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pH-Responsive Microgels: Promising Carriers for Controlled Drug Delivery

Zermina Rashid

Abstract

The development of a new drug entity is a time-consuming and an expensive process; therefore, the design of new drug delivery systems for an existing drug molecule can significantly improve the safety and efficacy of the drug with improved patient compliance. In recent years, polymeric carriers have been widely investigated and are playing an important role in controlled drug delivery, biomedical applications, and tissue engineering. Microgels are microscopic hydrogels and have attracted much attention as vehicle for drug delivery. Stimuli-responsive MGs are smart drug delivery carriers and have the capability to incorporate and release their host molecules in response to stimuli (pH, ionic strength, and temperature), for targeted drug delivery. Of the many stimuli, alteration in pH is markedly fascinating because of the availability of pH gradients admissible for drug targeting. For example, pH gradients between normal tissues and some pathological sites between the extracellular environment and some cellular compartments, and along the gastrointestinal (GI) tract, are well characterized. Microgels can be fabricated through different methods.

Keywords: controlled drug delivery, microgels, stimuli-responsive microgels, targeted delivery, pharmaceutical applications, types, methods of formulation

1. Introduction

Among the available biomaterials, hydrogels, three-dimensional polymeric networks capable of imbibing large amounts of water or biological fluids, have proved their value in diverse biomedical applications [1–3]. In addition to the swelling property of the hydrogels, their biocompatibility, good mechanical properties, tunable chemical structure, and three-dimensional physical structure have made them one of the promising class of materials for tissue engineering [4, 5], pharmaceutical applications [6, 7], and biomaterials science [8]. In recent years, with the advancements in technology, interest in microscopic (microgels) and nanoscopic hydrogels (nanogels) has increased [9, 10].

Microgels, hydrogel particles formed by physical or chemical cross-linking of polymer networks in microscale size [11], have exceptional properties like large surface area, tunable size from micrometers to nanometers, ease in synthesis, control over particle size, responsiveness to environmental factors, and an interior network for the incorporation of therapeutic agents [12, 13].

2. Stimuli-responsive microgels

Stimuli-responsive properties can be incorporated into gels. Microgels may respond to a number of stimuli like pH, ionic strength, specific ions, external fields, and temperature [14–17]. Such DDSs are designed whether to target tissues, to reach specific intracellular locations, or to promote drug release [18]. Brief overview of the types of stimuli-responsive microgels is given below.

2.1 Types of stimuli-responsive microgels

2.1.1 *Microgels responsive to temperature*

Several classes of polymers, including poly(N-isopropylacrylamide) and poly(ethylene glycol), demonstrate swelling/deswelling changes in response to temperature [19, 20]. With increase in temperature, these systems have reduced solvency and pronounced deswelling. Nolan et al. [21] demonstrated higher insulin release from poly(N-isopropyl acrylamide), with increasing temperature. Temperature-dependent aggregation property of such thermosensitive microgel systems may also be utilized in drug delivery, e.g., at elevated temperature; due to aggregation of PNIPAM microgels particle inside the cancerous cell, toxicity was observed [22].

2.1.2 *Microgels responsive to particular compounds*

Microgels can be designed to be triggered by the concentration of particular compounds, like insulin [23, 24]. For example, insulin containing poly(diethyl aminoethyl methacrylate) microgels conjugated with glucose oxidase [25]. The enzymatic conversion of glucose to gluconic acid causes pH-responsive swelling of the polymer network leading to release of insulin. In another study Sui et al. [26] reported trifluoperazine triggered volume transition in calmodulin-based hydrogels.

2.1.3 *Microgels responsive to external fields*

Microgel systems may also respond to external fields (ultrasound, light, and magnetic fields). Patnaik et al. [27] investigated photoresponsive drug release in azo-dextran nanogels based on (trans-cis) photoisomerization of an azobenzene present in the cross-linker. For this system, the release of drug was slower for trans-configuration while faster for cis-configuration.

Metal nanoparticles may be used for optical or magnetic heating. When temperature-responsive microgels are combined with metals, heat induced by the external fields may result in deswelling, leading to release of the absorbed drugs. Using this perspective, Wong et al. [28] explored Fe-containing PNIPAM microgels. The microgels showed ability to manifest local heating attributed to an oscillating magnetic field. With increasing temperature microgels deswelled. Similar kind of triggering was also manifested in other studies, where light-originated heating of absorbed metal nanoparticles was used to induce local heat, provoking permeability variations in temperature-responsive polymers [29–31].

2.1.4 *Microgels responsive to degradation*

Microgel degradation in response to stimuli offers another way of controlled drug delivery [32, 33]. Such systems are commonly based on biodegradable microgels, occasionally surrounded by a shell impermeable to the drug. In later case, microgel degradation causes increased osmotic pressure, finally breaking the

shell and drug release. Examples include dextran microgels coated by different polyelectrolyte multilayer systems [34] and lipid-coated microgels for the release of doxorubicin [35].

Biodegradable acrylamide/bisacrylamide microgels containing acetal linkers were investigated by Murthy et al. [36]. Biodegradation stimulated by low pH, resulting from acid-catalyzed hydrolysis of acetal linkage, was responsible for drug release. Similarly, Bromberg et al. [37] investigated poly (acrylic acid)-containing microgels cross-linked with disulfide groups. The chemical reduction of the disulfide bonds manifested the swelling of these systems.

2.1.5 Microgels responsive to pH

pH-responsive microgels represent one of the major approaches for microgel-based delivery of biomacromolecular drugs. Of the many stimuli, alteration in pH is markedly fascinating because of the availability of pH gradients admissible for drug targeting. For example, pH gradients between normal tissues and some pathological sites, between the extracellular environment and some cellular compartments, and along the gastrointestinal (GI) tract are well characterized [38]. Orally administered drug encounters a pH gradient as it move from the stomach (pH 1–2, fasted state) to the duodenum (pH of about 6) and along the jejunum and ileum (pH 6–7.5) [39, 40]; therefore, attempts to avoid deterioration of drug and/or to promote intestinal absorption by exploiting this pH gradient is promising. pH-responsive polymeric networks, hence, have been extensively studied for the design of efficient carriers for drug delivery [41].

pH-responsive polymers are generally fabricated by inserting pendant acidic or basic functional groups to the backbone of the polymer. These functional groups either accept or release protons in response to appropriate pH and changes in the ionic strength of the surrounding aqueous media [42]. Polymers with acidic groups are unexpanded at low pH values, since the acidic groups are protonated and unionized. While increasing pH acidic groups are ionized, the resulting negatively charged polymer expands. The opposite behavior will be observed in the case of polybasic polymers [43, 44]. These systems can form polyelectrolytes with water, and microgels fabricated from weak polyelectrolytes demonstrate a pH-responsive volume phase changes. On the basis of the framework of polyelectrolyte, pH-responsive microgels can be classified as cationic, basic, or amphoteric. For instance, poly(acrylic acid) and polyethylenimine are weak polyacid and a poly-base, respectively.

3. Synthesis of microgels

Methods used for the synthesis of microgels can be divided into two major ideas:

- (a) The synthesis of microgels in homogeneous phase
- (b) The synthesis of microgels in heterophase

3.1 Synthesis of microgels in homogeneous phase

The first approach is based on the investigations of Staudinger [45], who prepared inter- and intramolecularly cross-linked microgels by free radical cross-linking copolymerization of monomers in dilute solutions. However, the resulting internal structure of microgels was not well established, but investigations performed on these systems were key step to understand the process of gel formation [46].

Other techniques include coacervation and desolvation. In both techniques phase separation of readily formed polymers takes place, resulting in micro-/nanoparticles which are then cross-linked. **Figure 1** represents typical steps involved in coacervation method. Phase separation is usually induced by changing temperature, adding salt, nonsolvent addition, non-compatible polymer addition, or polymer-polymer interaction. The resulting coacervate (polymer droplet) is then solidified and stabilized forming microgel particle. This technique is usually employed in synthesis of microgels from biopolymers such as (modified) gelatin or chitosan. For example, pH-responsive chitosan nanoparticles were synthesized by complex coacervation [47] and two-step desolvation route was involved in synthesis of gelatin nanoparticles [48].

3.2 Synthesis of microgel in heterogeneous phase

Heterophase copolymerization of monomers with cross-linking agents in aqueous solution can be distinguished as:

- Dispersion/precipitation polymerization
- Miniemulsion polymerization
- Microemulsion polymerization

3.2.1 Dispersion/precipitation polymerization

In this technique, polymerization generally starts in a homogenous solution of monomers and cross-linkers [49, 50]; as polymerization progresses, the monomer and the developed oligomers remain soluble; after achieving the critical length phase, separation takes place by enthalpic precipitation leading to particle nuclei formation. The nuclei aggregate to form large particles that carry on growing resulting into microgel formation. In dispersion polymerization stabilizers can be added to regulate the particle size and to keep particles in narrow size distribution [51]. The described method is schematically presented in **Figure 2**.

Dispersion polymerization technique was employed for the synthesis of pH-sensitive poly((2-dimethylamino)ethyl methacrylate) microgels with diameter of about 100–200 nm in dry state [52]. The microgels exhibited volume phase change at about pH 8, with 32 times decrease in diameter. Dispersion polymerization was involved in the preparation of hydrophilic microparticles of poly(2-hydroxyethyl methacrylate) [53].

Duracher et al. [54] synthesized thermoresponsive microgels by precipitation polymerization of N-isopropylmethacrylamide. The prepared microgels were

Figure 1.
Schematic presentation of coacervation technique.

Figure 2. Precipitation polymerization (a) initiation of polymerization and chain growth, (b) precipitation and nuclei formation, (c) particle growth, and (d) microgels.

found to be temperature sensitive. Moreover, with the modifications in the synthetic protocol, more complex microgel structures can be synthesized. Examples include temperature- and pH-sensitive microgels prepared by copolymerization of N-isopropylmethacrylamide with acrylic acid [55], vinyl acetic acid [56, 57], or 2-aminoethyl methacrylate hydrochloride [58].

One approach to synthesize complex structures, e.g., core-shell microgels or hollow microgels, involves polymerization of different monomers and/or already formed seed particle. Core-shell microgels have structurally separated zones of different polymers. Zhou et al. [59] synthesized temperature sensitive microgels based on oligo(ethylene glycol). The microgels were stable across the important physiological temperature range with adjustable volume phase changes.

3.2.2 Synthesis of microgels in microemulsions

In general, microemulsions can be prepared as direct oil-in-water (O/W) or inverse water-in-oil (W/O) emulsions. The inverse emulsions are widely investigated for the formulation of hydrogel nanoparticles. In this approach, dispersed phase consists of either monomer having ability to polymerize or prepolymers with ability of cross-linking dissolved in water is added to a continuous phase of organic medium having large amount of oil-soluble surfactant. The mixture is stirred to achieve thermodynamically stable microemulsion. Synthesis of microgels takes place inside the droplets, e.g., via free radical polymerization. Initiation of polymerization takes place either from the interior of droplets or from the continuous phase [60]. **Figure 3** illustrates the microgel synthesis in W/O emulsion.

Shen et al. [61] synthesized poly(acrylamide-co-acrylic acid) microgels by polymerization in inverse microemulsion. The effect of chemical constitution on size, morphology, swelling behavior, thermal properties, and pH-sensitivity was explored. The size of p(AM-co-AA) microgels was larger in comparison to PAM microgels. The microgels exhibited pH-responsive behavior and have higher swelling ratio, with an increase in acrylic acid content.

In another study, microemulsion polymerization phenomenon was employed for the copolymerization of methacrylic acid and 2-ethylhexyl acrylate to demonstrate colon-specific delivery of drug. An anticancer drug (5-fluorouracil) was entrapped inside the copolymer through solvent evaporation method. In vitro drug release studies performed at different pH levels revealed pH-dependent release of 5-fluorouracil in a sustained manner [62].

3.2.3 Microgel synthesis in miniemulsions

Miniemulsions in general are kinetically stable emulsions; considerably less surfactant is required for the droplet stabilization [63]. This approach is versatile

Figure 3.
Illustration of microgel preparation via inverse emulsion polymerization.

and allows utilization of different monomers, functional compounds incorporation, and the accurate adaptation of droplets and particles size [64, 65]. In general, high deformation forces are applied to pre-emulsion of droplet leading to uniform distribution of well-defined nanodroplets (50–500 nm). The surfactant present in the system obstructs the coalescence of these nanodroplets; in addition, the costabilizer added to dispersed phase prevents Ostwald ripening leading to kinetically stable miniemulsion [66].

Miniemulsions can be classified as direct (oil-in-water) or inverse (water-in-oil) systems. Oil-in-water miniemulsification is a well-established approach for the polymerization of hydrophobic monomers for the formulation of polymeric latexes [63]; on the other hand, the inverse method involves diverse synthetic pathways for the formation of nanohydrogels [67]. One approach involves the free radical copolymerization of hydrophilic monomers with cross-linking agents in dispersed droplets

Figure 4.
Schematic illustration of radical cross-linking in inverse miniemulsion.

of either aqueous solutions of these compounds or their mixture without additional solvent. The monomers must be immiscible with the continuous phase. Examples include the formation of polyacrylamide (PAAm)- [68] and PHEMA-based [65] microgels. **Figure 4** schematically represents the described synthetic pathway.

Another approach is cross-linking of preformed polymers in inverse miniemulsion. In this method mixture of two W/O emulsions (A and B) are ultrasonicated. Emulsion A constitutes the solution of already formed polymer, and emulsion B constitutes solution of cross-linker. Ultrasonication leads to mixing of the components of both emulsions, inducing the cross-linking reaction. This method has been employed for the synthesis of covalently cross-linked gelatin microgels [69]. In another study, temperature-responsive nanogels poly(N-isopropylacrylamide) nanogels were fabricated by nanoemulsion polymerization as smart delivery systems [70].

4. Pharmaceutical applications of pH-responsive microgels

pH-responsive microgels have demonstrated a number of medical applications (**Table 1**). Few examples from the literature are demonstrated here.

pH-responsive p(NIPAAm/AA) microgels were fabricated for transferrin-based targeting of cancer [71]. These microgels were able for specific delivery to human cervical carcinoma cell line (HeLa) cells. In another study methacrylic-based copolymeric pH-sensitive nanogels were prepared for targeted delivery of 5-fluorouracil to the colon [62]. Recently, Eswaramma et al. [72] developed pH-sensitive interpenetrating polymer network (IPN) microgels of chitosan and guar gum-g-poly((2-dimethylamino)ethyl methacrylate) (GG-g-PDMAEMA) and treated as responsive drug carriers for an anticancer agent, 5-fluorouracil (5-FU). The microgels showed encapsulation efficiency up to 81%, and the release kinetics showed pH-dependent drug release with an excellent controlled release pattern for 5-FU over a period of more than 24 h.

Dadsetan et al. [73] used a copolymer of oligo(poly(ethylene glycol) fumarate) (OPF) and sodium methacrylate (SMA) to fabricate the pH-responsive microgels for the delivery of doxorubicin (DOX) in order to optimize its antitumor activity

Polymers	Polymeric DDSs	Drug	Application	Reference
GG-g-PDMAEMA	IPN-Microgels	5 fluorouracil	Antitumor activity	[72]
OPF-SMA microgels	Microgels	Doxorubicin	Antitumor activity	[73]
MEMA-co-IA	Microgels	Esomeprazole	Intestinal delivery	[76]
P(MMA-g-EG)	Microgels	Insulin	Oral peptide delivery	[82]
P(AM)-g-carrageenan and sodium alginate	Hydrogel beads	Ketoprofen	For colon-targeted delivery	[83]
Methacrylate derivatives of dextran and concanavalin	Microgels	Insulin	Self-regulated insulin delivery	[84]
Alg and chemically modified carboxymethyl CS	Microgels	Protein drug	For oral delivery	[85]

Table 1.
Examples of various applications of microgels as drug delivery carriers.

while minimizing its systemic toxicity. The resulting microgels exhibited sensitivity to the pH and ionic strength of the surrounding environment and demonstrated that DOX was efficiently loaded into the microgels and released in a controlled fashion via an ion exchange mechanism. The antitumor activity of the released DOX was assessed using a human chordoma cell line revealed that OPF-SMA microgels prolonged the cell-killing effect of DOX.

Tripahi et al. [74] developed a pH-sensitive intragastric floating polymer microgel beads containing clarithromycin for the treatment of peptic ulcer. The optimized formulation successfully maintained minimum inhibition concentration of clarithromycin at the infection site and potentially allowed penetration of the drug inside the mucus gel. Varma et al. [75] have chemically modified guar gum (GG) as a pH-sensitive copolymer and formulated intestinal-targeting esomeprazole magnesium (ESO) nanoparticles (NPs). Polyacrylamide-grafted guar gum copolymer was synthesized by free radical polymerization, and ESO-loaded pH-sensitive NPs were prepared by nanoemulsification polymer cross-linking method. In vitro release studies showed pH-dependent drug release. The pH-sensitive NPs resisted drug release in acidic pH and delayed the release in alkaline environment.

In another study novel pH-responsive poly(methoxyethyl metacrylate-co-itaconic acid) microgels were fabricated and evaluated for controlled and extended delivery of model acid labile drug (esomeprazole). The designed microgels successfully protected the drug from acidic environment of the stomach, with potential intestinal drug delivery over an extended period of time. Thus, suggesting p(MEMA-co-IA) micro-hydrogels as good candidate of an orally administrated site-specific and controlled drug delivery system, such as proton-pump inhibitors, proteins, and peptides [76]. In similar studies p(hydroxyethyl methacrylate-co-itaconic acid) microgels, poly(2-ethyl hexyl acrylate-co-IA) microgels, and poly(butyl acrylate-co-itaconic acid) microgels showed pH-responsive swelling and drug release behavior with maximum release at pH 7.4 and negligible release at pH 1.2 suggesting the potential use of these drug delivery system for oral intestinal delivery of therapeutics [77–79].

A novel 5-aminosalicylic acid (5-ASA)-loaded pH-sensitive poly(methoxy ethylene glycol-caprolactone-co-methacrylic acid-co-poly(ethylene glycol) dimethacrylate) microgels were prepared for treatment of ulcerative colitis. The microgels were found to be shrunk at pH 1.2 and expanded at pH 7.4. Safety evaluation of microgels was conducted by maximum tolerated dose (MTD) method. The 5-ASA/microgels were used to treat ulcerative colitis in mice, and free 5-ASA was used as positive control. It was found that 5-ASA has good efficacy for treating ulcerative colitis, and microgels entrapping 5-ASA could significantly enhance the colon targeting to improve its efficacy [80].

Xua et al. [81] fabricated novel biodegradable and pH-sensitive microgels based on poly(ϵ -caprolactone)-pluronic-poly(ϵ -caprolactone)-dimethacrylate, methyl acrylic acid, and poly(ethylene glycol)dimethacrylate cross-linked with N,N'-methylenebisacrylamide. Hydrophilic model drug (vitamin B12) was loaded to investigate in vitro release profile; the developed drug delivery system demonstrated pH-sensitive drug release behavior.

Lowman et al. [82] studied the use of poly(methacrylic-g-ethylene glycol) (P(MMA-g-EG)), a hydrogel microparticle that responds to a change in pH for the transport of orally administered insulin. This drug is a peptide labile to proteolytic degradation in the acidic stomach. Thus this pH-responsive carrier protected insulin in the acidic environment of the stomach as a result of the intermolecular interaction that prevented the hydrogel from swelling. But once the microparticles reached alkaline and neutral environments, namely, the intestine, the interaction that occurred previously was lost, and the pore size of the hydrogel increased, thus allowing insulin release.

5. Conclusion

This chapter has attempted the compilation of the advances in the field of stimuli-responsive microgel technology and their application in controlled release drug delivery carriers. The ultimate goal for controlled drug release is to maximize therapeutic activity while minimizing the negative side effects of the drug. In this regard, versatile micro- and nanoscale delivery approaches based on smart polymers have already been established to seek the distinct advantages in drug delivery. However, the new polymers and nanocarriers definitely require extensive consideration of toxicological and immunological issues, which are often ignored during the research phase.

Conflict of interest

There is no conflict of interest.

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