Saudi Pharmaceutical Journal (2016) **24**, 525–536

King Saud University

Saudi Pharmaceutical Journal

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REVIEW

A review of polymers as multifunctional excipients in drug dosage form technology

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Received 3 February 2015; accepted 28 February 2015
Available online 7 March 2015

KEYWORDS

Multifunctional polymers;
Polymer excipients;
Polymer therapeutics;
Smart polymer

Abstract In the article, groups of multifunctional polymers used in drug dosage form technology were classified and evaluated. These compounds, in addition to their basic function as excipients, may have additional properties, e.g. stimuli sensitivity, enzyme inhibition, intestinal epithelium penetration enhancement, efflux pump inhibition, taste-masking, pharmacological activity and the ability to interact with enzymes responsible for drug metabolism. While classifying specific groups of multifunctional polymers, special emphasis was placed on the advantages of using them when designing new drug. Such advantages include, i.a., increasing substance bioavailability, improving substance stability during formulation and the possibility of obtaining forms of controlled or localized release to a specific site in the organism.

Contents

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Peer review under responsibility of King Saud University.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.jsps.2015.02.025

1. Introduction

An important factor that influences the progress of potential new drug carriers is the development of excipients which have properties that may, depending on therapeutical needs, enhance the bioavailability and stability of the drug, as well as enable the construction of drug forms of controlled or localized substance release (Koo, 2011; Aleeva et al., 2009; Sene et al., 2004). Excipients are defined as inactive ingredients which are mixed with active pharmaceutical ingredients (API) in order to create a drug product that is ready for specified use (Koo, 2011). Although these substances are included in the inactive ingredients list put together by the FDA, they usually have well defined functions in a drug product (Deepak and Gaurav, 2013). Modern achievements in drug dosage form technology are based to a large extent on employing macromolecular compounds, which, apart from their basic function as excipients (i.e. performing variously as a tablet binder, lubricant, anti-adhesive agent, agent which prevents too rapid decomposition, tablet disintegrant, filling agent, coating agent, solubilizing agent, hydrophilization agent, viscosity enhancer, stabilizer in disperse systems, emulsifying agent, gelling agent, etc.), can also perform other additional functions in drug forms (Aleeva et al., 2009; Deepak and Gaurav, 2013). Polymeric excipients constitute a very large and varied group of substances, including macromolecular compounds of natural origin, e.g., sodium alginate, gelatin, chitosan and cellulose derivatives; semisynthetic polymers, e.g., cellulose derivatives; synthetic polymers, e.g., polyethylene glycols, poloxamers, polylactides, polyamides, acrylic acid polymers, etc.; and fermentation products, e.g., xanthan gum (Sene et al., 2004; Ogaji et al., 2012). These polymers are employed in drug dosage forms administered through every possible route: orally, parenterally, nasally, intravaginally, rectally, inhalationally, on the oral mucosa, topically and in ophthalmic preparations (Mansour et al., 2010).

Multifunctional polymers are macromolecular compounds which, according to definition, apart from their basic function, may have additional properties that have already been described in the literature, e.g., sensitivity to stimuli, mucoadhesion, inhibition of enzymes, intestinal epithelium penetration enhancement, efflux pump inhibition, increased buffer capacity, sorptive properties, taste-masking ability, pharmacological activity and the ability to form conjugates or interact with enzymes responsible for drug metabolism. In this article, the groups of these polymers which are employed in pharmaceutical technology will be evaluated.

2. Polymers sensitive to stimuli

One large group of macromolecular compounds is the so-called *smart polymers* or *stimuli-sensitive polymers*. These polymers are sensitive to physical stimuli, exhibiting changes in their physicochemical properties as a reaction to small changes in their surrounding environment, e.g., temperature, pH, ultrasounds, light, electric fields, and mechanical stress. They are also sensitive to chemical stimuli (e.g. pH, ionic strength) and biological stimuli (e.g., the presence of substances including, i.a., enzymes and biomolecules) (Almeida et al., 2012; Kim et al., 2009; Qiu and Park, 2012). The ability of polymers to produce fast microscopic changes in their structure in response to stimuli is rendered through changes to their shape, surface properties and solubility, or through sol–gel phase transition, which is employed in constructing drug carriers sensitive to stimuli (Jeong and Gutowska, 2002). The signal may be created artificially by ''external'' sources or may result from changes in the ''internal environment'', e.g. accompanying certain pathophysiological states. Many monomers may be characterized by sensitivity to certain stimuli; however, every monomer can create homopolymers that are sensitive to a specific signal, or copolymers that react to many stimuli (Kim et al., 2009). The diversity of macromolecular compounds constituents and methods of their synthesis enable polymers to be modified and the creation of carriers sensitive to specified stimuli in a narrow scope of changes. Consequently, these intelligent polymers can be used to construct more precise and programmed drug delivery systems. The stimuli cause a reaction by changing the molecular interactions between the polymer and solvent or between polymer's chains. Variations of these behaviours may include changes in the polymer's solubility, hydrophilic/hydrophobic balance and conformation. Tables 1 and 2 show the examples of polymers sensitive to specified stimuli and the possibilities of employing these compounds in drug delivery systems, respectively.

Thermosensitive polymers are macromolecular compounds which exhibit temperature dependence of the sol–gel transition in water solutions. The transition in these systems from a viscous liquid into elastic form takes place when exposed to a lower critical solution temperature (LCST) as a result of a fast viscosity increase (Jeong et al., 2002). In solutions of thermosensitive macromolecular compounds, the increase of temperature to LCST causes an entropy increase ($\Delta S > \Delta H$) and a decrease in the free energy of binding ($\Delta G < 0$), which facilitates the replacement of the interactions between polymer chain and solvent molecules by intra- and interchain hydrophobic interactions and intra- and intermolecular hydrogen bonds (Bromberg and Ron, 1998).