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Assessment of Modern Excipients in Controlled Delivery of Proteins and Peptides

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Abstract

Polymeric micelles are highly proficient of modulating the function, distribution of drugs in the body, and can overcome biological barriers hence provoked as novel nanomedicine via various formulations. Current review emphasis on application of several polymers, biomaterials, lipids for the preparation of polymeric micelles formed by several molecular interactions between the block co-polymers and encapsulated molecules. Micellar carriers will be selected on basis of the type of polymer/payload interaction, which includes biological interface focused on the internal chemistry and fabrication of block-co polymers. Several features of these carriers can be manipulated to catering a broad range of drugs through active sensing of body targets. The fine-tuning of their properties in response to particular stimuli, modulating the activity of the loaded drugs at the targeted sites, even at the subcellular level. To end with, the future perspective and impending challenges for polymeric micelles as nanomedicine are elaborated, anticipating prompting further innovations.

Keywords: Proteins, Peptides, Co-block Polymers, Lipids, Controlled, Drug Delivery.

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1. Introduction

Several pharmaceutical and biotechnology companies are focusing on the development of several new proteins and peptide-based compounds for treating a wide range of diseases. This was further supported by rapid advancement in the biotechnology and genome research fields. But, conversely, these new compounds are larger, hydrophilic, and relatively unstable in contrast with the traditional active moieties. All these features make them ineffective for permeation across biological barriers and enzymatic degradation, consequently, peptides and proteins are very difficult to deliver by conventional pathways like oral or transdermal, or nasal [1-4].

Owing to adsorption and low bioavailability through these routes, proteins and peptides are administered preferably by intramuscular or subcutaneous injection. However, half-lives of these proteins are only several minutes of a few hours, when administered parenterally, thus require frequent dosing for optimum therapeutic efficacy. Extensive research has been performed to overall the above issues discussed. Controlled release systems are one amongst them, to obtain the well-defined pharmacokinetic profile. One promising approach is to encapsulate the peptides or proteins in a polymer matrix, to protect them from degradation and rapid clearance thus prolongs the release of the drug [5-10]. A broad range of degradable and non-degradable polymers have been used as matrices to incorporate several drugs. Several carriers like nanocrystals, nanoparticles, ethosomes, have been formulated [10-13]. Among all these biodegradable polymers are preferred to avoid further surgical removal of the matrix after depletion of the drug from the system. The continuous release of drugs from the biodegradable polymer matrix could occur either by diffusion of the drug from the matrix or by the degradation of the polymer or by a combination of the two mechanisms.

Yet, a major concern for these systems is biocompatibility, the stability of encapsulated moieties during processing, release, and storage. Despite these challenges, several controlled-release formulations were approved and marketed. As shown below, the polymer matrix can be formulated either as nanospheres, microspheres, injectable gel, or implant. Spheres and gels are most recommended over the implants, as no surgical procedure for administration is required. List of controlled release systems formulated on basis of biodegradable polymers [14-20] [Table 1].

Table 1: List of controlled release systems and their application, formulated with biodegradable polymers

S. No	Product	Application
1.	Atridox® Doxycycline PLA gel	Periodontal disease
2.	Gliadel® Carmustin Polyanhydride wafer	Brain cancer
3.	Lupron Depot® Leuprolide acetate PLGA microspheres	Prostate cancer
4.	Nutropin Depot® Somatropin PLGA microspheres	Growth hormone deficiency
5.	Sandostatin LAR® Octreotide acetate PLGA-glucose microspheres	Growth hormone suppression
6.	TrelstarTM Depot Triptorelin PLGA microspheres	Prostate cancer
7.	Zoladex® Goserelin acetate PLGA rod	Prostate cancer

2. Biodegradable polymer matrices for controlled release:

The polymer should satisfy several criteria's such as biocompatible, degradable within a reasonable period (depending on application), and the non-toxic degradation products, to use as a drug delivery matrix. Additionally, the polymer should be able to provide an optimum environment for the encapsulated protein or peptide drug, to prevent denaturation, which may cause unwanted immunogenicity when administered. The release rate of the drug can be tailored by modifying the polymer characteristics to obtain optimal therapeutic efficacy. Several works have focused on poly(lactic-co-glycolic acid) (PLGA) copolymers. These polymers are in use for several decades as surgical suture materials and are known for their excellent biocompatible nature [21-25]. Their degradation is by Kreb's cycle to carbon dioxide and water. Despite the success with small peptides, such as luteinizing hormone-releasing analogues, there is considerable concern about the suitability of PLGA as a polymeric carrier for high molecular weight protein drugs [26-28].

Protein unfolding and aggregation often occurs during the storage or release, because of the interaction of protein molecules with the hydrophobic polymeric surface. Moreover, the low pH generated during polymer degradation could cause chemical degradation of entrapped proteins. Another major issue with these PLGA matrices is, limited possibilities to manipulate the protein release rate and frequently, the initial burst has been noticed from these matrices to result in the plateau of incomplete drug release [29-32]. Hence to overcome these issues, Amphiphilic block copolymers have gained increasing interest for drug delivery applications [32-36].

Introducing hydrophilic or hydrophobic blocks, a protein friendly environment can be created with modified drug release properties. In recent times, series of poly(ether-ester) multiblock copolymers composed of repeating blocks of hydrophilic poly(ethylene glycol)-terephthalate (PEGT) and hydrophobic poly(butylene terephthalate) (PBT) was introduced as a matrix for controlled release systems [37-40]. This multi-block polymer is currently applied for a broad range of pharmaceutical and biomedical applications, including FDA approved products Proliposomes, Microparticles, Solid lipid Nanoparticles, Nanoparticles, [41-43]. Several in-vitro and in-vivo studies have shown that PEGT/PBT copolymers are biocompatible and can be made biodegradable [44-48]. Quantitative in-vitro release of fully active lysozyme has been reported from these multiblock copolymers for Nanoemulsion, Nanocrystals, Nanowires, Self-nano emulsifying drug delivery system (SNEDDS) [49-52]. The controlled release of proteins for a longer period can be obtained by combining diffusion and degradation mechanisms. Additionally, various copolymer compositions could precisely modulate the release.

3. Biodegradable multiblock copolymers for protein delivery applications

The primary drawback of nucleic acids for pharmaceutical application is their inclination to enzymatic degradation in biological fluids. When mixed with plasma, naturally occurring nucleic acids get digest immediately and various strategies have been applied since the beginning to overcome the aforesaid issue. These are majorly divided into two approaches; one is a chemical modification of nucleotide backbone. A variety of chemically modified nucleotide backbones, including phosphorothioate, 2′-Omethylated ribose, and "locked (or bridged)" nucleotides, have been prepared to enhance the stability of nucleic acids, and some of them are used are clinically approved. The details in chemical modification approaches are elaborated by several researchers using Chitosan, Alginate, PLGA, Polyvinylpyrrolidone (PVP), Zein, Okra, [53-58]. Another approach is the encapsulation of nucleic acids within nanoparticulate formulations, such as PIC micelles. With this approach, nucleic acids can be protected from external stimuli as well as enzymatic degradation, leading to their longevity in biological fluids. Certainly, several cationic lipids and polymers have been employed for the preparation of PICs, polyplex, and termed lipoplex respectively, especially with negative charged nucleic acids. Predominantly, PIC micelles have been measured as one of the most capable systems for systemic oligonucleotide delivery because of the above-mentioned properties suitable for stable circulation in the bloodstream [59-62]. Oligonucleotide delivery further needs cautious design criteria for block copolymers and their assembly, owing to their inefficient cellular uptake and fragility of naked oligonucleotides.

Oligonucleotide delivery needs contradictory functions such as stable encapsulation and stealthiness in the systemic circulation for translocation into cytoplasm and endosome. A classy approach for the merging of these conflicting necessities is the creation of smart PIC micelles that use the desired function in the response to specific biological signals. The consecutive sections describe the prominent strategies to develop such PIC micelles directed to successful delivery using Hyaluronic Acid [63-65]. Stabilizing the systems can be done by using reversible cross-linking of the micellar core. Disulfide crosslinking has been considered as the most extensively explored mechanism, because of preferable diffusion into reductive cytoplasm having higher concentrations of glutathione. Accordingly, disulfide cross-linked PIC micelles loading siRNA showed a certain level of stability in serum having media and capable of enhancing

gene silencing in the cultured cells. On the other hand, still, their half-life was not considerably prolonged in comparison to non-cross-linked control micelles, probably due to leakage of siRNA payloads from the cross-linking network in the systemic circulation. The cross-linking approach can be combined with the hydrophobic stabilization using cholesterol-modified siRNA (Chol-siRNA), that is, CholsiRNA-loaded/disulfide cross-linked PIC micelles, which extensively improved the blood circulation [66-68]. In the meantime, all these results suggest the direct covalent conjugation of siRNA with catiomer segment via reversible bonds. Thiol functionality to both siRNA and catiomer segment can be done by disulfide bond. Alternatively, another approach is using natural siRNA structure for covalent conjugation with catiomer segments. Therefore, natural siRNA loaded in these micelles works as a cross-linker between PBA-functionalized segments [69-70]. Potential triggers for siRNA release from PIC micelles can happen through ligand exchange reaction and fluids containing cis-diol compounds. PBA-micelles were stable at blood levels of glucose (5 mM) and ATP (0.5 mM). They will release siRNA in the presence of intracellular levels of ATP, thus allowing the selective cytosolic release of siRNA [71-74]. These outcomes also suggest that the negative charges derived from triphosphate of ATP may be critical for the trigger release of siRNA from micelles and micelle destabilization.

4. Conclusion

Unique properties of peptide block copolymers make them unique carriers when compared to synthetic block copolymers. To bring these materials into the application, an in-depth understanding of the interplay between composition, assembly behavior and other physicochemical properties is essential. In this review, concise trends in protein building block design approach for preparation, characterization techniques, and potential applications were discussed. Recombinant technology has become a functional approach to engineer protein-based block polymers, as it provides advantages to various fields of biomaterials. Conjugation of a peptide block with a synthetic block results in the formation of novel biomaterials with advanced functions. Furthermore, the formulation of several novel biomaterials has become possible by applying the concept of polymer engineering. Biological peptides possess admirable building blocks from which materials desired functionality, structure, and architecture can be constructed. Biomaterials with programmed structures and functions can be made with the conjugation of peptide blocks with synthetic or biological blocks. Despite many thriving examples discussed here, functionality has begun receiving attention and the roles remain to be explored. Still, there are many challenges and opportunities to employ the concepts from nature and polymer science to adopt several suitable functional materials for a wide range of applications.

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