptide and their ion-induced disruption; (a) SEM micrographs of intact vesicles; (b) ruptured vesicles after the addition of potassium ions (adapted and reprinted from ref. [93]).

CONCLUSIONS AND OUTLOOK

This review has described recent examples of peptide-based soft structures as possible modalities for drug delivery. There are certain advantages associated with peptide-containing vehicles, which includes developed synthetic techniques for bulk preparation, biocompatibility, low levels of toxicity by the released building blocks, and ease of modification of functionalities present in the amino acid side-chain by cell-specific recognition elements.

Drug delivery and selective targeting will always remain an integral component of all drug discovery initiatives and emerging paradigms in biomedical arena, such as nanomedicine. Delivery research not only provides enormous research challenges, but also makes economic sense where much of the precious environment-sensitive, bioactive agents may be preserved and protected from unwanted catabolic reactions and losses at biochemical barriers *in vivo*. Thus, it is imperative that newer initiatives in drug delivery research consoli-

dates successful forays into conventional delivery vehicles, while taking into consideration the substantial progress being made in the area of directed self-assembly and nanotechnology.

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