International Journal of Pharmaceutics 428 (2012) 152–163

Contents lists available at SciVerse ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Review

Cyclodextrin-based nanogels for pharmaceutical and biomedical applications

Maria D. Moya-Ortega[a], Carmen Alvarez-Lorenzo[b], Angel Concheiro[b], Thorsteinn Loftsson[a,*]

[a] Faculty of Pharmaceutical Sciences, University of Iceland, Hofsvallagata 53, IS-107 Reykjavik, Iceland
[b] Departamento de Farmacia y Tecnologia Farmaceutica, Facultad de Farmacia, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

ARTICLE INFO

Article history:
Received 9 January 2012
Received in revised form 22 February 2012
Accepted 23 February 2012
Available online 2 March 2012

Keywords:
Nanogels
Cyclodextrins
Crosslinking
Key–lock
Polymerization

ABSTRACT

Hydrophilic nanogels combine the advantages of hydrogels with certain advantages that are inherent in their nanoscale size. Similar to macrogels, nanogels can contain and protect drugs and regulate their release by incorporating high-affinity functional groups, stimuli-responsive conformations and biodegradable bonds into the polymer network. Similar to nanoparticles, nanogels can easily be administered in liquid form for parenteral drug delivery. The nanoscale size of nanogels gives them a high specific surface area that is available for further bioconjugation of active targeting agents. Biodistribution and drug release can be modulated through size adjustments. The incorporation of hydrophilic cyclodextrin (CD) moieties into the polymeric network of the nanogels provides them with a drug loading and release mechanism that is based on the formation of inclusion complexes without decreasing the hydrophilicity of the network. The covalent attachment of CD molecules to the chemically crosslinked networks may enable the CDs to display fully their ability to form complexes, while simultaneously preventing drug release upon media dilution. The preparation, characterization and advantages for pharmaceutical and biomedical applications of CD-based nanogels are reviewed in this article.

Contents

1. Introduction

Poor aqueous solubility, lack of efficacy and toxicity of the drug candidates are major causes of failure during drug development. According to the Biopharmaceutics Classification System, 40% of the currently marketed drugs and approximately 90% of new drug candidates are not sufficiently water-soluble to achieve therapeutic concentrations in physiological fluids (Heimbach et al., 2007). Many water-soluble nanocarrier systems (with preferred diameters between 10 and 100 nm) are able to encapsulate hydrophobic drugs in colloidal structures to provide them with desirable drug pharmacokinetics and drug interactions to target specific tissue (Kreuter, 1994). Such nanometric systems can include liposomes, microemulsions, submicron lipid emulsions, lipid nanoparticles, polymeric nanoparticles, polymeric micelles, and nanogels (Fig. 1) (Rhee and Mansour, 2011; Kabanov and Gendelman, 2007; Ruggiero et al., 2010). Because the performance and safety of the nanocarriers cannot be evaluated by the current guidelines for conventional drug dosage mechanisms, a search for adequate regulatory criteria for these novel structures can be both challenging and time-consuming (Bawa, 2011). A better understanding of the physicochemical and biological properties of these nanosized systems may lead to the development of nanocarriers that possess acceptable efficacy/safety profiles.

---

* Corresponding author. Tel.: +354 525 4464; fax: +354 525 4071.
E-mail address: thorstlo@hi.is (T. Loftsson).

0378-5173/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2012.02.038

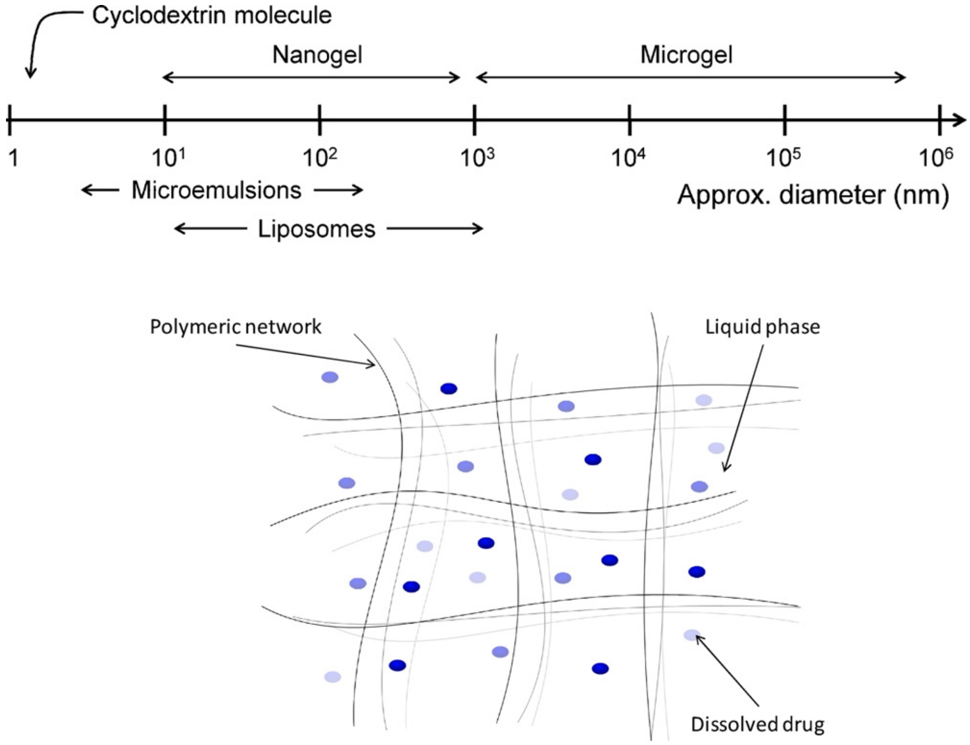


Fig. 1. Size distribution of cyclodextrin molecules, microemulsions, nanogels, liposomes and microgels.

Cyclodextrins (CDs) are attractive building blocks for various types of drug delivery systems due to their favorable toxicological profile and their inherent ability to partly or completely host biologically active molecules (e.g., drugs), and to protect them from the external environment (Irie and Uekama, 1997). Their capacity to form inclusion complexes is frequently maintained and even enhanced when the CD molecules self-assemble to form aggregates, crosslink together or copolymerize with other compounds. The high affinity of CDs for certain drug molecules is passed on to the carrier systems which endow them with a particular drug release mechanism (Alvarez-Lorenzo et al., 2009, 2010; Otero-Espinar et al., 2010). These properties are exploited to prepare supramolecular assembled entities—namely, poly(pseudo)rotaxanes and aggregates of amphiphilic CDs—for gene delivery or drug targeting (Bilensoy and Hincal, 2009; Daoud-Mahammed et al., 2007a; Harada et al., 2009; Li and Loh, 2008; Roux et al., 2007; Wouessidjewe et al., 1996) and crosslinked macrogels for mucosal- and ocular-controlled release.

The potential uses of microparticles and microcapsules containing CDs have been recently reviewed (Otero-Espinar et al., 2010). Less attention has been given to the preparation of nanoscale CD networks. This work provides a review of the design, synthesis and pharmaceutical applications of CD-based crosslinked nanogels in which the tie junctions occur by means of complex formation or by covalent bonds. First, a general overview of hydrogel networks is given, which is followed by specific examples of CD nanogels and their applications for drug delivery.

2. Nanogels

Gels exhibit properties that are between those of solids and liquids. Structurally, a gel consists of a relatively small amount of solid components, mostly entangled polymers, dispersed in a large volume of liquid in which the solids form three-dimensional structures (Alvarez-Lorenzo et al., 2011; Tanaka, 1981; Vinogradov et al., 2002; Vintiloiu and Leroux, 2008). Most biomedical gels contain water (i.e., they are hydrogels), and the polymer chains can be linked to each other either through weak interactions (physically crosslinked gels) or by covalent bonds (chemically crosslinked gels) (Peppas et al., 2000). Hydrogels formed by networks of chemically crosslinked hydrophilic polymers swell in aqueous media without dissolution (Alvarez-Lorenzo and Concheiro, 2008). True hydrogels are capable of absorbing large amounts of water or biological fluids (up to 99.9% in weight), which facilitates the diffusion of oxygen and nutrients and endows the hydrogels with a soft consistency (Alvarez-Lorenzo et al., 2011; Peppas et al., 2000). Gels prepared with an organic liquid phase (e.g., oil or organic solvent) are known as organogels (Vintiloiu and Leroux, 2008). The removal of the liquid phase by means of conventional (evaporation) or supercritical fluids-based methods leads to spongy structures of low (xerogels) or high (aerogels) porosity (Goksu et al., 2010; Quintanar-Guerrero et al., 2009). Table 1 summarizes the primary characteristics of various types of gels.

Nanogels combine the advantages of hydrogels with those that are inherent to their nanoscale size (Kettel et al., 2011). Thus, similar to macrogels, the nanogel network can host and protect drug molecules, and the release of the drug molecules from the nanogels can be regulated by the incorporation of high-affinity functional groups, stimuli-responsive conformations or biodegradable bonds into the polymer network (Sawada et al., 2011). The applications of stimuli-responsive nanogels for drug delivery have been recently reviewed by Zha et al. (2011). The hydrophilicity of the nanogels enables them to be easily dispersed in aqueous media forming free-flowing opalescent solutions (Oh et al., 2008; Samah et al., 2010; Sawada et al., 2011). Thus, nanogels can be easily administered in liquid dosage form for, for example, parenteral or mucosal administration. The nanoscale size of nanogels also leads to a high specific surface area that is available for the bioconjugation of active targeting agents. Size modulations of the nanogels can also affect their pharmacokinetics. Nanogels are able to carry encapsulated drug molecules to targeted tissues or cell structures without premature leakage of the drug into the blood stream or other tissues,

Table 1
Classification of gels, their primary characteristics and properties, and examples of their usage.

Gel	Subclassification	Approx. size	Network	Liquid	Properties	Usage	References
Hydrogels	Macrogel	>1 mm	Water soluble polymers	Water or aqueous solutions	High water content, soft and rubbery consistency, tunable chemical and physical structures, biocompatibility	Tissue engineering	Oh (2010), Van et al. (2011)
	Microgel	0.1–100 μm				Drug delivery systems Bionanotechnology	
	Nanogel	1–100 nm				Drug delivery systems Bionanotechnology	
Organogels			Gelator fibers such as poly(ethylene)	Organic solvent, vegetable oil or mineral oil	Depends on the nature of their network (solid or fluid fibers)	Matrices for delivery of bioactive agents	Sahoo et al. (2011), Vintiloiu and Leroux (2008)
Xerogels			Silica	Removed by evaporation	Porous, dry solid	Lipid bilayers supporter Drug delivery systems	Goksu et al. (2010), Quintanar-Guerrero et al. (2009)
Aerogels				Removed by solvent exchange and extraction with supercritical fluids	Superporous, extremely light	Drug carriers Regenerative medicine	García-González et al. (2011)

as recently confirmed in in vivo studies (Nukolova et al., 2011). Consequently, lower doses are required, and fewer side effects will be observed (Guerrero-Ramirez et al., 2008; Samah et al., 2010; Takahashi et al., 2011; Wang et al., 2008). Nanogels are also being explored as nonviral vectors for DNA transfection (Davis, 2009).

The synthetic methods used to obtain nanogels can be classified into two main groups: (a) methods that directly render nanometric networks, also known as bottom-up methods, and (b) methods that lead to macro networks that are subsequently broken down into nanoscale size, which are known as top-down methods (Kumar and Khan, 2010). In both methods, the starting point can be (i) preformed polymer chains, such as natural polysaccharides (chitosan, alginate) or semi-synthetic derivatives (cellulose ethers), which are bound together primarily through hydrophobic or ionic interactions or condensation reactions with crosslinking agents (Oh, 2010) or (ii) monomeric units (acrylic, vinyl) that undergo simultaneous polymerization and crosslinking reactions (Vinogradov et al., 2002). The nanogels obtained can exhibit a large variety of spatial arrangements, as depicted in Table 2. Because composition and shape are highly tunable, the physicochemical features and the performance of the nanogels as drug delivery systems can be remarkably varied. Several common analytical techniques used to characterize nanogels are summarized in Table 3. In oral drug delivery, nanogels have been used to protect chemically unstable peptides from harsh manufacturing and physiological environments and to enhance the drug absorption at specific sites within the gastrointestinal tract (Ichikawa et al., 2006; Ichikawa and Fukumori, 2007). For example, to target the colon, the dosage form must overcome various barriers within the gastrointestinal tract, such as a steep pH gradient, premature binding to the mucus layers, and premature clearance or cellular uptake (O'Donnell and Iii, 2011). Apart from their use as carriers for small molecular weight drugs, nanogels have been used to deliver therapeutic proteins, small interfering RNAs, oligonucleotides, antigens, vaccines and hormones via oral, rectal, ocular, nasal, pulmonary, and vaginal routes (Gupta et al., 2011; Kriegel and Amiji, 2011; Patel and Patel, 2010; Ravaine et al., 2008; Yadav et al., 2009). Nanogels have also been used for other biomedically related applications, such as artificial enzymes, functionalized coatings and biomarker sensors (Thorne et al., 2011).

The primary drawbacks to the use of nanogels compared with other delivery systems are their limited drug loading efficiency and still suboptimal regulation of drug release. These limitations have prompted a search for moieties that possess high affinities for specific drugs and retain them through electrostatic, van der Waals and/or hydrophobic interactions (Wang and von Recum, 2011). However, strong drug–polymer interactions can decrease the nanogel's hydrophilicity and cause the nanogel structure to collapse, irreversibly entrapping the drug molecules within the shrunken structure. Such phase separation can be avoided by enhancing the hydrophilicity of the nanogel matrix (Kabanov and Vinogradov, 2009); the ability of CDs to act as drug-hosting agents without compromising the hydrophilicity of the nanogel is a valuable asset, as explained below.

3. Cyclodextrin-based nanogels

General information regarding CD structure and its physicochemical features can be found in previously published reviews on the subject (Loftsson and Brewster, 2011; Loftsson and Duchene, 2007; Szejtili, 2004). The ability of CDs to form inclusion complexes with a wide variety of organic molecules and their ability to solubilize poorly soluble drugs is already well-established, and comprehensive information on the subject can be found in other texts (Brewster and Loftsson, 2007; Rekharsky and Inoue, 1998;

Table 2
Classification of nanogels (i.e., nanoparticulate hydrogels) according to their structure.

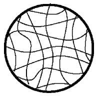
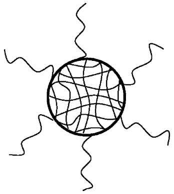
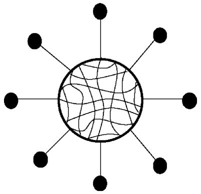
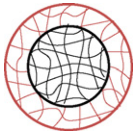
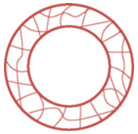
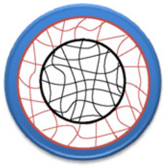
Type	Schematic structure	Network structure	Examples	References
Nanogel		Crosslinked	γCD nanogels HPβCD nanogels	Moya-Ortega et al. (2012)
		Self-assembled	Artificial chaperone, cholesterol-bearing pullulan (CHP) nanogel	Inomoto et al. (2009)
			Artificial chaperone, cholesterol enzymatically synthesized glycogen (CHESG) nanogel	Takahashi et al. (2011)
			MD-pβCD nanogel	Daoud-Mahammed et al. (2009)
		Semi-interpenetrating polymer network (semi-IPN)	Quantum dot nanogels	Wu et al. (2010)
Hairy nanogel		Crosslinked	Stimuli-responsive nanogels	Shen et al. (2011)
		Self-assembled		Delaittre et al. (2007)
Functionalized nanogel		Crosslinked	Poly(ethylene glycol)-*b*-poly(methacrylic acid) (PEG-*b*-PMA) with PEG-terminal aldehyde functionality	Nukolova et al. (2011)
Core–shell nanogel		Crosslinked	Stimuli sensitive/responsive nanogels	Sun et al. (2005), Zschoche et al. (2011)
Hollow nanogel		Interpenetrating polymer network (IPN)	Stimuli sensitive/responsive nanogels	Xing et al. (2011)
Multilayer nanogel		Crosslinked	Stimuli sensitive/responsive nanogels	Wong et al. (2009)

Table 3
Analytical techniques used to characterize nanogels.

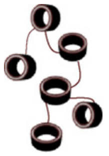
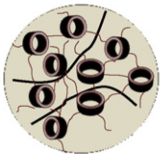
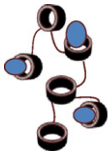
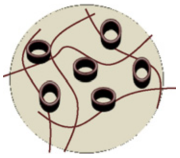
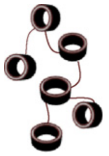
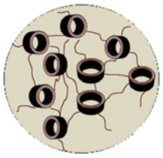
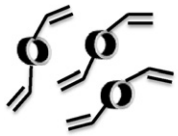
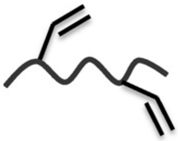
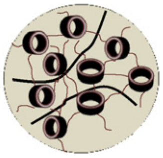
Physicochemical properties	Techniques	Reference
Nanogel formation	Dark-field microscopy	Gref et al. (2006)
	NMR studies	Gref et al. (2006), Guerrero-Ramirez et al. (2008), Kettel et al. (2011), Takahashi et al. (2011), Vinogradov et al. (2002)
	RAMAN spectra	Kettel et al. (2011)
	FTIR	Guerrero-Ramirez et al. (2008), Kettel et al. (2011)
Structure/morphology	TEM	Chen et al. (2011), Daoud-Mahammed et al. (2007b), Gref et al. (2006), Morimoto et al. (2005a,b), Takahashi et al. (2011)
	SEM	Kettel et al. (2011), Oh (2010)
	AFM	Shen et al. (2011)
Amount of CD in the nanogel	Titration with phenolphthalein, adsorption of 3-methyl benzoic acid	Kettel et al. (2011)
Aggregation number of an associating cholesterol domain (nanogels used as artificial chaperones)	Fluorescence quenching technique	Morimoto et al. (2005b)
Mean diameter and size distribution	DLS	Chen et al. (2011), Daoud-Mahammed et al. (2009), Daoud-Mahammed et al. (2007b), Gref et al. (2006), Guerrero-Ramirez et al. (2008), Inomoto et al. (2009), Kettel et al. (2011), Shen et al. (2011), Takahashi et al. (2011), Wang et al. (2008)
	SANS/SAXS	Inomoto et al. (2009), Chen et al. (2011)
Molecular weight, polydispersity index and z-average root-mean-square radius of gyration	SEC-MALS system	Morimoto et al. (2005b), Takahashi et al. (2011)
Swelling ratio	Equation of crowther and vincent	Wang et al. (2008)
Cytocompatibility	MTT assay	Shen et al. (2011)
	Macro-CTAs with lung cancer cell A549	
Mucoadhesion[a]		
In vitro	Analytical method using porcine urinary bladders from the slaughterhouse	Barthelmes et al. (2011)
	Mucin absorption	Saboktakin et al. (2011)
	Franz cells using fresh small intestine (jejunum) as the membrane	Moghaddam et al. (2009)
	Mucin and fluorimetry	Ramteke et al. (2008)
In vivo	X-ray	Ramteke et al. (2008)
Stability	Turbiscan MA 2000	Daoud-Mahammed et al. (2007b)
	Freeze-drying	Shen et al. (2011)
	Flocculation in biological medium	Shen et al. (2011)
	UV–vis (aminolysis and hydrolysis of the main transfer agents, CTAs)	Shen et al. (2011)
Thermosensitivity	^{1}H NMR	Shen et al. (2011)
Inclusion complex formation	Phase solubility studies	Daoud-Mahammed et al. (2009)
	Circular dichroism	Daoud-Mahammed et al. (2009), Takahashi et al. (2011)
	ITC	Daoud-Mahammed et al. (2009)
Drug entrapment	UV spectrophotometry	Daoud-Mahammed et al. (2009), Gref et al. (2006), Pasetto et al. (2009), Takahashi et al. (2011), Wang et al. (2008)
Drug release	Equilibrium dialysis technique	Vinogradov et al. (2002)
	Franz-diffusion cells	Samah et al. (2010)

Nomenclature: AFM: atomic force microscopy; DLS: dynamic light scattering; FTIR: Fourier transform infrared; ITC: isothermal titration calorimetry; SANS: small-angle neutron scattering; SAXS: small-angle X-ray scattering; SEC-MALS: size exclusion chromatography-multi-angle laser light scattering; SEM: scanning electron microscopy; TEM: transmission electron microscopy.

[a] Studies carried out with nanoparticles.

Uekama et al., 1998; Vemula, 2010). Although CDs are recognized by the pharmaceutical, cosmetic and personal care industries as promising host agents, drug–CD complexes have not, in general, led to sustained release profiles, nor have they been adapted to target drug delivery to specific diseased cells and tissues (Daoud-Mahammed et al., 2009; Jansook et al., 2010; Kettel et al., 2011; Loftsson and Brewster, 2010; Messner et al., 2010; Moya-Ortega et al., 2010). However, the ability of CDs to form drug inclusion complexes and their favorable toxicological profiles make CDs suitable building blocks for the design of advanced materials for the delivery of both hydrophobic and hydrophilic drugs and even genes (Alvarez-Lorenzo et al., 2011; Ortiz-Mellet et al., 2011; Otero-Espinar et al., 2010). Incorporation of CD moieties into a matrix structure has a twofold purpose: (1) to provide an affinity-based mechanism for drug loading and control of drug release through the formation of inclusion complexes and (2) to enhance the hydrophilicity of the polymer matrix. The benefits of CD incorporation over the conventional macro/micro-hydrogels used for sustained delivery have already been demonstrated (Trotta et al., 2011). Covalent attachment of CDs to chemically crosslinked

Table 4
Synthetic methods for the preparation of CD-based nanogels.

Primary building block	Secondary building block	Reaction	Gel structure	Ref.
Key–lock assembly				
		Inclusion complex →		Gref et al. (2006)
		→		Daoud-Mahammed et al. (2007a, 2009)
Crosslinked CDs				
		Crosslinking agent →		Daoud-Mahammed et al. (2007b), Moya-Ortega et al. (2012)
		Crosslinking agent →		Rodriguez-Tenreiro et al. (2007a), Trotta et al. (2011)
Polymerized CD monomers				
		Free-radical polymerization →		Liu et al. (2009), Kettel et al. (2011)

networks may enable CDs to fully display their complexation capabilities, while preventing the dilution phenomenon (i.e., the drug release upon vehicle dilution that occurs when physical gels or CD-containing solutions are administered). Nanogels dispersed in water form CD-rich colloidal networks that are able to interact with the guest drug molecules and are capable of controlling drug release by utilizing the affinity of the drug molecules for the CD cavities. As previously mentioned, nanogels combine the advantages of hydrogels and nanoparticles into a single carrier that can be tailored for specific therapeutic molecules, such as low molecular weight drugs, peptides or relatively large proteins, and target them to specific tissues or cells. Alternatively, CDs can be grafted onto free polymeric chains to play a dual role: as the crosslinking agent and as the host for the guest drug. To perform both functions, certain CD cavities can be involved in forming complexes with the hydrophobic groups of adjacent polymeric chains, acting as tie junctions or crosslinking points, while the other CDs interact with the drug molecules. The different methods for the preparation of CD-based nanogels are depicted in Table 4. Taking into account the nature of the crosslinking points, these methods can be classified into three groups: (i) key–lock interactions among preformed chains, with some bearing CDs and others possessing groups that fit into the CDs, (ii) direct covalent crosslinking of CD units by condensation with suitable bi/multifunctional agents, (iii) polymerization of CD monomers bearing acrylic or vinyl moieties (Alvarez-Lorenzo et al., 2009; Gref et al., 2006; Kettel et al., 2011).

3.1. *Key–lock nanogels*

The mixing of two different polymer chains, one containing covalently bonded CD moieties and the other containing moieties that are able to form complexes with the CD moieties of the first, leads to a spontaneous assembly in aqueous media. Such CD-mediated crosslinking of the chains resembles a zipper, or key–lock fitting, and is being studied to find ways of increasing the apparent viscosity of the entire system or to prepare nano-sized aggregates dependent on the total concentration of both polymers that lead to networked hydrogels with desirable physical properties (reversibility) and chemical properties (high stability upon dilution). The dynamic character of the complex formation enables the tie junctions to break when forced to pass through fine-gauged needles (e.g., during injection) and to re-form within a few seconds once the force is removed (e.g., after injection) (Daoud-Mahammed et al., 2007b). Key–lock networks have been reported for blends of polymers containing pendant βCDs and polymers with functional groups, such as 4-tert-butyl anilide, dodecyl or adamantyl, poly(ethylene glycol), cholesterol or aromatic rings (Auzely-Velty and Rinaudo, 2002; Hashidzume et al., 2005; Osman et al., 2011; van de Manakker et al., 2009; Wenz et al., 2000; Wintgens et al., 2005, 2008).

Stable nanogel particles have been obtained by mixing polymers of βCD (poly-βCD) with dextrans bearing alkyl side chains at concentrations ranging between 0.1 and 1% (w/w) (Gref et al., 2006). The nanogels are loaded with drugs that form complexes with the poly-βCD before mixing with the dextran. The remaining empty CDs participate in the tie junctions with the alkyl chains of the dextran. The formation and stability of these self-assembled nanogels were found to depend on the percentage of the glucose units that had been substituted with alkyl chains in the dextran (dextran grafted with alkyl moieties, MD), the polymer concentration, the number of carbons in the alkyl chains, the poly-βCD molar mass and the weight ratio of MD to poly-βCD. These nanogels can be freeze-dried and reconstituted in water without any change in particle size. Other advantages of these self-assembled systems include the stability of the nanogel upon dilution in water and the rapidity of the nanogel formation (Gref et al., 2006). The presence of a hydrophobic guest molecule (benzophenone, BZ) in the system hinders the sequestration of the dextran alkyl moieties by the βCD in the polymer without impeding the formation of 100–200-nm associative nano-assemblies or compromising their stability (Daoud-Mahammed and Grossiord, 2007). Moreover, the highest BZ loadings were obtained by solubilizing +-BZ in both the poly-βCD and MD solutions before mixing them to form nanogels (Daoud-Mahammed et al., 2009). These types of gels enabled the sustained delivery of benzophenone and tamoxifen for more than one week (Daoud-Mahammed and Grossiord, 2007). Furthermore, the grafting ratio of βCD and adamantly can be modulated to finely tune the association properties of the polymers and thus the size and the swelling properties of the nanogels (Wintgens et al., 2011). These features in combination with the available in vivo compatibility data greatly increase the possible applications for self-assembling CD gels in the biomedical field. In fact, these systems have been considered promising candidates for controlled/targeted drug delivery, due to their unique ability to disrupt in a controlled manner. Nielsen et al. (2009) studied the controlled disruption of the self-assembling microparticles formed by poly-βCD and hydrophobically modified dextran. The disruption occurred with the addition of hydroxy-adamantane, which has a strong affinity toward the βCD cavities. The disruption provoked a change in the shape of the particles from the spherical shape found in the fresh particles to a more random one.

3.2. Nanogels of crosslinked CD units

The large number of reactive hydroxyl groups in the native CD structure and the hydroxyl, carboxylic acid or amine groups in the CD derivatives can be exploited to prepare covalently crosslinked networks by means of condensation reactions with bi/multifunctional agents. These groups may also be used to synthesize reactive CD monomers suitable for polymerization reactions (this last point is covered in next section). Several crosslinking agents containing aldehyde, ketone, isocyanate or epoxide groups have been evaluated for the first approach (Alvarez-Lorenzo et al., 2009). The reaction with epichlorohydrine (EPI) has been described in detail, and the resulting microgels with sizes that depend on the relative proportion and total concentration of CDs and EPI have been shown to be useful as selective traps for the extraction of contaminants from water or food. These microgels have also found use in separation science and as platforms for drug delivery systems (Crini, 2005; Liu et al., 2004; Schneiderman and Stalcup, 2000; Zhang et al., 2008). A series of quaternary ammonium βCD (QAβCD) nanoparticles with differing charge densities were synthesized by a one-step condensation polymerization of βCD, choline chloride, and EPI (Gil et al., 2009). These nanoparticles showed an enhanced permeability across bovine brain microvessel endothelial cell (BBMVEC) monolayers, with their permeation being dependent upon the number of quaternary ammonium groups. No toxic effect was found in BBMVEC when cultured in the presence of particles (500 μg/mL) for 24 h. Therefore, QAβCD nanoparticles are considered promising carriers across the blood brain barrier (BBB) for doxorubicin (Gil et al., 2009) and other therapeutics (Gil and Lowe, 2008) to treat brain disorders.

Active carbonyl compounds have been used as crosslinkers to obtain CD nanosponges (CDNS) (Ansari et al., 2011a; Trotta and Cavalli, 2009; Trotta et al., 2011). These nanosponges are solid nanoparticles and can be prepared in crystalline form with a spherical shape using an ultrasound-assisted preparation method (top-down approach) (Trotta and Cavalli, 2009). The particle sizes ranged from 350 to 600 nm with low polydispersity indices (Ansari et al., 2011a,b; Swaminathan et al., 2010; Trotta and Cavalli, 2009). CDNS are nanoporous materials with pore sizes that can be modulated by the suitable choice of a CD/crosslinker mole ratio (Mele et al., 2011). CDNS and nanogels are able to carry both lipophilic and hydrophobic drugs (i.e., itraconazole, Swaminathan et al., 2007; dexamethasone, Trotta and Cavalli, 2009; and resveratrol, Ansari et al., 2011a). Furthermore, CDNS are able to form inclusion complexes with gases, which is a property that can be useful for many biomedical applications (Cavalli et al., 2010; Trotta et al., 2011). CDNS crosslinked with pyromellitic dianhydride (PMA) have shown swelling properties, which rise to the level of gel-like behavior, in the presence of aqueous solutions (Mele et al., 2011).

The crosslinking reactions can be adapted to directly synthesize nanogels by applying the water-in-oil heterogeneous gelation approach, which is a gentle way of obtaining micro- and nanogels from natural polysaccharides (Antoniette and Landfester, 2002; Oh et al., 2009). CDs have also been shown to be useful for regulating the nanostructure of coalescent polymers (Tonelli, 2008) or for creating novel nano- and microstructures for drug delivery (Johnson et al., 2010; Marui et al., 2010). The water-in-oil emulsion method involves two steps: (i) emulsification of an aqueous solution of CD and the crosslinking agent in an oily phase containing a suitable surfactant and (ii) the treatment of the emulsion under adequate pH/temperature conditions to induce the crosslinking reaction and the formation of the nanogels. The therapeutic agents and, if needed, polysaccharides can be added to the aqueous phase before emulsification. The nanogels adopt the spherical morphology of the droplets in the internal phase of the emulsion. The size of the spheres is primarily determined by the energy applied for the emulsification and by the nature and proportion of the surfactant (Oh et al., 2009). The nanogels can be recovered from the oily phase by dialysis or by centrifugation and subsequently stored as a freeze-dried powder. This technology has been applied to prepare α-cyclodextrin (αCD) nanospheres (diameter = 185–1600 nm) crosslinked with isophorone diisocyanate in hexadecane (Baruch-Teblum et al., 2010). Diisocyanates can also be used to obtain CD-based hydrophilic, hyperbranched polymers that exhibit the ability to form complexes with guest molecules (Chen et al., 2003) and to prepare nanoporous CD particles that rapidly retain solutes from aqueous environments and release them into organic phases (Ma and Li, 1999). An emulsion technique for the interfacial crosslinking of βCDs with diacyl chlorides has been developed to prepare microcapsules with walls made of crosslinked CDs (Pariot et al., 2000). This capsule-like structure has the advantage of the easy accessibility of guest molecules to the CD cavities, thereby enabling completion of the loading in 5 min. Furthermore, the microcapsules control the release of propranolol for several hours (Pariot et al., 2002). βCD microparticles containing anionic polysaccharides (carboxymethyl or sulfopropyl pullulan) have been prepared using 3-(glycidoxypropyl) trimethoxysilane. This crosslinking agent can act both through grafting with the epoxy-end on the hydroxyl groups of the CD and the polysaccharide and through hydrolysis and condensation of the methoxy silane groups at the other end. The microparticles demonstrated the capability to retain water pollutants (phenol and benzoic acid

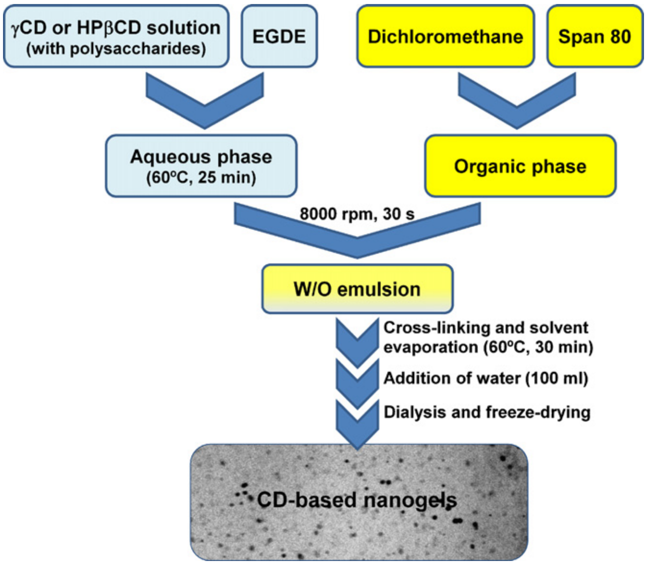


Fig. 2. Flow chart for the preparation of CD-based nanogels.

derivatives, β-naphthol), drugs (salicylic acid, indomethacin) and proteins (lysozyme) (Mocanu et al., 2009).

The water-in-oil emulsion method has recently been adapted to prepare γ-cyclodextrin (γCD) or hydroxypropyl-β-cyclodextrin (HPβCD) nanogels in which the crosslinking takes place simultaneously with an emulsification/solvent evaporation process (Fig. 2) (Moya-Ortega et al., 2012). The aqueous phase consisted of 20% (w/w) CDs with or without hydroxypropyl methylcellulose (HPMC) or agar at various concentrations, to which the cross-linker agent ethylene glycol diglycidyl ether (EGDE) was added. It has been previously shown that CDs can directly react with bifunctional epoxide groups, such as EGDE, to form networks comprising not only CDs but also other polysaccharides or acrylic polymers that enable a fine modulation of the mechanical properties and the drug delivery features (Komiyama and Hirai, 1987; Lopez-Montero et al., 2009; Moya-Ortega et al., 2010; Rodriguez-Tenreiro et al., 2006, 2007a,b). An EGDE:CD 1:1 (w/w) ratio was chosen to provide a sufficient amount of crosslinking agent to react with 2 out of 3 of the hydroxyl groups on each CD glucopyranose unit. The aqueous solution was heated at 60 °C for 25 min before mixing with the organic phase to trigger the reaction of the CDs with the EGDE. A reduction in the reaction time led to the migration of the EGDE to the organic solvent and a poor reaction yield, while heating for more than 30 min increased the risk of the formation of a conventional hydrogel in the aqueous solution prior to the addition of the organic phase. In certain cases, surfactants may be not needed to prepare the emulsions, due to the intrinsic capability of the CDs to act as emulsifiers (Inoue et al., 2009).

3.3. *Nanogels obtained by the polymerization of CD monomers*

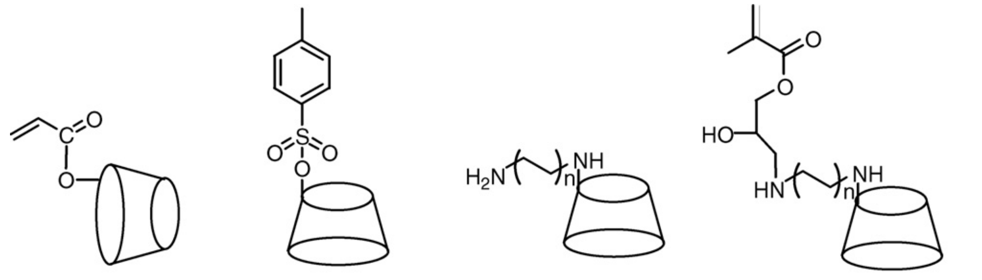
Nanogels of CDs can be also prepared by the heterogeneous free-radical polymerization of CD units previously modified with reactive double bonds. A large variety of CD monomers has been described in the literature (Alvarez-Lorenzo et al., 2009). The presence of a high number of equally reactive hydroxyl groups makes the preparation of monofunctional monomers particularly challenging. Thus, most publications describe multifunctional monomers (Fig. 3). To obtain discrete micro- and nanogels instead of bulk soft gels or macroporous monoliths, relatively high crosslinking ratios and a large volume of solvent are required (Alvarez-Lorenzo and Concheiro, 2006; Cormack and Elorza, 2004). In contrast to the numerous examples of CD-containing hydrogels that are ground to render nanosized particles (Alvarez-Lorenzo et al., 2010; Asanuma et al., 2000), direct synthesis of CD-containing nanogels is still rarely reported.

Precipitation polymerization has been applied to the synthesis of βCD-co-poly(N-isopropylacrylamide) nanogels (Liu et al., 2009). This method involved the preparation of a monovinyl β-CD monomer (GMA-EDA-β-CD; Fig. 3d) dispersed in an aqueous solution of N-isopropylacrylamide (NIPAAm), N,N-methylenebis(acrylamide) (BIS, crosslinker), and surfactant. The initiator (ammonium persulfate) was added to the dispersion, and the solution was maintained at 70 °C under stirring for 5 h. The crosslinker is essential, due to the solubility of the copolymer in the aqueous medium. Thus, in the absence of BIS, linear chains would be formed instead of nanoparticles. These nanogels (diameter = 106–115 nm) were subsequently used as cores to be coated with shell layers of pNIPAAm, applying a second precipitation polymerization step, with the purpose of combining the ability of the CDs to form inclusion complexes with the temperature-responsiveness of the pNIPAAm. In fact, the core-shell nanogels (diameter = 133–142 nm) shrank at 37 °C (diameter = 65–90 nm). Paeonol was loaded onto the core–shell nanogels by immersion in aqueous solutions and underwent sustained released at 37 °C. The yield in the polymerization of the monovinyl βCD monomer was notably low; therefore, the contribution of the inclusion complexes to the drug release control was minor (Liu et al., 2009).

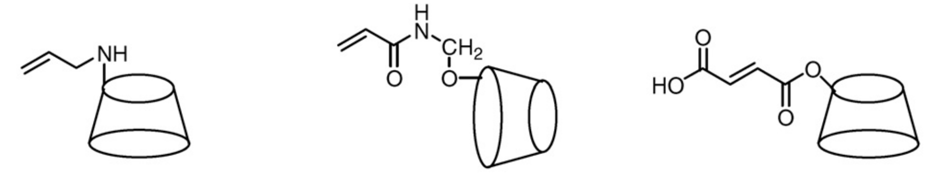
Nanogels based on poly(N-vinylcaprolactam) and α-, β- or γCD have recently been prepared by surfactant-free precipitation polymerization (Kettel et al., 2011). The CDs were previously modified to have 2, 4 or 6 acryloyl substituents (Fig. 3a) and were subsequently added to aqueous solutions containing N-vinylcaprolactam, acetoacetoxyethyl methacrylate (AAEM), and an initiator. The bi/multifunctional polymerizable groups in the CDs made the use of the crosslinker BIS optional. After stirring at 70 °C for 12 h, the obtained nanogels were purified by ultrafiltration. The incorporation efficiency of the CDs ranged between 47 and 80%, and the size of the nanogels diminished from 230 to 60 nm as their CD content increased. The nanogels, after being freeze-dried, could be easily redispersed in water to form aggregate-free dispersions with excellent colloidal stability. The presence of poly(N-vinylcaprolactam) endowed the nanogels with temperature responsiveness, swollen at temperatures below 32 °C and collapsed at higher temperatures. Poly(N-vinylcaprolactam)-co-CD nanogels can be transferred to organic solvents, thereby allowing the potential incorporation of water-insoluble compounds into the nanogel structure. These nanogels can be also utilized in reaction catalysis or separation processes (Kettel et al., 2011).

Fully biodegradable nanogels have been prepared from a polylactic acid (PLA) macromonomer and a vinyl βCD monomer (obtained by the reaction of 1-allyloxy-2,3-epoxy propane, AGE) (Fig. 4) (Lu et al., 2008). The size ranged between 60 and 260 nm depending on the PLA/βCD ratio and the degree of substitution of the vinyl βCD monomer. An increase in vinyl groups on the βCD monomer from 1 to 7 led to a higher crosslinking density, which resulted in a decrease in the swelling ratios and the rate of degradation (50–23% weight loss in 42 days). Although these nanogels were not tested with regards to their ability to load/release drugs, they might be useful as biodegradable and biocompatible carriers.

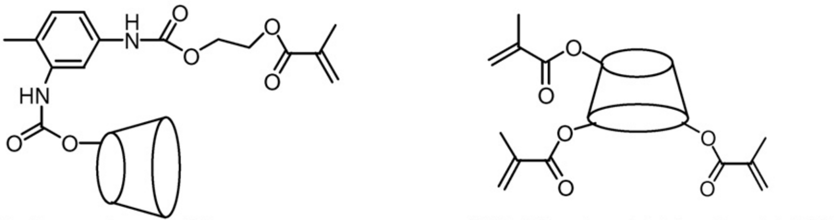
In recent years, the use of nanogels as artificial chaperones has been studied (Asayama et al., 2008; Ikeda et al., 2006; Inomoto et al., 2009; Morimoto et al., 2005a,b; Sasaki et al., 2011; Sawada et al., 2011; Takahashi et al., 2011). Amphiphilic enzymatically synthesized glycogen (ESG) nanoballs were synthesized by introducing a cholesterol group to ESG (CHESG). CHESG was assembled into a structure containing a few molecules to form cluster nanogels (measuring approximately 35 nm in diameter) in water. The cluster nanogels were dissociated by the addition of cyclodextrin



(a) Acryloyl-CD (b) 6-O-(p-tosyl)-CD (c) 6-(alkylenediamine)-CD (d) GMA-(alkylenediamine)-CD



(e) Mono-(6-N-allylamino-6-deoxy)-CD (f) Acrylamidomethyl-CD (g) Maleic anhydride (MAH)-CD



(h) Urethane-methacrylate-CD (i) 2,3-di-O-methacrylated-6-methacrylated-CD

Fig. 3. Structures of the monomeric derivatives of CD used for synthesizing polymeric networks.
Adapted from Alvarez-Lorenzo et al. (2010).

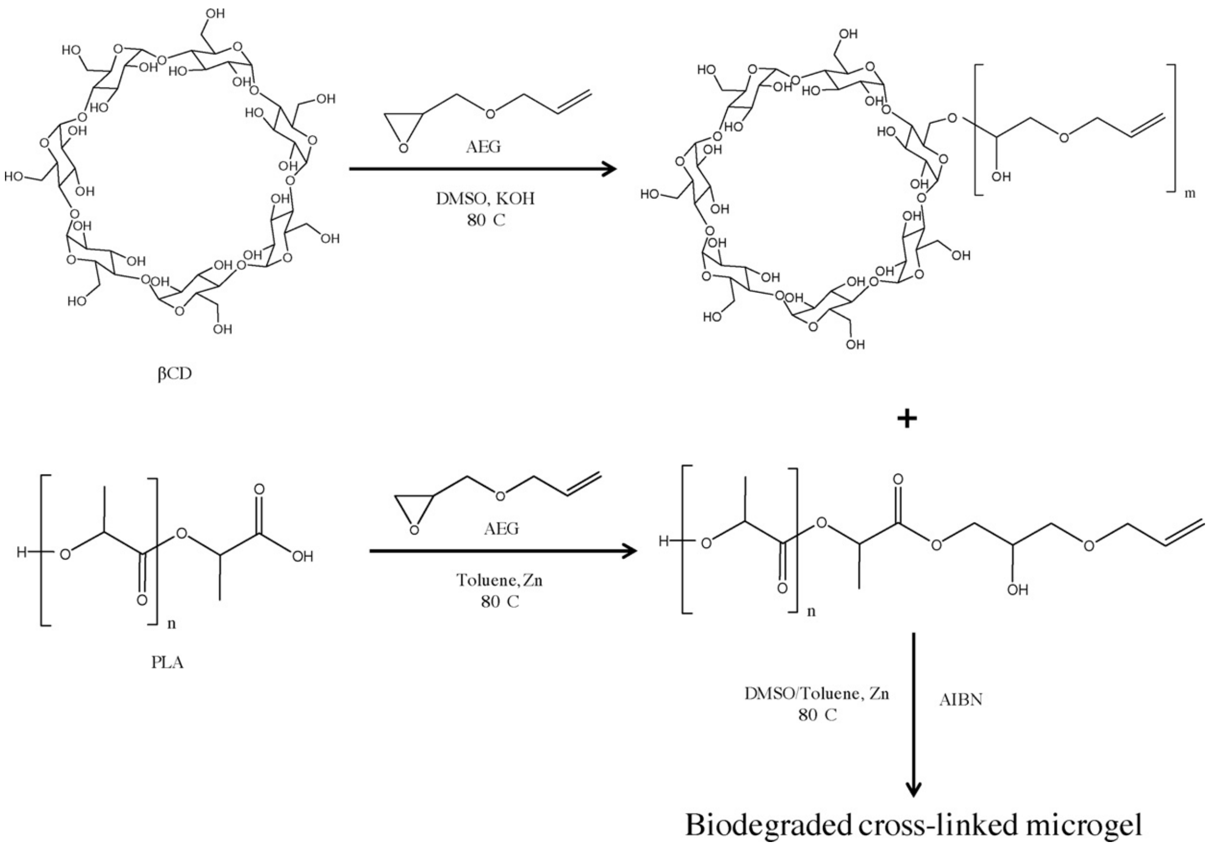


Fig. 4. The synthesis of polymerizable macromonomers and biodegradable microgels.
Adapted from Lu et al. (2008).

(CD) to form a supramolecular CHESG-CD nanocomplex through cholesterol/CD complexation. The CHESG nanogel exhibited a high protein-complexation capacity, and the CHESG-CD nano-complex showed great chaperone-like activity for the thermal stabilization of enzymes (Sasaki et al., 2011; Sawada et al., 2011; Takahashi et al., 2011). Hybrid hydrogels with nanogel domains are another type of system containing nanogels that can be used as artificial chaperones (Morimoto et al., 2005a). The immobilized nanogels retained their ability to trap and release protein by the host–guest interactions between the cholesteryl group and the CD and exhibited high chaperone-like activity for the refolding of chemically denatured proteins.

Cyclodextrin-based nanogels provide useful functionalities, such as effective bioconjugation, good surface adhesion, controlled complexation and release of drugs, and utility as cosmetic ingredients, dyes or antimicrobial agents (Guerrero-Ramirez et al., 2008; Gupta et al., 2011; Ikeda et al., 2006; Kettel et al., 2009). They also find utility in protein stabilization, gene therapy, tissue engineering, regenerative medicine and biosensors (Gref et al., 2006; Jensen et al., 2012; Oh et al., 2008; Samah et al., 2010; Sawada et al., 2006).

The chemical functionality of nanogels is highly important for their application as drug delivery systems. For this purpose, CD-based nanogels have been developed. As referenced above, CDs are integrated as the functional units of nanogels in polymer networks in which the CD moieties act as carriers of molecules with poor water solubility. The size of the CD-based nanogels allows their application on both a molecular and cellular level, and the large surface-to-weight ratio of the nanoparticles leads to CD-moieties that are more accessible than the larger three-dimensional bulk gels. Moreover, CD-based nanogels provide useful functionalities, such as effective bioconjugation, good adhesion to surfaces, controlled complexation and the relatively rapid release of drugs, in addition to their utility as cosmetic ingredients, dyes or antimicrobial agents (Kettel et al., 2011). Studies are ongoing regarding the use of CD-based nanogels in drug delivery (Daoud-Mahammed et al., 2009; Moya-Ortega et al., 2012).

4. Conclusions

Nanogels containing CDs are promising tools for the delivery of drugs and other applications in the biomedical field, owing to their unique set of properties that ideally fit the conditions of drug transport via systemic routes of administration. The use of nanogels allows the improvement of the biopharmaceutical parameters of entrapped drugs. As research in this field continues, it is becoming clear that nanogels hold great promise as nanoscale platforms for multifunctional biomaterials.

Conflict of interest

The authors declare that they have no conflicts of interest to disclose.

Acknowledgements

This work was supported by RANNÍS (Icelandic Centre for Research), The University of Iceland, MICINN (SAF2011-22771), FEDER and Xunta de Galicia (10CSA203013PR), Spain.

References

Alvarez-Lorenzo, C., Concheiro, A., 2006. Molecularly imprinted gels and nano- and microparticles. Manufacture and applications. In: Arshady, R., Kono, K. (Eds.), Smart Nano- and Microparticles. Kentus Books, London, pp. 279–336.

Alvarez-Lorenzo, C., Concheiro, A., 2008. Intelligent drug delivery systems: polymeric micelles and hydrogels. Mini-Rev. Med. Chem. 8, 1065–1074.

Alvarez-Lorenzo, C., Bromberg, L., Concheiro, A., 2009. Light-sensitive intelligent drug delivery systems. Photochem. Photobiol. 85, 848–860.

Alvarez-Lorenzo, C., Bucio, E., Burillo, G., Concheiro, A., 2010. Medical devices modified at the surface by gamma-ray grafting for drug loading and delivery. Expert Opin. Drug Deliv. 7, 173–185.

Alvarez-Lorenzo, C., Moya-Ortega, M.D., Loftsson, T., Concheiro, A., Torres-Labandeira, J.J., 2011. Cyclodextrin-based hydrogels. In: Bilensoy, E. (Ed.), Cyclodextrins in Pharmaceutics, Cosmetics, and Biomedicine: Current and Future Industrial Applications. John Wiley & Sons, Inc., Hoboken, NJ.

Ansari, K.A., Vavia, P.R., Trotta, F., Cavalli, R., 2011a. Cyclodextrin-based nanosponges for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. AAPS PharmSciTech 12, 279–286.

Ansari, K.A., Torne, S.J., Vavia, P.R., Trotta, F., Cavalli, R., 2011b. Paclitaxel loaded nanosponges: in vitro characterization and cytotoxicity study on MCF-7 cell line culture. Curr. Drug Deliv. 8, 194–202.

Antoniette, M., Landfester, K., 2002. Polyreactions in miniemulsions. Prog. Polym. Sci. 27, 689–757.

Asanuma, H., Hishiya, T., Komiyama, M., 2000. Tailor-made receptors by molecular imprinting. Adv. Mater. 12, 1019–1030.

Asayama, W., Sawada, S.-i., Taguchi, H., Akiyoshi, K., 2008. Comparison of refolding activities between nanogel artificial chaperone and GroEL systems. Int. J. Biol. Macromol. 42, 241–246.

Auzely-Velty, R., Rinaudo, M., 2002. New supramolecular assemblies of a cyclodextrin-grafted chitosan through specific complexation. Macromolecules 35, 7955–7962.

Barthelmes, J., Perera, G., Hombach, J., Dünnhaupt, S., Bernkop-Schnürch, A., 2011. Development of a mucoadhesive nanoparticulate drug delivery system for a targeted drug release in the bladder. Int. J. Pharm. 416, 339–345.

Baruch-Teblum, E., Mastai, Y., Landfester, K., 2010. Miniemulsion polymerization of cyclodextrin nanospheres for water purification from organic pollutants. Eur. Polym. J. 46, 1671–1678.

Bawa, R., 2011. Regulating nanomedicine. Can the FDA handle it? Curr. Drug Deliv. 8, 227–234.

Bilensoy, E., Hincal, A.A., 2009. Recent advances and future directions in amphiphilic cyclodextrin nanoparticles. Expert Opin. Drug Deliv. 6, 1161–1173.

Brewster, M.E., Loftsson, T., 2007. Cyclodextrins as pharmaceutical solubilizers. Adv. Drug Deliv. Rev. 59, 645–666.

Cavalli, R., Akhter, A.K., Bisazza, A., Giustetto, P., Trotta, F., Vavia, P., 2010. Nanosponge formulations as oxygen delivery systems. Int. J. Pharm. 402, 254–257.

Chen, H., Zhu, H., Hu, J., Zhao, Y., Wang, Q., Wan, J., Yang, Y., Xu, H., Yang, X., 2011. Highly compressed assembly of deformable nanogels into nanoscale suprastructures and their application in nanomedicine. ACS Nano 5, 2671–2680.

Chen, L., Zhu, X., Yan, D., He, X., 2003. A straightforward method to synthesize cyclodextrin-based hyperbranched polymer from natural cyclodextrin. Polym. Prepr. 44, 669–670.

Cormack, P.A.G., Elorza, A.Z., 2004. Molecularly imprinted polymers: synthesis and characterization. J. Chromatogr. B 804, 173–182.

Crini, G.g., 2005. Recent developments in polysaccharide-based materials used as adsorbents in wastewater treatment. Prog. Polym. Sci. 30, 38–70.

Daoud-Mahammed, S., Couvreur, P., Gref, R., 2007a. Novel self-assembling nanogels: stability and lyophilisation studies. Int. J. Pharm. 332, 185–191.

Daoud-Mahammed, S., Ringard-Lefebvre, C., Razzouq, N., Rosilio, V., Gillet, B., Couvreur, P., Amiel, C., Gref, R., 2007b. Spontaneous association of hydrophobized dextran and poly-Î^{2}-cyclodextrin into nanoassemblies: formation and interaction with a hydrophobic drug. J. Colloid Interface Sci. 307, 83–93.

Daoud-Mahammed, S., Grossiord, J.L., 2007. Self-assembling cyclodextrin based hydrogels for the sustained delivery of hydrophobic drugs. J. Biomed. Mater. Res. A 86A, 736–748.

Daoud-Mahammed, S., Couvreur, P., Bouchemal, K., Cheron, M., Lebas, G., Amiel, C., Gref, R., 2009. Cyclodextrin and polysaccharide-based nanogels: entrapment of two hydrophobic molecules, benzophenone and tamoxifen. Biomacromolecules 10, 547–554.

Davis, M.E., 2009. The first targeted delivery of siRNA in humans via a self-assembling, cyclodextrin polymer-based nanoparticle: from concept to clinic. Mol. Pharm. 6, 659–668.

Delaittre, G., Save, M., Charleux, B., 2007. Nitroxide-mediated aqueous dispersion polymerization. From water-soluble macroalkoxyamine to thermosensitive nanogels. Macromol. Rapid Commun. 28, 1528–1533.

García-González, C.A., Alnaief, M., Smirnova, I., 2011. Polysaccharide-based aerogels—promising biodegradable carriers for drug delivery systems. Carbohydr. Polym. 86, 1425–1438.

Gil, E.S., Lowe, T.L., 2008. Invention of polysaccharide-based nanoparticles for enhancing drug permeability across the blood brain barrier. NSTI Nanotechnol. Nanotechnol. Conf. Trade Show, Tech. Proc. 2, 379–381.

Gil, E.S., Li, J., Xiao, H., Lowe, T.L., 2009. Quaternary ammonium beta-cyclodextrin nanoparticles for enhancing doxorubicin permeability across the in vitro blood–brain barrier. Biomacromolecules 10, 505–516.

Goksu, E.I., Hoopes, M.I., Nellis, B.A., Xing, C., Faller, R., Frank, C.W., Risbud, S.H., Satcher Jr., J.H., Longo, M.L., 2010. Silica xerogel/aerogel-supported lipid bilayers: consequences of surface corrugation. BBA-Biomembranes 1798, 719–729.

Gref, R., Amiel, C., Molinard, K., Daoud-Mahammed, S., Sebille, B., Gillet, B., Beloeil, J.-C., Ringard, C., Rosilio, V., Poupaert, J., Couvreur, P., 2006. New self-assembled nanogels based on host-guest interactions: characterization and drug loading. J. Control. Release 111, 316–324.

Guerrero-Ramirez, L.G., Nuno-Donlucas, S.M., Cesteros, L.C., Katime, I., 2008. Smart copolymeric nanohydrogels: synthesis, characterization and properties. Mater. Chem. Phys. 112, 1088–1092.

Gupta, S., Gabrani, R., Ali, J., Dang, S., 2011. Exploring novel approaches to vaginal drug delivery. Rec. Pat. Drug. Deliv. Formul. 5, 82–94.

Harada, A., Hashidzume, A., Yamaguchi, H., Takashima, Y., 2009. Polymeric rotaxanes. Chem. Rev. 109, 5974–6023.

Hashidzume, A., Ito, F., Tomatsu, I., Harada, A., 2005. Macromolecular recognition by polymer-carrying cyclodextrins: interaction of a polymer bearing cyclodextrin moieties with poly (acrylamide)s bearing aromatic side chains. Macromol. Rapid Commun. 26, 1151–1154.

Heimbach, T., Fleisher, D., Kaddoumi, A., Stella, V.J., Borchardt, R.T., Hageman, M.J., Oliyai, R., Maag, H., Tilley, J.W., 2007. Overcoming Poor Aqueous Solubility of Drugs for Oral Delivery Prodrugs. Springer, New York, pp. 157–215.

Ichikawa, H., Fukumor, Y., Kamiya, H., 2006. Functional stimuli-responsive nanogelparticles for oral peptide delivery: preparation, drug-release behaviors and in vitro cellular interaction. Nanotechnology 2, 392–395.

Ichikawa, H., Fukumori, Y., 2007. Design of nanohydrogel-incorporated microcapsules for appropriate controlled-release of peptide drugs. Yakuga. Zasshi 127, 813–823.

Ikeda, K., Okada, T., Sawada, S.-i., Akiyoshi, K., Matsuzaki, K., 2006. Inhibition of the formation of amyloid Î^2-protein fibrils using biocompatible nanogels as artificial chaperones. FEBS Lett. 580, 6587–6595.

Inomoto, N., Osaka, N., Suzuki, T., Hasegawa, U., Ozawa, Y., Endo, H., Akiyoshi, K., Shibayama, M., 2009. Interaction of nanogel with cyclodextrin or protein: study by dynamic light scattering and small-angle neutron scattering. Polymer 50, 541–546.

Inoue, M., Hashizaki, K., Taguchi, H., Saito, Y., 2009. Preparation and characterization of n-alkane/water emulsion stabilized by cyclodextrin. J. Oleo Sci. 58, 85–90.

Irie, E., Uekama, K., 1997. Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation. J. Pharm. Sci. 86, 147–162.

Jansook, P., Stefánsson, E., Thorsteinsdóttir, M., Sigurdsson, B.B., Kristjánsdóttir, S.S., Bas, J.F., Sigurdsson, H.H., Loftsson, T., 2010. Cyclodextrin solubilization of carbonic anhydrase inhibitor drugs: formulation of dorzolamide eye drop microparticle suspension. Eur. J. Pharm. Biopharm. 76, 208–214.

Jensen, L.B., Griger, J., Naeye, B., Varkouhi, A.K., Raemdonck, K., Schiffelers, R., Lammers, T., Storm, G., Smedt, S.C., Sproat, B.S., Nielsen, H.M., Foged, C., 2012. Comparison of polymeric siRNA nanocarriers in a murine LPS-activated macrophage cell line: gene silencing, toxicity and off-target gene expression. Pharmaceut. Res. 29, 669–682.

Johnson, J.A., Turro, N.J., Koberstein, J.T., Mark, J.E., 2010. Some hydrogels having novel molecular structures. Prog. Pol. Sci. 35, 332–337.

Kabanov, A.V., Gendelman, H.E., 2007. Nanomedicine in the diagnosis and therapy of neurodegenerative disorders. Prog. Pol. Sci. 32, 1054–1082.

Kabanov, A.V., Vinogradov, S.V., 2009. Nanogels as pharmaceutical carriers: finite networks of infinite capabilities. Angew. Chem., Int. Ed. 48, 5418–5429.

Kettel, M.J., Groll, J., Schaefer, K., Moeller, M., 2009. Complexation of permethrin in cyclodextrin containing nanogel and its application on textiles. In: Proceedings of the Aachen-Dresden International Textile Conference, 3rd November 26–27, 2009, Aachen, Germany, kettel1/1–kettel1/13.

Kettel, M.J., Dierkes, F., Schaefer, K., Moeller, M., Pich, A., 2011. Aqueous nanogels modified with cyclodextrin. Polymer 52, 1917–1924.

Komiyama, M., Hirai, H., 1987. Preparation of immobilized b-cyclodextrins by use of alkanediol diglycidyl ethers as cross-linking agents and their guest binding abilities. Polym. J. 19, 773–775.

Kreuter, J., 1994. Nanoparticles. In: Kreuter, J. (Ed.), Colloidal Drug Delivery Systems. Marcel Dekker Inc., New York, pp. 219–342.

Kriegel, C., Amiji, M.M., 2011. Dual TNF-α/cyclin d1 gene silencing with an oral polymeric microparticle system as a novel strategy for the treatment of inflammatory bowel disease. Clin. Trans. Gastroenterol. 2, e2.

Kumar, S.A., Khan, M.I., 2010. Heterofunctional nanomaterials: fabrication, properties and applications in nanobiotechnology. J. Nanosci. Nanotechnol. 10, 4124–4134.

Li, J., Loh, X.J., 2008. Cyclodextrin-based supramolecular architectures: syntheses, structures, and applications for drug and gene delivery. Adv. Drug Deliv. Rev. 60, 1000–1017.

Liu, Y.Y., Fan, X.D., Kang, T., Sun, L., 2004. A cyclodextrin microgel for controlled release driven by inclusion effects. Macromol. Rapid Commun. 25, 1912–1916.

Liu, Y.-Y., Yu, Y., Tian, W., Sun, L., Fan, X.-D., 2009. Preparation and properties of cyclodextrin/PNIPAm microgels. Macromol. Biosci. 9, 525–534.

Loftsson, T., Duchene, D., 2007. Cyclodextrins and their pharmaceutical applications. Int. J. Pharm. 329, 1–11.

Loftsson, T., Brewster, M.E., 2010. Pharmaceutical applications of cyclodextrins: basic science and product development. J. Pharm. Pharmacol. 62, 1607–1621.

Loftsson, T., Brewster, M.E., 2011. Pharmaceutical applications of cyclodextrins: effects on drug permeation through biological membranes. J. Pharm. Pharmacol. 63, 1119–1135.

Lopez-Montero, E., Santos, J.-F.R.d., Torres-Labandeira, J.J., Concheiro, A., Alvarez-Lorenzo, C., 2009. Sertaconazole-loaded cyclodextrin—polysaccharide hydrogels as antifungal devices. Open Drug Deliv. J. 3, 1–9.

Lu, D., Yang, L., Zhou, T., Lei, Z., 2008. Synthesis, characterization and properties of biodegradable polylactic acid-b-cyclodextrin cross-linked copolymer microgels. Eur. Polym. J. 44, 2140–2145.

Ma, M., Li, D.Q., 1999. New organic nanoporous polymers and their inclusion complexes. Chem. Mater. 11, 872–874.

Marui, Y., Kida, T., Akashi, M., 2010. Facile morphological control of cyclodextrin nano- and microstructures and their unique organogelation ability. Chem. Mater. 22, 282–284.

Mele, A., Castiglione, F., Malpezzi, L., Ganazzoli, F., Raffaini, G., Trotta, F., Rossi, B., Fontana, A., Giunchi, G., 2011. HR MAS NMR, powder XRD and Raman spectroscopy study of inclusion phenomena in bCD nanosponges. J. Incl. Phenom. Macro. 69, 403–409.

Messner, M., Kurkov, S.V., Jansook, P., Loftsson, T., 2010. Self-assembled cyclodextrin aggregates and nanoparticles. Int. J. Pharm. 387, 199–208.

Mocanu, G., Mihai, D., LeCerf, D., Picton, L., Moscovici, M., 2009. Cyclodextrin-anionic polysaccharide hydrogels: synthesis, characterization, and interaction with some organic molecules (water pollutants, drugs, proteins). J. Appl. Polym. Sci. 112, 1175–1183.

Moghaddam, F.A., Atyabi, F., Dinarvand, R., 2009. Preparation and in vitro evaluation of mucoadhesion and permeation enhancement of thiolated chitosan-pHEMA core–shell nanoparticles. Nanomed. Nanotechnol. 5, 208–215.

Morimoto, N., Endo, T., Iwasaki, Y., Akiyoshi, K., 2005a. Design of hybrid hydrogels with self-assembled nanogels as crosslinkers: interaction with proteins and chaperone-like activity. Biomacromolecules 6, 1829–1834.

Morimoto, N., Endo, T., Ohtomi, M., Iwasaki, Y., Akiyoshi, K., 2005b. Hybrid nanogels with physical and chemical cross-linking structures as nanocarriers. Macromol. Biosci. 5, 710–716.

Moya-Ortega, M.D., Alvarez-Lorenzo, C., Sigurdsson, H.H., Concheiro, A., Loftsson, T., 2010. γ-Cyclodextrin hydrogels and semi-interpenetrating networks for sustained delivery of dexamethasone. Carbohydr. Polym. 80, 900–907.

Moya-Ortega, M.D., Alvarez-Lorenzo, C., Sigurdsson, H.H., Concheiro, A., Loftsson, T., 2012. Cross-linked hydroxypropyl-β-cyclodextrin and γ-cyclodextrin nanogels for drug delivery: physicochemical and loading/release properties. Carbohydr. Polym. 87, 2344–2351.

Nielsen, A.L., Steffensen, K., Larsen, K.L., 2009. Self-assembling microparticles with controllable disruption properties based on cyclodextrin interactions. Colloids Surf. B 73, 267–275.

Nukolova, N.V., Oberoi, H.S., Cohen, S.M., Kabanov, A.V., Bronich, T.K., 2011. Folate-decorated nanogels for targeted therapy of ovarian cancer. Biomaterials 32, 5417–5426.

O'Donnell, K.P., Iii, R.O.W., 2011. Nanoparticulate systems for oral drug delivery to the colon. Int. J. Nanotechnol. 8, 4–20.

Oh, J., Drumright, R., Siegwart, D., Matyjaszewski, K., 2008. The development of microgels/nanogels for drug delivery applications. Prog. Polym. Sci. 33, 448–477.

Oh, J.K., Lee, D.I., Park, J.M., 2009. Biopolymer-based microgels/nanogels for drug delivery applications. Prog. Polym. Sci. 34, 1261–1282.

Oh, J.K., 2010. Engineering of nanometer-sized cross-linked hydrogels for biomedical applications. Can. J. Chem. 88, 173–184.

Osman, S., Brandl, F., Zayed, G., Tessmar, J., Gopferich, A., 2011. Cyclodextrin based hydrogels: inclusion complex formation and micellization of adamantane and cholesterol grafted polymers. Polymer 52, 4806–4812.

Ortiz-Mellet, C., Garcia-Fernandez, J.M., Benito, J.M., 2011. Cyclodextrin-based gene delivery systems. Chem. Soc. Rev. 40, 1586–1608.

Otero-Espinar, F.J., Torres-Labandeira, J.J., Alvarez-Lorenzo, C., Blanco-Méndez, J., 2010. Cyclodextrins in drug delivery systems. J. Drug Deliv. Sci. Technol. 20, 289–301.

Pariot, N., Edwards-Levy, F., Andry, M.C., Levy, M.C., 2000. Cross-linked b-cyclodextrin microcapsules: preparation and properties. Int. J. Pharm. Sci. 211, 19–27.

Pariot, N., Edwards-Levy, F., Andry, M.C., Levy, M.C., 2002. Cross-linked b-cyclodextrin microcapsules. II. Retarding effect on drug release through semi-permeable membranes. Int. J. Pharm. Sci. 232, 175–181.

Pasetto, P., Flavin, K., Resmini, M., 2009. Simple spectroscopic method for titration of binding sites in molecularly imprinted nanogels with hydrolase activity. Biosens. Bioelectron. 25, 572–578.

Patel, H.A., Patel, J.K., 2010. Nanogel as a controlled drug delivery system. Int. J. Pharm. Sci. Rev. Res. 4, 37–41.

Peppas, N.A., Bures, P., Leobandung, W., Ichikawa, H., 2000. Hydrogels in pharmaceutical formulations. Eur. J. Pharm. Biopharm. 50, 27–46.

Quintanar-Guerrero, D., Ganem-Quintanar, A., Nava-Arzaluz, M.G., Piñón-Segundo, E., 2009. Silica xerogels as pharmaceutical drug carriers. Expert Opin. Drug Deliv. 6, 485–498.

Ramteke, S., Ganesh, N., Bhattacharya, S., Jain, N.K., 2008. Triple therapy-based targeted nanoparticles for the treatment of *Helicobacter pylori*. J. Drug Target 16, 694–705.

Ravaine, V.r., Ancla, C., Catargi, B., 2008. Chemically controlled closed-loop insulin delivery. J. Control. Release 132, 2–11.

Rekharsky, M.V., Inoue, Y., 1998. Complexation thermodynamics of cyclodextrins. Chem. Rev. 98, 1875–1918.

Rhee, Y.-S., Mansour, H.M., 2011. Nanopharmaceuticals. I: Nanocarrier systems in drug delivery. Int. J. Nanotechnol. 8, 84–114.

Rodriguez-Tenreiro, C., Alvarez-Lorenzo, C., Rodriguez-Perez, A., Concheiro, A., Torres-Labandeira, J.J., 2006. New cyclodextrin hydrogels cross-linked with diglycidylethers with a high drug loading and controlled release ability. Pharmaceut. Res. 23, 121–130.

Rodriguez-Tenreiro, C., Alvarez-Lorenzo, C., Rodriguez-Perez, A., Concheiro, A., Torres-Labandeira, J.J., 2007a. Estradiol sustained release from high affinity cyclodextrin hydrogels. Eur. J. Pharm. Biopharm. 66, 55–62.

Rodriguez-Tenreiro, C., Diez-Bueno, L., Concheiro, A., Torres-Labandeira, J.J., Alvarez-Lorenzo, C., 2007b. Cyclodextrin/carbopol micro-scale interpenetrating networks (ms-IPNs) for drug delivery. J. Control. Release 123, 56–66.

Roux, M., Perly, B., Djedaini-Pilard, F., 2007. Self-assemblies of amphiphilic cyclodextrins. Eur. Biophys. J. 36, 861–867.

Ruggiero, C., Pastorino, L., Herrera, O.L., 2010. Nanotechnology based targeted drug delivery. In: Conference Proceedings of the International Conference of IEEE Engineering in Medicine and Biology Society, 2010, pp. 3731–3732.

Saboktakin, M.R., Tabatabaie, R.M., Maharramov, A., Ramazanov, M.A., 2011. Development and in vitro evaluation of thiolated chitosan—poly(methacrylic acid) nanoparticles as a local mucoadhesive delivery system. Int. J. Biol. Macromol. 48, 403–407.

Sahoo, S., Kumar, N., Bhattacharya, C., Sagiri, S.S., Jain, K., Pal, K., Ray, S.S., Nayak, B., 2011. Organogels: properties and applications in drug delivery. Des. Monomers Polym. 14, 95–108.

Samah, N.A., Williams, N., Heard, C.M., 2010. Nanogel particulates located within diffusion cell receptor phases following topical application demonstrates uptake into and migration across skin. Int. J. Pharm. 401, 72–78.

Sasaki, Y., Asayama, W., Niwa, T., Sawada, S.-i., Ueda, T., Taguchi, H., Akiyoshi, K., 2011. Amphiphilic polysaccharide nanogels as artificial chaperones in cell-free protein synthesis. Macromol. Biosci. 11, 814–820.

Sawada, S.-i., Nomura, Y., Aoyama, Y., Akiyoshi, K., 2006. Heat shock protein-like activity of a nanogel artificial chaperone for citrate synthase. J. Bioact. Compat. Polym. 21, 487–501.

Sawada, S.-i., Sasaki, Y., Nomura, Y., Akiyoshi, K., 2011. Cyclodextrin-responsive nanogel as an artificial chaperone for horseradish peroxidase. Colloid Polym. Sci. 289, 685–691.

Schneiderman, E., Stalcup, A.M., 2000. Cyclodextrins: a versatile tool in separation science. J. Chromatogr. B 745, 83–102.

Shen, W., Chang, Y., Liu, G., Wang, H., Cao, A., An, Z., 2011. Biocompatible, antifouling, and thermosensitive core–shell nanogels synthesized by RAFT aqueous dispersion polymerization. Macromolecules 44, 2524–2530.

Sun, H., Yu, J., Gong, P., Xu, D., Zhang, C., Yao, S., 2005. Novel core–shell magnetic nanogels synthesized in an emulsion-free aqueous system under UV irradiation for targeted radiopharmaceutical applications. J. Magn. Magn. Mater. 294, 273–280.

Swaminathan, S., Vavia, P.R., Trotta, F., Torne, S., 2007. Formulation of beta-cyclodextrin based nanosponges of itraconazole. J. Incl. Phenom. Macro. 57, 89–94.

Swaminathan, S., Pastero, L., Serpe, L., Trotta, F., Vavia, P., Aquilano, D., Trotta, M., Zara, G., Cavalli, R., 2010. Cyclodextrin-based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. Eur. J. Pharm. Biopharm. 74, 193–201.

Szejtli, J., 2004. Past, present, and future of cyclodextrin research. Pure Appl. Chem. 76, 1825–1845.

Takahashi, H., Sawada, S.-i., Akiyoshi, K., 2011. Amphiphilic polysaccharide nanoballs: a new building block for nanogel biomedical engineering and artificial chaperones. ACS Nano 5, 337–345.

Tanaka, T., 1981. Gels. Sci. Am. 244, 124–138.

Thorne, J.B., Vine, G.J., Snowden, M.J., 2011. Microgel applications and commercial considerations. Colloid Polym. Sci. 289, 625–646.

Tonelli, A.E., 2008. Cyclodextrins as a means to nanostructure and functionalize polymers. J. Incl. Phenom. Macro. 60, 197–202.

Trotta, F., Cavalli, R., 2009. Characterization and applications of new hyper-cross-linked cyclodextrins. Compos. Interface 16, 39–48.

Trotta, F., Cavalli, R., Martina, K., Biasizzo, M., Vitillo, J., Bordiga, S., Vavia, P., Ansari, K., 2011. Cyclodextrin nanosponges as effective gas carriers. J. Incl. Phenom. Macro. 71, 189–194.

Uekama, K., Hirayama, F., Irie, T., 1998. Cyclodextrin drug carrier systems. Chem. Rev. 98, 2045–2076.

van de Manakker, F., Braeckmans, K., el Morabit, N., De Smedt, S.C., van Nostrum, C.F., Hennink, W.E., 2009. Protein release behavior of self-assembled PEG-beta-cyclodextrin/PEG-cholesterol hydrogels. Adv. Funct. Mater. 19, 2992–3001.

Van, V., Dubruel, P., Schacht, E., 2011. Biopolymer-based hydrogels as scaffolds for tissue engineering applications. A review. Biomacromolecules 12, 1387–1408.

Vemula, V., 2010. Solubility enhancement techniques. Int. J. Pharm. Sci. Rev. Res., 5.

Vinogradov, S.V., Bronich, T.K., Kabanov, A.V., 2002. Nanosized cationic hydrogels for drug delivery: preparation: properties and interactions with cells. Adv. Drug Deliv. Rev. 54, 135–147.

Vintiloiu, A., Leroux, J.-C., 2008. Organogels and their use in drug delivery—a review. J. Control. Release 125, 179–192.

Wang, Q., Xu, H., Yang, X., Yang, Y., 2008. Drug release behavior from in situ gelatinized thermosensitive nanogel aqueous dispersions. Int. J. Pharm. 361, 189–193.

Wang, N.X., von Recum, H.A., 2011. Affinity-based drug delivery. Macromol. Biosci. 11, 321–332.

Wenz, G., Weickenmeier, M., Huff, J., 2000. Association thickener by host–guest interaction of b-cyclodextrin polymers and guest polymers. ACS Sym. Ser., 765.

Wintgens, V., Charles, M., Allouache, F., Amiel, C., 2005. Triggering the thermosensitive properties of hydrophobically modified poly(N-isopropylacrylamide) by complexation with cyclodextrin polymers. Macromol. Chem. Phys. 206, 1853–1861.

Wintgens, V., Daoud-Mahammed, S., Gref, R., Bouteiller, L., Amiel, C., 2008. Aqueous polysaccharide associations mediated by b-cyclodextrin polymers. Biomacromolecules 9, 1434–1442.

Wintgens, V., Nielsen, T.T., Larsen, K.L., Amiel, C., 2011. Size-controlled nanoassemblies based on cyclodextrin-modified dextrans. Macromol. Biosci. 11, 1254–1263.

Wong, J.E., Mueller, C.B., Diez-Pascual, A.M., Richtering, W., 2009. Study of layer-by-layer films on thermoresponsive nanogels using temperature-controlled dual-focus fluorescence correlation spectroscopy. J. Phys. Chem. B 113, 15907–15913.

Wouessidjewe, D., Skiba, M., LeroyLechat, F., LemosSenna, E., Puisieux, F., Duchene, D., 1996. A new concept in drug delivery based on skirt-shaped cyclodextrin aggregates—present state and future prospects. STP Pharma Sci. 6, 21–28.

Wu, W., Aiello, M., Zhou, T., Berliner, A., Banerjee, P., Zhou, S., 2010. In situ immobilization of quantum dots in polysaccharide-based nanogels for integration of optical pH-sensing, tumor cell imaging, and drug delivery. Biomaterials 31, 3023–3031.

Xing, Z., Wang, C., Yan, J., Zhang, L., Li, L., Zha, L., 2011. Dual stimuli responsive hollow nanogels with IPN structure for temperature controlling drug loading and pH triggering drug release. Soft Matter 7, 7992–7997.

Yadav, N., Morris, G., Harding, S.E., Ang, S., Adams, G.G., 2009. Various non-injectable delivery systems for the treatment of diabetes mellitus. Endocr. Metab. Immune Disord. Drug Targets 9, 1–13.

Zha, L., Banik, B., Alexis, F., 2011. Stimulus responsive nanogels for drug delivery. Soft Matter 7, 5908–5916.

Zhang, J.T., Xue, Y.N., Gao, F.Z., Huang, S.W., Zhuo, R.X., 2008. Preparation of temperature-sensitive poly(N-isopropylacrylamide)/β-cyclodextrin-grafted polyethylenimine hydrogels for drug delivery. J. Appl. Polym. Sci. 108, 3031–3037.