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Responsive polymers in controlled drug delivery

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ABSTRACT

This article reviews the state-of-the art in responsive polymer systems for controlled drug delivery applications. The paper describes different types of stimuli-sensitive systems and gives an account of their synthesis through methods such as group transfer polymerization, atom transfer radical polymerization and reversible addition-fragmentation chain transfer polymerization. The article also discusses classification of various drug delivery systems: diffusion controlled systems, chemically controlled systems, swelling-controlled systems and modulated release systems. A survey of the recent literature on various stimuli-responsive polymer hydrogels in controlled drug delivery is also included.

Contents

1. Introduction 1089
2. Responsive stimuli-sensitive materials 1089
   2.1. Polymer blends 1090
   2.2. Interpolymer complexes 1091
   2.3. Interpenetrating polymer networks 1091
      2.3.1. Classifications of interpenetrating networks 1091
      2.3.2. Supramolecular morphology: polymer brushes 1093
      2.3.3. Supramolecular morphology: nanoparticles 1094
   2.4. Block copolymers 1094

Abbreviations: αCDS, α-cyclodextrins; AA, acrylic acid; AMPSA, 2-acrylamide-2-methyl-1-propane sulfonic acid; ATRP, atom transfer radical polymerization; CBDS, 2-cyano-2-butyl dithiobenzoate; CDB, cumyl dithiobenzoate; CDDS, controlled drug delivery system; CPDB, 2-cyano-prop-2-yl dithibenzoate; CP, carboxy vinyl polymer; CPS, conducting polymers; CS, chitosan; DEA, 2-(dimethylamino) ethyl methacryl; DMA, 2-(dimethylamino) ethyl methacrylate; DSC, differential scanning calorimetry; EGDMA, ethylene glycol dimethacrylate; ETPFU, tetrahydrophthalimide-5-fluorouracil; FTIR, Fourier transmission infrared; GMA, glicidyl methacrylate; GTP, group transfer polymerization; HA, hyaluranate; HEA, hydroxylethyl acrylate; HEMA, 2-hydroxy ethyl methacrylate; HFA, heptadecafluorodecylacrylate; IPC, Iinterpolymer complexes; IPN, interpenetrating polymer networks; LCST, lower critical solution temperature; MA-Inulin, methacrylated inulin; MBA, *N,N′*-methylene bisacrylamide; MC, methyl cellulose; MDIC, macrodiisocyanate; ODIC, oligodiisocyanate; PAA, poly(acrylic acid); PAAm, polyacrylamide; PAMS, poly(acrylamide-co-styrene); PCL, poly(ε-caprolactone); PCLA, poly(ε-caprolacone-co-lactide); PDMAM, poly(*N,N*-dimethylacrylamide); PEG, polyethylene glycol; PEO, polyethylene oxide; PFA, pentafluoropropylacrylate; PFS, pentafluorostyrene; PHE, antipyretic phenacetin; PHEMA, poly(2-hydroxyethyl methacrylate; PLA, poly(D,L-lactic acid); PLGA, poly(D,L-lactic acid-co-glycolic acid); PLLA, poly(L-lactide); PMAA, poly(methacrylic acid); PMMA, poly(methylmethacrylate); PNIPAAm, poly-*N*-isoproply acrylamide; PnBuA, poly(*n*-butyl acrylate); PST, polystyrene; PVA, poly(vinyl alcohol); PVP, polyvinyl pyrrolidone; RAFTP, reversible addition-fragmentation transfer polymerization; SCK, shell crosslinked knedel; (SEVA-C), corn starch/ethylene-co-vinyl alcohol; SPH, superporous hydrogel; SSM, stimuli-sensitive material raft; tBuA, tert-butylacrylate; tBuMA, tert-butyl methacrylate; TC, tetracycline; THF, tetrahydrofuran; TFA, trifluoroethylacrylate; TMSMA, trimethylsilyl methacrylate; UCST, upper critical solution temperature.

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2.4.1. General considerations 1094
2.4.2. Preparative methods of polymerization for block copolymers 1096
3. Responsive polymers in controlled drug delivery 1098
3.1. Drug delivery profiles and systems 1098
3.2. Diffusion-controlled systems 1099
3.2.1. System types 1099
3.2.2. Reservoir (membrane) systems 1100
3.2.3. Matrix (monolithic) systems 1101
3.3. Chemically controlled systems 1102
3.3.1. Bioerodible and biodegradable systems 1102
3.3.2. Pendant chain systems 1102
3.4. Swelling-controlled systems 1104
3.5. Modulated-release systems 1105
3.6. Temperature-sensitive release systems 1106
3.6.1. Negative thermosensitive hydrogels 1106
3.6.2. Positive thermosensitive hydrogels 1106
3.7. pH sensitive release systems 1107
3.7.1. Cationic hydrogels 1108
3.7.2. Anionic hydrogels 1108
3.8. Magnetic-sensitive release systems 1110
3.9. Electric-sensitive release systems 1112
4. Challenges and prospects 1112
5. Conclusions 1113
References 1114

1. Introduction

Hydrogels are three-dimensional high-molecular weight networks composed of a polymer backbone, water and a crosslinking agent. They are gaining tremendous importance in a wide variety of applications in medical, pharmaceutical and related fields, e.g. wound dressings [1], contact lenses [2], artificial organs and drug delivery systems [3].

Hydrogels are polymeric materials that do not dissolve in water at physiological temperature and pH. They swell considerably in an aqueous medium [4] and demonstrate extraordinary capacity (>20%) for imbibing water into the network structure. Gels exhibiting a phase transition in response to change in external conditions such as pH, ionic strength, temperature and electric currents are known as "stimuli-responsive" or "smart" gels [5]. Being insoluble, these three-dimensional hydrophilic networks can retain a large amount of water that not only contributes to their good blood compatibility but also maintains a certain degree of structural integrity and elasticity [6]. Hydrophilic functional groups such as –OH, –COOH, $–CONH_2$, and $–SO_3H$ present in the hydrogel are capable of absorbing water without undergoing dissolution.

Hydrogels can be prepared from natural or synthetic polymers [7]. Although hydrogels made from natural polymers may not provide sufficient mechanical strength and may contain pathogens or evoke immune/inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability and biologically recognizable moieties that support cellular activities. Synthetic hydrogels, on the other hand, do not possess these inherent bioactive properties. Fortunately, synthetic polymers usually have well-defined structures that can be modified to yield tailored degradability and functionality [8].

2. Responsive stimuli-sensitive materials

Hydrogels have been developed as stimuli-responsive materials, which can undergo abrupt volume change in response to small changes in environmental parameters: temperature, pH, ionic strength, etc. (Fig. 1). These unique characteristics of hydrogels are of great interest in drug delivery, cell encapsulation and tissue engineering [9–12]. Stimuli-responsive polymers play an important role in the development of novel smart hydrogels [13].

The most important systems from a biomedical point of view are those sensitive to temperature and/or pH of the surroundings. The human body exhibits variations of pH along the gastrointestinal tract, and also in some specific areas like certain tissues (and tumoral areas) and subcellular compartments.

Polymer–polymer and polymer–solvent interactions show an abrupt readjustment in small ranges of pH or temperature. This is attributed to a chain transition between extended and compacted coil states. In the case of pH sensitive polymers, the key element of the system is the presence of ionizable weak acidic or basic moieties attached to a hydrophobic backbone. Upon ionization, the coiled chains

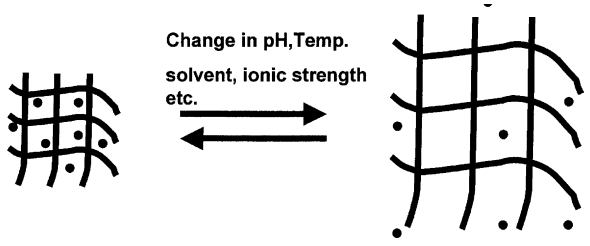

Fig. 1. Intelligent, stimuli-responsive hydrogels, modulated release of drug (circles).