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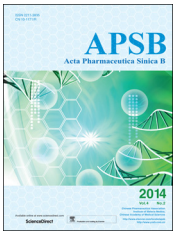

REVIEW

Smart polymers for the controlled delivery of drugs – a concise overview

Honey Priya James, Rijo John, Anju Alex, Anoop K.R.*

Department of Pharmaceutics, Amrita School of Pharmacy, Amrita Vishwa Vidyapeetham University, AIMS Healthcare Campus, Kochi, Kerala 682041, India

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Abstract Smart polymers have enormous potential in various applications. In particular, smart polymeric drug delivery systems have been explored as "intelligent" delivery systems able to release, at the appropriate time and site of action, entrapped drugs in response to specific physiological triggers. These polymers exhibit a non-linear response to a small stimulus leading to a macroscopic alteration in their structure/properties. The responses vary widely from swelling/contraction to disintegration. Synthesis of new polymers and crosslinkers with greater biocompatibility and better biodegradability would increase and enhance current applications. The most fascinating features of the smart polymers arise from their versatility and tunable sensitivity. The most significant weakness of all these external stimuli-sensitive polymers is slow response time. The versatility of polymer sources and their combinatorial synthesis make it possible to tune polymer sensitivity to a given stimulus within a narrow range. Development of smart polymer systems may lead to more accurate and programmable drug delivery. In this review, we discuss various mechanisms by which polymer systems are assembled *in situ* to form implanted devices for sustained release of therapeutic macromolecules, and we highlight various applications in the field of advanced drug delivery.

*Corresponding author. Tel.: +91 9961366366.
E-mail address: anoopkrpharma@gmail.com (Anoop K.R.).

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1. Introduction

Pharmaceutical and biological therapeutics are often limited by short half-lives, poor bioavailability, and physical and chemical instability. Physical instability mainly includes alteration of highly ordered protein structure, leading to undesirable processes such as denaturation, aggregation and precipitation. Reactions such as oxidation, deamidation, hydrolysis and racemisation contribute to the chemical instability of drugs. Stimuli-responsive polymers offer a drug delivery platform that can be utilised to deliver drugs at a controlled rate and in a stable and biologically active form. Over many decades, interest in stimuli-responsive polymers has increased and great deal of work has been committed to developing environmentally sensitive macromolecules that can be moulded into new smart polymers. Table 1 lists various stimuli and smart polymers that can mediate such dramatic behaviour. Smart polymers are becoming increasingly important in the fields of controlled drug delivery, biomedical applications, and tissue engineering, and it is often beneficial to employ polymers that can respond to stimuli which are inherently present in natural systems. Table 2 summarises the various smart polymeric drug delivery systems.

Table 1 Various stimuli and responsive materials.

Environmental stimulus	Responsive material
Temperature	Poloxamers Poly(*N*-alkylacrylamide)s Poly(*N*-vinylcaprolactam)s Cellulose, xyloglucan Chitosan
pH	Poly(methacrylicacid)s Poly(vinylpyridine)s Poly(vinylimidazole)s
Light	Modified poly(acrylamide)s
Electric field	Sulfonated polystyrenes Poly(thiophene)s Poly(ethyloxazoline)
Ultrasound	Ethylenevinylacetate

2. Stimuli-responsive polymers

A stimuli-sensitive or smart polymer undergoes an abrupt change in its physical properties in response to a small environmental stimulus. These polymers are also called as intelligent polymers because small changes occurs in response to an external trigger until a critical point is reached, and they have the ability to return to their original shape after trigger is removed[1–3]. The exclusivity of these polymers lies in their nonlinear response triggered by a very small stimulus and which produces a noticeable macroscopic alterations in their structure. Fig. 1 depicts various stimuli responsible for controlling drug release from smart polymeric drug delivery systems. These transitions are reversible and include changes in physical state, shape and solubility, solvent interactions, hydrophilic and lipophilic balances and conductivity. The driving forces behind these transitions include neutralisation of charged groups by the addition of oppositely charged polymers or by pH shift, and change in the hydrophilic/lipophilic balance or changes in hydrogen bonding due to increase or decrease in temperature. The major benefits of smart polymer-based drug delivery systems includes reduced dosing frequency, ease of preparation, maintenance of desired therapeutic concentration with single dose, prolonged release of incorporated drug, reduced side effects and improved stability[4–6].

Responses of a smart polymeric solution can be of various types. Responsiveness of a polymeric solution initiated by physical or chemical stimuli is limited to the destruction and formation of various secondary forces including hydrogen bonding, hydrophobic forces, van der Waals forces and electrostatic interaction[7,8]. Chemical events include simple reactions such as oxidation, acid–base reaction, reduction and hydrolysis of moieties attached to the polymer chain. In some cases, dramatic conformational change in the polymeric structure occurs, *e.g.*, degradation of the polymeric structure due to irreversible bond breakage in response to an external stimulus. Critical attributes of a smart polymer should include: biodegradability and biocompatibility; controlled release

Table 2 Various smart polymeric drug delivery systems.

Stimulus	Advantage	Limitation
Temperature	Ease of incorporation of active moieties Simple manufacturing and formulation	Injectability issues under application conditions. Low mechanical strength, biocompatibility issues and instability of thermolablile drugs
pH	Suitable for thermolabile drugs	Lack of toxicity data Low mechanical strength
Light	Ease of controlling the trigger mechanism Accurate control over the stimulus	Low mechanical strength of gel, chance of leaching out of noncovalently attached chromophores Inconsistent responses to light
Electric field	Pulsative release with changes in electric current	Surgical implantation required Need of an additional equipment for external application of stimulus Difficulty in optimising the magnitude of electric current
Ultrasound	Controllable protein release	Specialized equipment for controlling the release Surgical implantation required for nonbiodegradable delivery system
Mechanical stress	Possibility to achieve the drug release	Difficulty in controlling the release profile