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Review

Silk fibroin nanoparticle as a novel drug delivery system

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ABSTRACT

Design and synthesis of efficient drug delivery systems are of vital importance for medicine and healthcare. Nanocarrier-based drug delivery systems, in particular nanoparticles, have generated great excitement in the field of drug delivery since they provide new opportunities to overcome the limitations of conventional delivery methods with regards to the drugs. Silk fibroin (SF) is a naturally occurring protein polymer with several unique properties that make it a suitable material for incorporation into a variety of drug delivery vehicles capable of delivering a range of therapeutic agents. SF matrices have been shown to successfully deliver anticancer drugs, small molecules, and biomolecules. This review will provide an in-depth discussion of the development of SF nanoparticle-based drug delivery systems.

Contents

1. Introduction

In recent years, in order to optimize the efficacy of therapeutics, many drug delivery systems have been designed to administer multiple

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drugs and release them in a controlled manner [1–4]. The use of these systems offers many advantages such as enhancing the bioavailability of drugs by reducing their degradation rate, improving cellular uptake, allowing targeting and control of drug release, and reducing side effects [5]. To date, both synthetic and natural polymers have been used for drug delivery applications. Among a wide range of applied synthetic polymers, polyesters, polyorthoesters, polyanhydrides, polyphosphazenes, and polyphosphoesters have found extensive application [6–8]. However, despite the wide range of available materials, the majority of licensed drug delivery systems are based on the FDA (U.S. Food and Drug Administration)-approved polymer, poly(lactic-*co*-glycolic acid) (PLGA), because of properties such as suitable pharmacokinetics and controllable degradation rate [9,10]. However, the usefulness of PLGA is limited in applications such as protein therapeutics due to some of its intrinsic properties and processing requirements [11–14]. Therefore, natural polymers (e.g., alginates, chitosan, collagen, dextran, pullulan and gelatin) represent an attractive alternative with higher biocompatibility and biodegradability than PLGA [15–24]. In addition to their composition, the structure of drug delivery systems also needs serious consideration. To date, many systems have been designed with different morphologies and structures, including films, gels, foams, microparticles, and nanoparticles [25]. In the 1960s, liposomal carriers were the first nano-systems to be approved for delivery of proteins and drugs [26]. Additionally, many studies have reported the high capacity of nanoparticles for therapeutic molecules [27–29]. In most cases, the use of particulate carriers reduces the rate of delivery of solubilized drugs by introducing a second limiting step [30,31]. Furthermore, nanoparticles have many features, which are useful for drug delivery such as a high surface to volume ratio [32], an ability to act as modifiable platforms [33], and a tunable size [34]. Therefore, applying the principals of nanotechnology to the design of drug delivery systems will not only improve their therapeutic efficacy but could also preserve the properties of bioactive molecules [35]. It is necessary to consider the properties of biomaterials in terms of composition, structure, mechanical properties, and function to fabricate particulate drug delivery carriers. Silk proteins are FDA-approved polymers that have been used successfully as both sutures and drug delivery systems. These proteins have excellent mechanical properties, a flexible preparation process, and high biocompatibility [25]. So far, many review papers have been published concerning the use of silk proteins in the field of tissue engineering. While there are many original articles about the application of silk nanoparticles as drug delivery vehicles, to the best of our knowledge, no comprehensive review on their use for drug delivery has yet been published. Therefore, in this review, we provide an extensive overview on recent efforts in constructing silk protein nanostructures for drug delivery. Firstly, we introduce the different applications of nanotechnology-based systems. Secondly, the properties of silk proteins are discussed clearly, and finally, nanoparticulate silk proteins are considered in detail.

2. Drug delivery systems

2.1. Drug delivery systems based on nanotechnology vs. conventional carriers

Historically, drug delivery systems were usually based on orally administered or injectable drugs. However, these have been found to be inappropriate for novel therapeutics such as proteins and nucleic acids. Novel technologies are required for delivery of new drug molecules in order to reduce their side effects, optimize their efficacy, and enhance patient compliance. Recently, the use of nanotechnology has led to the development of many novel carriers capable of controlled release and targeted delivery of a wide range of small molecules, proteins, peptides, and genes [36–41]. These devices can have many different structures, including liposomes, micelles, quantum dots, dendrimers, fullerenes, ferritin, and nanoparticles [42–45]. Among them, nanoparticles based on biodegradable and biocompatible polymers have potential applications in cancer therapy and as sustained drug delivery vehicles. These carriers can also be designed as low toxicity systems with suitable physical and chemical structures and specific targeting properties [46]. It was reported that particle size is the most important factor when designing drug delivery systems. Therefore, it is crucial to use nanoparticles for the delivery and targeting therapeutic molecules [47,48]. These systems also have other advantages, including prolonged drug half-life, improved solubility of hydrophobic drugs, reduced immunogenicity, and reduced administration frequency [49]. As mentioned earlier, the possibility of targeted drug delivery is one of the main advantages of nanoparticles. It is strongly believed that conjugation of different ligands to nanoparticles could improve the targeting efficacy of them as compared to conventional therapeutics [50]. The small size of nanoparticles also affects the targeting efficacy. Generally, nanosized particles experience efficient uptake, selective drug accumulation in the targeted site, and are able to penetrate into the endothelium at inflammatory sites, epithelium (e.g., intestinal tract and liver), tumors, or microcapillaries [51,52]. The ability to co-deliver multiple drugs is another advantage of nano-based drug delivery systems in comparison to conventional systems [53]. Co-delivery of drugs offers several benefits such as the possibility of synergistic effects [54], suppressed drug resistance [55] and the ability to adjust the dosage of drugs to the level of a single nanoparticle carrier.

2.2. Important parameters for nanoparticle-based drug delivery

Understanding the interactions between nanomaterials and cell/lipid bilayers is important in the fields of phototherapy, imaging, and drug/gene delivery. The reason for this is the small size of nanoparticles as compared to microparticles. In order to address this issue, Desai et al. have shown that the cellular uptake of 100-nm nanoparticles was 2.5 and six times higher than 1-μm and 10-μm microparticles, respectively [51]. It was also reported in a similar study that cellular uptake of 100-nm nanoparticles was 15–250 times higher than 1- and 10-μm microparticles [56]. Chithrani et al. have claimed that efficient uptake of nanoparticles depends on their size. To this end, they have shown that 50-nm gold particles undergo the most effective uptake [57]. They have also stated that spherical nanoparticles experience five times greater uptake than rod-shaped particles. Therefore, it appears that size and shape are the two important factors that affect the cellular uptake of particles [57]. It is also known that, in addition to influencing the cellular uptake, particle size can also influence drug loading, drug release, and the stability of nanoparticles [58]. Along with size and shape, the nanoparticle's surface properties are also important. Surface characteristics such as hydrophobicity and hydrophilicity determine the level of absorbance of blood components such as opsonins [59,60]. However, it has been shown in *in vitro* studies that there is a connection between the extent of opsonization and the surface charge of nanoparticles and that less opsonization occurs in neutrally charged particles in comparison to charged particles [61]. For this reason, the use of shielding groups that are capable of blocking the electrostatic and hydrophobic interactions result in the binding of opsonin to the surface of nanoparticles. A brief description of the effects of particle size and the surface properties of nanoparticles is summarized in Diagram 1.

2.3. Polymeric nanosystems for drug delivery

Polymeric nanoparticles have been of great interest to many researchers for decades. Since the discovery of dendrimeric “starburst” polymers in the 1980s, numerous other drug delivery strategies such as self-assembled micelles and encapsulated drug molecules have been developed [62,63]. Biodegradable polymeric nanocarriers are predominantly used for their ability to control the release rate of drugs, and for this purpose, many synthetic and natural polymers have been used [36]. Synthetic polymers have greater structural integrity and higher purity, which makes the preparation of nanoparticles more reproducible, than natural polymers [36]. However, only synthetic polymers with an