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Review

Advancement of multifunctional hybrid nanogel systems: Construction and application in drug co-delivery and imaging technique

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ABSTRACT

Nanogel-based multifunctional drug delivery systems, especially hybrid nanogels and multicompartment nanogels have drawn more and more extensive attention from the researchers in pharmacy because it can result in achieving a superior functionality through the synergistic property enhancement of each component. The unique hybrid and compartmentalized structures provide the great potential for co-delivery of multiple agents even the multiple agents with different physicochemical properties. Otherwise the hybrid nanogel encapsulating optical and magnetic resonance imaging contrast can be utilized in imaging technique for disease diagnosis. More importantly through nanogel-based multifunctional drug delivery systems the stimuli-responsive features might be easily employed for the design of targeted release of drug. This review summarizes the construction of diverse hybrid nanogels and multicompartment nanogels. The application in co-delivery of multiple agents and imaging agents for diagnosis as well as the application in the design of stimuli-responsive multifunctional nanogels as drug delivery are also reviewed and discussed. The future prospects in application of multifunctional nanogels will be also discussed in this review.

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1. Introduction

In the past decades, nanotechnology has made a significant impact on the development of drug delivery systems. Among, nanogels formed into a three-dimensional network structure by crosslinking polymer chains become an advanced research hotspot for drug delivery because nanogels have the advantages including site-specific controlled drug delivery, protection drugs from hostile environments [1], a sustained drug release behavior, less toxicity and high biocompatibility [2]. Kinds of modification studies were conducted on nano-sized drug carriers, which endowed them with multi-functionalities [3,4]. For instance, by incorporating the poly(ethylene glycol) chains (PEG), targeting moiety, permeation enhancer, contrast agent and stimuli-sensitive group, drug carriers can combine such properties as longevity, target-ability, intracellular penetration, contrast loading and multiple stimuli-sensitive controlled release [5]. Especially, according to the different physiological environment around pathological tissues, various stimuli responsive nanogel drug delivery systems have been widely used to prolong drug release and achieve targeted release in recent years. For example, pH sensitive [6,7], redox sensitive [8,9] and glucose sensitive [10] nanogels have been developed by Xue si Chen's research group. Additionally, Lin Zhang et al. prepared a cyto-compatible injectable nanogels with pH and temperature sensitivity based on carboxymethyl chitosan-*graft*-poly (*N*-isopropyl acrylamide)-glycidyl methacrylate (CMCS-PNIPAm-GMA) in which PNIPAm was the thermosensitive polymer as localized drug carriers for anticancer drug and anti-inflammatory drug [11]. Although the aforementioned multifunctional strategies applied to nanogels have endowed them with the above advantageous properties, the nanogel-based drug delivery carriers not yet meet all requirements like the difficulty to deliver small hydrophilic drug molecules, low drug loading of hydrophobic drugs and the not well regulated release behavior of the loaded molecules [12]. Further studies on multifunctional nanogels have been conducted in an attempt to address these issues in recent years.

The goal of this review is to discuss the construction of novel multifunctional nanogels, especially hybrid nanogels and compartment nanogels. The application of designing stimuli responsive multifunctional nanogels for drug delivery is also discussed. The prospective interests of these multifunctional nanogels for drug co-delivery systems coupled with the application in imaging technique will also be emphasized.

2. Construction of various nanogel-based drug delivery systems (Table 1)

2.1. Nanoparticle (NP)–hydrogel nanocomposites

Diverse nanoparticles have attracted the attention of pharmaceutical researchers because they offer a strategy to solve the limitation of drugs including poor solubility, high toxicity, high dosage, aggregation and short circulating half-life in recent decades [13]. For instance, various polymeric nanoparticles [14–16] and inorganic nanoparticles [17] have been widely studied as drug delivery carriers. However, nanoparticles are far from perfect due to such facts like the low drug loading, instable properties, burst release of drug. Hence, newly nanoparticle composite strategies which combine other structure with nanoparticles have been proposed. The innovative structural combination may result in a synergistic property enhancement of each component and a superior functionality may be endowed [18]. Based on these promising envision, a series of new attempts on hybrid NPs have been conducted. Among, nanogels which hold extraordinary characteristics such as easily mixed with pharmaceutical agents (hydrophilic drug, proteins, kinds of nanoparticle carriers), extra biocompatibility and low toxicity, have been extensively selected as the other component to establish hybrid systems. Additionally, multi-responsive nanogels are also easily employed to serve as a depot for controlled and sustained drug delivery. Such nanoparticle-hydrogel nanocomposites, including polymeric NP-nanogel composites and diverse inorganic nanoparticle hybrid nanogels (as illustrated in Fig. 1) as well as their potential in drug delivery will be highlighted in the first part of this review.

2.1.1. Polymeric NP-hydrogel nanocomposites

To maximize chemotherapeutic efficacy and reduce systemic toxicity, polymeric NPs composed of micelles, dendrimers, polymersomes and liposomes have been developed by distinct modification to deliver drug, gene or other agents effectively. Therein, it has been proved that the combination of polymeric NPs and hydrogels exhibits multi-functionality because the composites can overcome the limitation of each carrier and gather the both advantages of two kinds of formation. For example, as to many hydrophobic drugs, when they mix with nanogel sol, the drugs tend to aggregate due to the hydrophobic interaction and not can be well-dispersed in the sol. So these hydrophobic drugs always are firstly encapsulated in a suitable vector such as polymeric micelles, liposomes, prodrug conjugates and then loaded into nanogels to form a homogeneous system with promising interests. Moreover, the coating nanogels may serve as the protective cover for the other polymeric NPs. For example, Sanyog Jain designed a novel nanogel composite by coating the lipid core with gelatin, which successfully overcame the limitations of liposomes and nanogels [19]. The improved stability of lipid system in gastrointestinal fluids owing to the protection of gelatin coating coupled with the superior biocompatibility of lipid carrier resulted in the increased oral bioavailability of Amphotericin B (AmB) loaded hybrid lipid nanogels. Another system composed of cross-linked cyclodextrin-based hybrid nanogels has been proved to be a promising carrier for the controlled and sustained drug delivery [20]. For the further study, a hybrid prodrug nanogel system fabricated by conjugating drug molecule to the nanogels has been explored by the group of Prachi Gupta [21]. In this case, acrylated quercetin was reacted with amines of poly(β-amino esters) (PβAE) to form crosslinked gel via Michael addition mechanism. Subsequently, the quercetin-PβAE nanogels were

Table 1
Summary of the several recent studies on various hybrid nanogels.

Types	Nanoparticles	Matrix/coating	Function	Ref
Polymer NPs composites	Lipid NPs	Gelatin	Enhanced oral bioavailability	[19]
Polymer NPs composites	β-cyclodextrin	HPMC	Controlled and sustained drug release	[20]
Polymer NPs composites	Prodrug	PβAE	Controlled particle size and sustained drug release	[21]
Inorganic NPs composites	MSN	Gelatin	High drug loading and pH-sensitive controlled release	[23]
Inorganic NPs composites	Ag NPs	Ultra-short peptides hydrogels	Controlled and sustained drug release	[27]
Inorganic NPs composites	Ag NPs	Furfuryl-modified gelatin	Controlled and sustained drug release	[28]
Inorganic NPs composites	Nanotubes	PVI-co-AA	High drug loading and pH-sensitive controlled release	[29]
Inorganic NPs composites	IONPs	2-vinylpyridine and diviylbenzene	pH-responsive, imaging contrast agents in MRI, PTT	[30]
Multicompartment nanogels		PON triblock polymer	Thermosensitive	[35]
Multicompartment nanogels		PEP-PEO-P(NIPAm-*co*-AA) triblock polymer	Temperature and pH-sensitive	[36]
Multicompartment nanogels		PPS-b-PDMA-b-PNIPADM	ROS-sensitive	[37]