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REVIEW

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

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Multifunctional polymers;
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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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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).

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Table 1 Examples of intelligent polymers (Almeida et al., 2012; Schmaljohann, 2006; Aguilar et al., 2007; Jeong et al., 2002; Xu et al., 2013; Priya et al., 2014).

Type of stimulus	Polymers
pH	pH responsive dendrimers i.e. poly-amidoamide (PAMAM), dendrimers, poly(propyleneimine) dendrimers, Poly(L-lisine) ester, Poly(hydroxyproline), Poly(propyl acrylic acid), Poly(methacrylic acid), Carbopol®, Polysilamine, Eudragit® S-100, Eudragit® L-100, Chitosan, Poly(methacrylic acid) (PMMA), PMAA-PEG copolymer, Maleic anhydride (MA), N,N-dimethylaminoethyl methacrylate (DMAEMA)
Temperature	Poloxamers (Pluronics®), Prolastin, Poly(N-substituted acrylamide), Poly(organophosphazene), cyclotriphosphazenes with poly(ethyleneglycol) and amino acid esters, block copolymers of poly(ethylene glycol)/ poly(lactic-co-glycolic acid), Poly(ethylene glycol) (PEG), Poly(propylene glycol) (PPG), PMAA, Poly(vinyl alcohol) (PVA), various silk-elastin-like polymers, Poly(silamine), Poly(vinyl methyl ether) (PVME), Poly(vinyl methyl oxazolidone) (PVMO), Poly(vinyl pyrrolidone) (PVP), Poly(N-vinylcaprolactam), poly(N-vinyl isobutyl amid), poly(vinyl methyl ether), poly(N-vinylcaprolactam) (PVCL), Poly(siloxyethylene glycol), poly(dimethylamino ethyl methacrylate), triblock copolymer poly(DL-lactide-co-glycolide-b-ethylene glycol-b-DL-lactide-co-glycolide) (PLGA-PEG-PLGA), Cellulose derivatives, Alginate, Gellan, Xyloglucan
Magnetic field	Poly(N-isopropylacrylamide) (PNIPAAm) hydrogels containing ferromagnetic material PNIPAAm-co-acrylamide
Electrical signals	Chitosan, Sulfonated polystyrenes, Poly(thiophene)s, Poly(ethyloxazoline)
Ions	Sodium alginate (Ca^{2+}), Chitosan (Mg^{2+})
Photosensitive	Modified poly(acrylamide)s

Temperature-sensitive polymers can be divided into four groups: polymers whose phase transition is based on LCST, polymers whose sol–gel transition is connected with the existence of amphiphilic balance, biopolymers and artificial polypeptides (Aguilar et al., 2007). The thermosensitive synthetic polymers characterized by phase transition in LCST include poly(N-isopropylacrylamide) (PNIPAAm), poly(N-vinyl isobutyl amid), poly(vinyl methyl ether), poly(N-vinylcaprolactam) (PVCL) and poly(dimethylamino ethyl methacrylate). The amphiphilic macromolecular compounds include mostly three-block copolymers built of polyoxyethylene and polyoxypropylene (PEO-PPO-PEO) and copolymers created as a result of replacing the PPO part in macromolecule structure with other blocks, i.e., poly(1,2-oxybutylene) (PBO), poly(L-lactic acid) (PLLA) or poly(lactide-co-glycolate) (PLGA) (Schmaljohann, 2006). Polysaccharides of thermosensitive properties are cellulose derivatives: ethylcellulose, hydroxyethyl cellulose (HEC) and ethyl hydroxyethyl cellulose (EHC), natural polysaccharides, e.g. agarose, amylose, amylopectin, carrageenan, gellan and its derivative, benzyl ester, creating in water solutions a double spiral structure stabilized by hydrogen bonds. Artificial polypeptides, e.g. elastin-like polymer (ELP) or silk-elastin-like block copolymers (SELPs), are polymers that dissolve in water below the phase transition temperature, forming a gel after it is exceeded as a result of desolvation and aggregation of the polymer's subunits (Aguilar et al., 2007; Chilkoti et al., 2002).

Many examples can be found among numerous publications describing the application of temperature-sensitive polymers in orally administered drug delivery systems, which brings many additional advantages. In drug dosage form technology such advantages may be realized by employing the copolymers of polyacrylic acid and poloxamer, macromolecular compounds forming an *in situ* gel in the gastroesophageal reflux therapy or, in the case of oral administration of peptide drugs, maintaining the stability in the above-mentioned carriers during their passage through the stomach. The microspheres or beads described by Serres et al. (1996) and Ramkissoon-Ganorkar et al. (1999), obtained using the copolymer of poly-N-isopropylacrylamide with butylmethacrylate and acrylic acid P(NIPAM-co-BMAco-AAC) in the alkaline environment of intestines, were subjected to disintegration and released active substances, e.g. calcitonin and insulin.

Another benefit of using thermosensitive polymers in drug carriers is the possibility of achieving a greater concentration of the drug, e.g. in the rectal cavity, and the advantageous decrease of this concentration in the serum. This was achieved in the case of administrating mitomycin in a xyloglucan-based carrier. The release of the drug regulated through changes in body temperature was, in turn, proposed by Csoka et al. (2007), who designed a thermosensitive system for transdermal application of the drug based on a multifunctional polymer – hydroxypropyl methylcellulose. The sensitivity of the designed carrier to temperature changes was additionally modulated through introducing sodium chloride, potassium chloride or sodium bicarbonate in different concentrations to the carrier. Adding 8% potassium chloride to the formulation enabled, depending on the applied temperature, various release speeds of diclofenac sodium salt to be obtained. At 40 °C, this accessibility was about 3 times higher in comparison with an examination conducted at 25 °C (Csoka et al., 2007). On the basis of thermosensitive polymers, e.g. poly(N-isopropylacrylamide), Pluronic and xyloglucan, modern ophthalmic drug forms may also be constructed. Due to the existence of numerous defence barriers in the eye, its limited capacity and the poor ability of liquid and semi-solid preparations to stay in the area of the defence apparatus and anterior segment of the eyeball, it may be possible to increase the efficiency of the therapy through employing gels formed *in situ* after application. This enables the form to stay longer on the surface of the eye and the longer contact of the water and active substances it contains with eye epithelium (Hsiue et al., 2002; El-Kamel, 2002; Miyazaki et al., 2001; Hongyi et al., 2006). Similar to the temperature-sensitive polymers described above, pharmaceutical technology macromolecular compounds which react to the change of environmental pH are being employed. This is particularly relevant because of the existence of areas of different pH values in the organism (Table 3).

Examples of pH-sensitive polymers applied in pharmaceutical formulations include poly(acrylic acid), poly(methacrylic acid) and poly(2-ethylacrylic acid), in which the carboxyl group remains non-ionized and keeps the drug in the carrier

Table 2 Examples of application of polymers sensitive to stimuli in drug delivery systems (Kim et al., 2009; Priya et al., 2014).

Stimulus	Polymer	Application
Temperature	Poly(N-isopropylacrylamide)	Hydrogel, doxorubicin release
Ultrasound	Polyanhydride, polyglycolide, polylactide	Ultrasound-enhanced biodegradation
	poly(hydroxyethyl methacrylate-co-N,N′-dimethylaminoethyl methacrylate)	Ultrasound-enhanced drug release rate
Magnetic field	Poly(ethylene-co-vinylacetate)	Prompted BSA release from matrix magnetic field
Oxidation	PEG-b-poly(propylene sulphide)-b-PEG	Oxidation-sensitive polymer vesicle disintegration
Light	Poly(N,N-dimethylacrylamide-co-4-phenyl-azophenyl acrylate)	Photo-sensitive active site-gating of streptavidin
	Poly(N,N-dimethyl acrylamide-co-4-phnyl-azophenyl acrylamide)	
Electricity	Poly(ethylenediamine-co-1,10-bis(chloro-carbonyl)decane) polyethyloxazoline/poly(methacrylate)	Electric-sensitive capsule Electrically erodible matrix for insulin delivery
Mechanical stress	Dihydrazide-crosslinked polyguluronate poly(methyl methacrylate)/poly(vinyl alcohol) or/cellulose ether	Pressure-sensitive hydrogel Pressure-sensitive adhesive
pH	Poly(acrylic acid)-g-PEG	Oral insulin delivery
	PEG-b-poly(L-histidine)	Doxorubicin release
	Poly(n-isopropylacrylamide-co-propylacrylic acid-co-butylacrylate) alginate and chemically modified carboxymethyl chitosan	Fibroblast growth factor: improvement of angiogenesis, providing the advantage of acidic microenvironment of ischaemic myocardium Protein drug for oral delivery: protecting the drug from the harsh acidity of stomach with potential release in the intestine
Ionic strength	Poly(NIPAAm-co-benzo-18-crown[6]-acrylamide)	Ba^{2+}-sensitive membrane pore
Enzymes	[a]PEG-peptide linker-doxorubicin	Doxorubicin release by lysosomal enzyme-mediated peptide degradation
	[a]Poly(N-(2-hydroxypropyl)methacrylamide)-peptide linker-doxorubicin	
Biomolecules	PEO-b-poly(2-glucosyloxyethyl acrylate)	Glucose-sensitive micelle for insulin delivery
	Thiolate PEG-b-poly(L-lysine)	Glutathione-sensitive micelle for anti-sense DNA delivery
	[b]Poly(RCOOH-co-butyl acrylate-co-pyridyl disulphide acrylate)	Glutathione- and pH-sensitive copolymers for oligodeoxynucleotide delivery

[a] Peptide linker = GFLG.
[b] R = $–CH_3$, $–CH_2CH_3$, or $–CH_2CH_2CH_3$.

Table 3 The pH of chosen tissues and compartments of the organism (Almeida et al., 2012).

Tissue/cell compartment	pH
Blood	7.35–7.45
Stomach	1.0–3.0
Duodenum	4.8–8.2
Colon	7.0–7.5
Early endosome	6.0–6.5
Late endosome	5.0–6.0
Lysosome	4.5–5.0
Golgi complex	6.4
Tumor – extracellular medium	7.2–6.5

structure in the acid-pH stomach environment (Aguilar et al., 2007; Xu et al., 2013). On the other hand, in the alkaline or neutral environment of the small intestine these groups get ionized, and the polymer swells due to their electrostatic repulsion while simultaneously releasing the drug to the environment. Carriers designed on the basis of polycationic polymers, i.e. poly(vinylamine), poly(2-vinylpyridine), poly(4vinylpyridine), poly(N,N-dimethylaminoethyl methacrylate), poly(N,N-diethylaminoethyl methacrylate), poly(N,N-diakyl aminoethyl methacrylates), poly(lysine), poly(ethylenimine) and chitosan exhibited other behaviours in different pH environments (Aguilar et al., 2007). In neutral or alkaline pH, amine groups of these polymers exist in a non-ionized form and keep the drug in the carrier structure; when the pH value decreases below pK_a, these groups become ionized, and the polymer net swells due to the electrostatic repulsion of the neighbouring positively charged groups, thus releasing the drug to the environment (Almeida et al., 2012).

3. Mucoadhesive polymers

Mucoadhesive polymers constitute an important group of excipients employed when designing drug forms such as tablets, capsules, powders, multi-compartment systems, thin strips, inserts, solutions, suspensions, gels and foams. These forms are applied, i.a., on the oral cavity mucosa, sublingually, orally, intravaginally, rectally, nasally and ophthalmically. Their use in these forms prolongs the time that the drug form resides at the site of drug absorption, thus ensuring a high concentration gradient of the released substance, its protection from enzymatic degradation and, as a result, improved absorption. Polymers, because of the kind of created mechanism responsible for mucoadhesion, are classified as being in the group of noncovalently and covalently bonding macromolecular compounds. In the case of noncovalently bonding

polymers, this mechanism is a result of creating hydrogen bonds, ionic interactions and van der Waals forces, while in the second polymer group it results from forming covalent bonds between mucus and the polymer (Vigl, 2009). The noncovalently bonding mucoadhesive polymers include anionic, cationic and nonionic compounds. The interaction of anionic polymers, e.g. polyacrylates, carboxymethyl cellulose sodium salt and alginates, thiolated alginates, pectins, polyacrylates, sodium carboxymethyl cellulose, xanthan gum and hyaluronic acid with mucus, takes place through forming hydrogen bonds between carboxylic polymer groups and mucus glycoproteins hydroxyl groups (Nallathambi and Gopal, 2013). However, in this case the environmental pH strongly influences the swelling of polymers. At low pH, swelling is minor due to the protonation of carboxylic polymer groups, whereas an increase of acidity in the environment may lead to major swelling and the loss of mucoadhesion. At low pH values in the stomach the alginate shrinks and turns into insoluble acid, which results in the lack of release of the drug administered in the system designed on this basis. Passing further along the gastrointestinal tract, the polymer becomes soluble and viscous, which enables a controlled drug release to be achieved. Thiolation of alginate improves not only its mucoadhesion, but also the swelling and its cohesiveness, thus increasing the stability of the network. Modifying polymers through introducing long hydrophobic alkyl chains to its structure leads in turn to increased drug encapsulation, but disables the fast dissolution and thus sustained substance release is obtained. Cross-linking the alginate or complexing it with other polymers, e.g. pectins, chitosans or Eudragit, increases the encapsulation efficiency, limiting the leaching of the drug through the pores of the obtained alginate hydrogel (Vigl, 2009).

The most frequently used cationic mucoadhesive polymers include chitosan, aminodextran, diethylaminoethyl (DEAE)-dextran and polylysine, which – due to the presence of amine groups – interact with anionic substructures of sialic acid residues in the mucus layer (Nallathambi and Gopal, 2013). Chitosan is quickly hydrated in low pH environments, e.g. gastric acid pH, does not swell and does not exhibit greater mucoadhesion in pH above 6.5. Mucoadhesive polymers also include macromolecular nonionic compounds, i.e. cellulose derivatives: hydroxypropyl cellulose (HPC), HEC, polyvinyl alcohol and polyvinylpyrrolidone, macrogols, whose properties depend to a small extent on the pH environment and concentration of electrolytes in a solution. The main mechanism of mucoadhesion in their case seems to be only the physical interpenetration and the later entanglement of polymer chains. Some of these polymers, e.g. polyethylene oxide, may additionally form hydrogen bonds, which, however, play a small role in the mucoadhesion mechanism.

Thiomers are also counted among mucoadhesive polymers forming covalent bonds. They are obtained by attaching thiol groups of ligands to polymers, i.e. polyacrylates or chitosan (Kafedjiiski and Franzens, 2004). Thiomers are covalently anchored in the mucus layer, which results from forming disulphide bonds with cysteine-rich subdomains of secreted glycoproteins in the replacement thiol/disulphide reaction and/or oxidation reactions. The formed connections are stronger than non-covalent bonds, i.e. hydrogen bonds or van der Waals forces, and display significantly larger mucoadhesion in comparison with corresponding non-modified polymers (Kawadkar and Chauhan, 2010; Kushawaha et al., 2010; Mythri et al., 2011; Kast and Bernkop-Schnurch, 2002; Sreenivas and Pai, 2009).

4. Polymers inhibiting action of enzymes

Macromolecular compounds with enzyme-inhibiting properties include polyacrylic acid, sodium alginate, carboxymethyl cellulose, chitosan citrate, thiomers, polymer-enzyme inhibitor conjugates, chitosan-EDTA conjugates and the copolymers poly(methacrylic acid) and poly(ethylene glycol) (P(MAA-g-EG) or starch and polyacrylic acid (Bernkop-Schnurch, 2000; Bonferoni et al., 2008; Lv et al., 2014; Nakamura et al., 2008). Enzyme-action inhibition may result from binding Ca^{2+} and Zn^{2+} ions, which play a key role in the thermodynamic enzyme stability, or from the enzyme–polymer interaction decreasing the free enzyme concentration as well as from a fall in the pH value below the optimal level required for its activity (Kawadkar and Chauhan, 2010; Lv et al., 2014). Acrylic acid polymers inhibit the proteolytic enzymes action by binding the metals' ions, the indispensable components of these proteins' structure, which may lead to conformational changes and may induce their autolysis. Moreover, it is presumed that acrylic acid polymers bind trypsin, contributing to the inactivation of the enzyme. In the case of chitosan, the polymer itself exhibits weak enzyme-inhibiting properties and only its conjugation with an enzyme-inhibitor, i.e. the Bowman-Birk inhibitor, elastinal or complexing with EDTA, leads to enzyme-inhibition (Guggi and Bernkop-Schnurch, 2003). Proteases-inhibitors of the Bowman-Birk family have a low molecular mass, usually 600–16,000 Da, and are polypeptides that contain on average 60–90 amino acids, maintaining their compact structure due to the presence of a significant number of disulphide bonds. Attaching a trypsin-inhibitor (Bowman-Birk) to soybean polyacrylate, as in the case of chitosan, improves its trypsin- and chymotrypsin-inhibiting properties while decreasing its mucoadhesion. In turn, immobilizing EDTA on chitosan prevents the secretion of Zn-dependent peptidases. Employing thiomers, e.g. polycarbophil-cysteine, as compounds to inhibit enzyme action enabled greater inhibitory polymer influence on the action of carboxypeptidase A, carboxypeptidase B and chymotrypsin (Bernkop-Schnurch, 2000). It was also proved that thiolated polycarbophil had significantly larger inhibitory influence than unmodified polycarbophil on the activity of aminopeptidase N. The apparently better carboxypeptidase A-, carboxypeptidase B- and aminopeptidase N-inhibiting properties of modified polycarbophil may be also explained by the binding of Zn^{2+} ions in the enzyme structure, and were further improved by connecting this polymer with L-cysteine (Kawadkar and Chauhan, 2010). Employing thiomers and inhibitor-polymer conjugates enables greater benefits to be obtained than in the case of traditional low molecular weight drugs that inhibit enzymes due to the fact that these compounds are not absorbed from the gastrointestinal tract and are only covalently bound to the surface of non-absorbable polymers; thus, they exhibit no toxicity. As a result of polymer mucoadhesion, the inhibitor stays in contact with the absorption membrane for a longer period of time and the inhibitory effects of its activity are localized (Kushawaha et al., 2010). In the case of enzyme inhibition as a result of the complexation of

Table 4 Examples of polymeric enzyme-inhibitors (Vigl, 2009; Lv et al., 2014; Guggi and Bernkop-Schnurch, 2003).

Enzyme	Polymeric inhibitor
Trypsin	Polyacrylic acid, thiomers, polymer–enzyme–inhibitor conjugates, sodium alginate
Chymotrypsin	Polymer–enzyme–inhibitor
Elastase	Polymer–enzyme–inhibitor
Exopeptidases	Polyacrylic acid, thiomers, polymer–enzyme–inhibitor conjugates
Nucleases	Chitosan–aurintricarboxylic acid, chitosan–EDTA, thiomers

essential metal ions, polymers can act without getting into close contact with the target enzyme through the diffusion mechanism. Examples of polymers with enzyme-inhibiting properties can be found in Table 4.

Tardajos et al. also described the dose- and structure-dependent influence of copolymers of sulfonated N-vinylpyrrolidone with methyl maleate on their inhibiting activity on acidic fibroblast growth factor-mediated mitogenesis of fibroblasts (Tardajos et al., 2012).

5. Polymers enhancing the intestinal epithelium penetration

The intestinal epithelium constitutes a main barrier to the absorption of peptide drugs. In order to decrease this barrier function simultaneously with protein drugs, polymers to enhance their penetration through mucosa are administered. The strong effect of increasing drug penetration, obtained after employing polymers, i.e. chitosan and carbomer, is accompanied by a decrease in transepithelial resistance caused by the loosening of tight junctions between the epithelium cells. The exact mechanism of the thiolated polyacrylate activity is not entirely explained, but it is probably based on the binding of Ca^{2+} ions. Cationic ions, such as chitosan, can interact with negatively charged residues on the cell surface, causing conformational changes in the structure of the membrane and proteins tightly bound to its surface. The attachment of thiol groups to a mucoadhesive polymer may additionally improve their permeability-enhancing properties, which is explained by inhibiting the action of the protein tyrosine phosphatase (PTP), which through dephosphorylation of extracellular tyrosine group mediates in closing tight junctions. The effect is also attributed to the covalent binding of the polymer to cysteine residues (Vigl, 2009; Kawadkar and Chauhan, 2010). Rambharose et al. (2014) examined the influence of multifunctional excipients, i.e. polyacrylic acid, sodium alginate, carboxymethyl cellulose, polyoxyethylene glycol, on the permeability of pig mucosa to the antiviral drugs anionic tenofovir and cationic didanosine. For tenofovir, it was found that drug penetration improved each time, whereas for cationic didanosine, the increase in permeability was obtained only through employing polyoxyethylene glycol. In another part of their research, the focus was on analyzing the influence of concentrations of polyoxyethylene glycol on the penetration of both drugs. At 0.25–5% concentrations, an increase in both substances penetration was recorded – for tenofovir the greatest effect was achieved at 4% polymer concentrations, whereas for didanosine it was 0.5% (Rambharose et al., 2014).

It should be mentioned here that in comparison with other groups of substances known to enhance drug penetration through the intestinal epithelium, i.e. surface active agents, fatty acids, salicylates or chelating agents, employing multifunctional polymers is additionally advantageous due to lack of their absorption and their remaining in high concentration in the target site.

6. Efflux pump-inhibiting polymers

The bioavailability of certain active substances after *per os* administration is regulated and dependent, i.a., on the activity of protein transporting drugs (Aleeva et al., 2009; Srivalli and Lakshmi, 2012). These proteins remove them from the intestinal epithelium cells back to the intestinal lumen. The best known drug transporter is P-glycoprotein, present in the cell membrane, which via the active transport mechanism (“pump”) pumps out drugs from cells to extracellular spaces, preventing their accumulation (Bernkop-Schnurch and Grabovac, 2006; Bansal et al., 2009). P-glycoprotein has a wide substrate specificity, recognizes many compounds of very different structures and physicochemical properties, of the 330–4000 Da weight. The substrates for this protein are, i.a. drugs with antineoplastic activity which act on the central nervous system and cardiovascular system, and antimicrobial drugs (Srivalli and Lakshmi, 2012). Inhibiting the activity of P-glycoprotein through multifunctional polymers in the intestinal epithelium cells may be the reason behind the decrease in the transport of drugs to the intestinal lumen and thus they contribute to the increase in their bioavailability. Due to simultaneous administration of active substances with polysaccharides such as xanthan gum, gellan gum, guar gum, agar, tragacanth, sodium alginate, thiolated chitosan, thiolated polycarbophil or chitosan-4-thio-butyl-amidine, the removal of protein substrates drugs is prevented (Bernkop-Schnurch and Grabovac, 2006; Bansal et al., 2009; Gaikwad and Bhatia, 2013). The administration of paclitaxel in a carrier designed on the basis of thiolated polycarbophil may serve as an example. As a result of employing this polymer, an increase of drug concentration in the blood plasma was obtained and a decrease in the growth of a mammary tumour in rats was noticed.

The polymeric inhibitors of P-glycoprotein also include synthetic polymers, i.e. poloxamers, PEG, poly(lactide), poly(D,L-lactide-co-glycolide) (PLGA), poly(caprolactone), methoxypolyethylene glycol-block-polycaprolactone, polyoxylates and dendrimers, as well as copolymers such as mPEG-polycaprolactone, PEG-phosphatidylethanolamine, PEG-b-PLA, mPEG-poly(caprolactone-trimethylene carbonate), Eudragit S100 and dendrimers (Bernkop-Schnurch and Grabovac, 2006; Bansal et al., 2009; Gaikwad and Bhatia, 2013; Mohammadzadeh et al., 2014; Zastre et al., 2007). One example of their use is the improvement of penetration of ganciclovir through the intestinal mucous membrane in rats, which is classified as a BCS class III drug and was obtained by using PEG and Pluronic F-68 and using PEG in studies on verapamil penetration (Li et al., 2011).

Another activity that block copolymers from the poloxamers group may inhibit, apart from that of P-glycoprotein, is the activity of transporters such as MRP (multidrug resistance proteins) and BCRP (breast cancer resistance proteins)

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(Bernkop-Schnurch and Grabovac, 2006; Batrakova and Kabanov, 2008). Because of this, increases in bioavailability and improvements to the therapeutic efficiency of antineoplastic drugs, e.g. paclitaxel, are possible. It is thought that inhibiting the activity of an ATP-dependent pump in this way is caused by nonspecific changes in the conformation of lipids and proteins and their mobility, and may additionally be a result of inhibiting drug sequestration in an acidic environment and detoxification, with the participation of glutathione S-transferase, due to the energy derived from the breakdown of ATP. The ATP deficit caused by the ATPase activity inhibition by copolymers may be the cause of a higher sensitivity of the cells to the applied treatment (Batrakova and Kabanov, 2008).

7. Polymers of increased buffer capacity

Another feature of certain multifunctional polymers (i.e. chitosan, polyacrylic acid) is their increased buffer capacity (Vigl, 2009). Anionic and cationic polymers act like ion-exchange resins maintaining the constant pH value inside the polymer network for a certain period of time. This may contribute to the increase in stability of the incorporated drug, limiting its pH-dependent denaturation or enzymatic degradation. Hydrated ionic polymers can maintain the pH value of around 7, even in a gastric fluid environment, thus protecting the embedded macromolecular drugs from degradation. An example of such a concept being applied is the use of a tablet containing neutralized carbomer which is able to buffer the drug inside a swollen matrix for several hours in an artificial gastric fluid with a pH value of 2. Similarly, in order to prevent degradation of the substance in the intestine, polyacrylates in their acidic form may be used (Bernkop-Schnurch, 2002). This pH value also inhibits the activity of proteases, i.e. trypsin and chymotrypsin, which are active only at pH values greater than 4.

8. Polymers with sorptive properties

Another advantage of using select polymers with multifunctional properties, such as chitosan, is the possibility of using them as substances with sorptive properties. In research studies it was stated that polymers with a high molecular weight adsorb lipid droplets better than polymers of a low molecular weight. The reasons for this are due to the creation of different shapes of cationic loops and tails and in the higher surface activity of the chitosan particles of high weight. It should be noted that different kinds of polymers bind different kinds of bile acids with different strengths. The sorptive properties of chitosan are attributed to the creation of a viscous polysaccharide solution in a lipid environment and the presence of an amine group in the structure of chitosan, facilitating the emergence of electrostatic forces between the polymer and anionic substances, i.e. fatty acids and bile acids (Rodriguez and Albertengo, 2005; Ahmad et al., 2005).

9. Polymers with taste-masking ability

Copolymers of dimethylaminoethyl, butyl methacrylate and methyl methacrylate have an ability to mask the taste of administered active substances, which is explained by the influence of complementary ionic groups. Taste-masking is, then, an effect of the interaction between cationic drugs and anionic polymer, or vice versa. Randale et al. (2010) have designed fast disintegrating tablets containing metoclopramide with the substance's taste masked. They achieved this result through complexing the drug in different ratios by extrusion method and precipitation with aminoalkyl methacrylate copolymer (Eudragit EPO). In the conducted tests, the drug-polymer complex with a components ratio of 1:2 exhibited significant taste-masking, as confirmed in the taste assessment by volunteers. These complexes turned out to possess a significant taste-masking ability with a degree of bitterness at or below the threshold value (0.5) in 10 s, whereas the substance itself – metoclopramide chlorhydrate – was assessed in the same conditions as intensively bitter with a score of degree of bitterness 3 for 10 s (Koo, 2011).

10. Polymers which interact with enzymes involved in drug metabolism

Martin et al. (2013) examined the influence of ten polymers on seven isoforms of cytochrome P450 (CYP450) using CYP450 enzymes derivatives of the entire concentration range. All excipients caused noticeable activity effects – inhibiting or increasing activity – on at least one CYP450 isoform, which indicates that they have the potential to change pharmacokinetics of administered drugs. Table 5 presents the influence of some polymers, i.e. poly(ethylene glycol) (PEG), Pluronic F-68, Pluronic F-127, sodium carboxylmethyl cellulose (NaCMC), hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), poly(vinyl alcohol) (PVA), Kollicoat, hydrolyzed gelatin (HG) and polyvinylpyrrolidone 30 K (PVP) on the activity of chosen isoforms of cytochrome P450 (Martin et al., 2013).

11. Polymers with pharmacological activity

An interesting example of the properties of polymers is their ability to inhibit the development of numerous viruses as well as their immunostimulating, antibacterial, antioxidant and fat absorption-decreasing activity.

Polyanionic compounds, i.e. sulphated polysaccharides (dextrin-2-sulphate, carrageenan, dextran, cellulose sulphate) may inhibit the growth of the HIV virus, herpes simplex virus (HSV), cytomegalovirus (CMV) through limiting the absorption of viruses to the surface of host cells (Duncan, 2003; Franz et al., 2000; Gyotoku et al., 1999; Neurath et al., 2002; Shaunak et al., 1998; Campo et al., 2009; Schaeffer and Krylov, 2000). Poly(amidoamine) (PAMAM) dendrimers covalently modified with naphthyl sulfonate residues on the surface exhibited antiviral activity against the HIV virus (Svenson and Tomalia, 2005). A copolymer of divinyl ether and maleic anhydride (DIVEMA) stimulates the creation of glycoprotein, inhibiting the translation of viral RNA in cells and the division of antineoplastic cells. The antibacterial activity of DIVEMA worked against both the Gram-positive and Gram-negative bacteria and the antifungal activity of this polymer worked against *Cryptococcus neoformans*, a species of yeast that attacks mice lungs and brains (Popescu et al., 2011; Oledzka and Sobczak, 2012; Munoz-Bonilla and

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Table 5 Activity of the CYP450 enzyme after treatment with preparations containing polymers as excipients (Martin et al., 2013).

Polymer	EC50[a] i (IC50)[b] (μM)						
	CYP2E1	CYP3A4	CYP3A5	CYP2C9	CYP2C19	CYP1A2	CYP2D6
PEG	(75.3 ± 2.1)	–	(78.0 ± 17.8)	(365.6 ± 32.8)	(139.0 ± 22.4)	–	(409.6 ± 34.5)
Pluronic F-68	(203.7 ± 48.3)	(59.1 ± 13.6)	(209.9 ± 29.7)	(244.8 ± 13.2)	–	–	387.6 ± 31.9
Pluronic F-127	(218.9 ± 13.3)	32.8 ± 11.8	–	355.0 ± 77.4	–	–	101.6 ± 19.9
NaCMC	–	12.6 ± 4.6	83.7 ± 17.3	113.2 ± 24.2	373.8 ± 68.2	(224.7 ± 14.8)	–
HPC	–	–	–	–	89.5 ± 16.1	139.0 ± 4.0	148.3 ± 21.3
HPMC	(253.5 ± 17.9)	–	(19.4 ± 0.6)	–	211.8 ± 57.9	106.7 ± 23.1	159.3 ± 26.9
PVA	(548.9 ± 30.4)	–	–	–	–	–	354.8 ± 84.9
Kollicoat	(598.1 ± 26.1)	–	–	259.8 ± 46.1	36.1 ± 1.8	(10.0 ± 3.9)	(89.9 ± 2.9)
HG	(141.2 ± 14.1)	–	–	249.5 ± 24.3	20.5 ± 5.3	(40.9 ± 8.4)	379.9 ± 22.3
PVP	–	(107.3 ± 11.2)	–	–	–	(78.3 ± 4.2)	–

[a] Values without brackets – half maximal effective concentration (EC50).
[b] Values in brackets – half maximal inhibitory concentration (IC50). Lack of any entered values indicates lack of measurable effect. NaCMC – sodium carboxymethyl cellulose; HPC – hydroxypropyl cellulose; HPMC – hydroxypropyl methycellulose; Kollicoat – copolymer poly)vinyl alcohol)-graft-poly(ethylene glycol); HG – hydrolyzed gelatin.

Fernandez-Garcia, 2012). In Table 6, other, non-antiviral activities of maleic anhydride copolymers are shown.

Antibacterial activities, which are explained by a change in the properties of bacteria cell membranes, are also a feature of chitosan (poly-D-glucosamine), its derivatives (chitooligosaccharides COSs) and polypropylenimine (PPI) dendrimers with tertiary alkyl ammonium groups attached to the surface (Svenson and Tomalia, 2005; Aranaz et al., 2009; Cunha et al., 2012). A positively charged amine group of glucosamine units interacts with negatively charged components of the membranes of Gram-negative bacteria and prevents the passing of nutrients into the cell interior or causes a leakage of intracellular content. Another possible explanation of this activity is that chitosan penetrates into the cell and binds with DNA, which in turn inhibits of RNA transcription, and thus leads to the inhibition of protein synthesis. The influence of deacetylation degree and the molecular weight of chitosan during its antibacterial activity is presented in Table 7 (Aranaz et al., 2009; Cunha et al., 2012; Zheng and Zhu, 2003). These polymers' antibacterial activity, as well as the antiviral activity against the HIV-1 virus, was also proved by adding cellulose acetate phthalate (CAP) to the bacterial vaginosis infection therapy. The result of the polymer's activity is explained by lowering the pH, buffering and hydrophobicity, and the effect of the polymer remaining in micronized form in the vaginal environment is similar to the activity of surface active agent (Neurath et al., 2000). Only in this form, however, does CAP have the ability to remove viruses from physiological fluids through their adsorption on the surface of micronized particles (Neurath et al., 2002).

Chitosan may also have an antitumour activity which is observed particularly in low-molecular-weight forms of polymer (Aranaz et al., 2009). In an experiment carried out on rodents, it was proved that partially acetylated chitosan inhibits the growth of neoplastic sarcoma 180 cells. In in vitro studies on HEK 293 and HeLa cell lines, the latter obtained from cervical cancer cells, it was confirmed that copper-chitosan complexes obtained in different component ratios may be employed as potential antineoplastic drugs (Zheng and Zhu, 2003). Antiangiogenic properties are also possessed by dextrin-2-sulphate, which in patients with AIDS induced a regression of Kaposi sarcoma (Duncan, 2003).

In the literature reports can be found of an antioxidant activity of the low-molecular-weight chitosan, partially deacylated. Although the mechanism of this activity is still

Table 6 Activity of maleic anhydride copolymers (MA) (Popescu et al., 2011).

Copolymer	Activity
MA–2-cyclohexyl-1,3-dioxap-5-ene	Antitumor activity, immunostimulator, activation of macrophages
MA–2-isopropenyl-1,3-dioxap-5-ene	Antitumor activity
MA–ethylene	Antitumor and antiviral activity
Maleic acid–acrylic acid	Antitumor activity
MA–dihydropyran MA–dihydrofuran	Antitumor activity
MA–vinyl adenine	Activation of macrophages
MA–styrene (MA–styrene)-block-styrene (MA–styrene)-block-styrene derivatives with mannose or glucose	Inhibition of HIV-1 infection
MA–styrene	Inhibitor of spermatozoa motility, damaging the spermatozoa membrane

Table 7 Influence of deacetylation degree and molecular weight of chitosan on its antibacterial activity (Aranaz et al., 2009).

Physico-chemical property	Effect on antimicrobial activity
↑ DD	↑ Electrostatic binding to membrane ↑ Permeabilizing effect
↑ Mw	↓ Permeation into the cell nucleus

DD: deacetylation degree; Mw: molecular weight.

unexplained, it is primarily attributed to the existence of an amine group and hydroxyl groups in the respective positions C-2, C-3 and C-6, which react with free radicals, thus creating more stable macromolecular radicals. A second reason may be the chelation of iron ions, which is why chitosan is considered as a potential natural antioxidant (Aranaz et al., 2009).

There are also reports of chitosan and its oligomers displaying hemostatic and antithrombogenic activities, which have been confirmed in in vitro tests. The anticoagulant activity of chitosan seems to be an effect of binding the positively charged polymer to the membranes of negatively charged red blood cells (Aranaz et al., 2009; Cunha et al., 2012; Ray, 2011). Microcrystalline chitosan with a molecular weight 10^3–10^6 and deacetylation degree of 60–100%, obtained through the modification of chitosan by the method of aggregation, in turn has platelets reactivity decreasing properties, thus lowering the risk of vascular occlusions, which is proved by inhibiting the release of P-selectin from α-granules of the platelets and the inhibition of Ibα internalization.

Some researchers have stated that chitosan exhibits analgesic activity. Results suggest that the main reason for this effect is the absorption of positively charged ions that are released in the inflammation area. Due to their polycationic nature, free amine groups of chitosan may be protonated in the presence of cations and, as a result, may lower the pH level, which is the main reason for the polymer's analgesic activity (Aranaz et al., 2009).

The anti-cholesterol activity of chitosan was also described and its mechanism may be explained in two ways. On one hand, it may be caused by creating a viscous solution of polysaccharide, thus decreasing the absorption of fat and cholesterol from the diet; on the other hand, it could be due to the presence of an amine group in chitosan structure, which facilitates the emergence of electrostatic forces between the polymer and anionic substances, i.e. fatty and bile acids. Another possible mechanism theory involves the assumption of chitosan adsorption to the lipid emulsions surface and the creation of a protective layer (Aranaz et al., 2009; Cunha et al., 2012; Ray, 2011). The influence of the deacetylation degree and molecular weight of chitosan on the binding and metabolism of fats is presented in Table 8. Hipolipidemic activity is also attributed to carrageenans (campo et al., 2009).

The anti-inflammatory effects of chitosan and its derivatives, as well as their antidiabetic, neuroprotective, immune system-stimulating and antibacterial activity in the prevention and treatment of periodontal disease, have also been documented in the literature (Cunha et al., 2012) (see Table 9).

Olendzka et al. described the hydrochloric acid-neutralizing effect obtained after employing a linear polymer of uronic acids – alginic acid (mannuronic acid conjugated β-1,4 and L-guluronic acid glycosidically conjugated α-1,4). This polymer retains water in the stomach, thus decreasing irritation and pain. Another polymer, polyvinylpyrrolidone, is in turn employed as substance with antidiarrhoeal effects. Its amphoteric properties enable pH normalization in the stomach and intestines through adsorption of acids and bases, which usually form as a result of fermentation and decomposition (Oledzka and Sobczak, 2012).

Sulfated glycosaminoglycans (GAGs), i.e. dextran sulphate, gellan sulphate and fucosylated chondroitin sulphate, possess properties inhibiting the growth of *Plasmodium falciparum* by inhibiting the invasion of merozoites into erythrocytes in in vitro conditions. Dextran sulphate and fucosylated chondroitin sulphate prevent the cytoadherence of Plasmodium-

Table 8 Influence of deacetylation degree and molecular weight of chitosan on binding and metabolism of fats (Aranaz et al., 2009).

Physico-chemical property	Effect in vitro	Effect in vivo
↑ DD	↑ Electrostatic force between chitosan and fatty and bile acid	↓ Plasma cholesterol ↓ LDL ↑ HDL
↑ Mw	↑ Adsorption to lipid droplets ↓ adsorption to droplet surface of lipase	↓ Body weight gain ↓ Adsorption and blood distribution ↓ Liver total lipid and cholesterol

DD: deacetylation degree; Mw: molecular weight; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 9 Polymer–drug conjugates in clinical studies (Sanchis et al., 2010).

Conjugate	Company	Status of development
HPMA copolymer-Dox PK1	Pfizer Inc., Cancer Research Campaign, UK	II
HPMA copolymer-Dox-galactosamine PK2	Pfizer Inc., Cancer Research Campaign, UK	I/II
OxDextran-Dox AD-70	–	I
PGA-CPT CT-2106	Cell Therapeutics Inc.	I/II
Cyclodextrin-CPT IT-10	Cerulean	I
Fleximer™-CPT XMT-1001	Mersana	I
HPMA copolymer-CPT MAG-CPT	–	I
PEG-CPT Pegamotecan	Nektar	II
Carboxymethyl-dextran-exatecan DE-310	–	I
PEG-irinotecan NKTR-102	Nektar	II
HPMA copolymer-PTX PNU 166945	Pfizer Inc.	I
PGA-PTX CT-2103 (Opaxio™)	Cell Therapeutics Inc.	III
PEG-docetaxel NKTR-105	Nektar	I
HPMA copolymer-malonato-platinate AP5280	Access Pharmaceuticals Inc.	I
HPMA copolymer-DACH-platinate AP5346 (ProLindac™)	Access Pharmaceuticals Inc.	II

HPMA: N-(2-Hydroxypropyl)methacrylamide; OxDextran: Oxidized dextran; CPT: Camptothecin; DACH: Diaminocyclohexane; Dox: Doxorubicin; PEG: Poly(ethylene glycol); HPMA: *N*-(2–2-hydroxypropyl)methacrylamide; PGA: Poly-l-glutamic acid; PTX: Paclitaxel.

infected red blood cells in vitro. The gellan sulphate mechanism has been studied in order to explain whether it inhibits parasite adhesion to red blood cells similar to other glycosaminoglycans (Recuenco et al., 2014).

11. Polymer–drug conjugates

Polymer–drug conjugates are obtained on the basis of biocompatible macromolecular compounds connected covalently, usually with biologically active molecules, i.e. peptides and proteins of low macromolecular weight. This connection enables the improvement of their solubility, stability or decreasing immunogenicity. In most cases, the polymer's presence increases the solubility of a hydrophobic drug and improves its pharmacokinetic profile, causing the extension of drug's half-life time in the blood plasma while simultaneously increasing the volume of distribution and decreasing the renal and hepatic clearance. The polymer protects the drug from degradation and may actively participate in its release in specified conditions controlled through pH changes or the presence of enzymes. Polymers employed as components of designed conjugates include: polyoxyethylene glycol, β-cyclodextrin, dextran, poly(γ-glutamic acid), polyacrylic acid, poly (styrene – maleic acid), poly(α-glutamic acid), poly(dimethylamino) ethyl methacrylate (pDMAEMA), *N*-[2-hydroxypropyl]methacrylamide and poly-K8-(VPGXG)60 (VPGXG: Valine-proline-glycine-X-glycine) (Pasut and Veronese, 2007; Vilar et al., 2012).

Progress in the development of synthesis methods and polymer chemistry resulted in polymer–drug conjugates at first employed in cancer therapy, and then in the treatment of other diseases, i.e. diabetes, hypertension, infections, gastrointestinal tract diseases or rheumatoid arthritis (RA). Currently, in clinical trials, the efficacy of 14 designed conjugates containing antineoplastic active substances is being confirmed. The most advanced studies are conducted on the Opaxio® conjugate, which is obtained by connecting poly-L-glutamic acid to paclitaxel and is expected be employed in the near future as a potential drug in the therapy of ovarian cancer, non-small cell lung cancer and esophageal cancer (Duncan, 2003).

Drug-PEG conjugates are widely described in the literature. They are passively targeted into neoplastic tumours – this phenomenon is known as the enhanced permeability and retention effect (EPR). Such effect involves the passive accumulation of substances, usually liposomes or macromolecular drugs, in the tumour tissue, caused by a lack of efficient lymphatic drainage in a solid tumour and its increased vascular permeability resulting from endothelial discontinuity (Kim et al., 2009).

The design of γ-PGA-PRZ connections containing phloridzin (PRZ), classified as SGLT1 protein, constituting a new class of oral antidiabetic drugs inducing glycosuria, is an example of how conjugates have been used in the treatment of diabetes. These proteins constitute a group of sodium-dependent glucose cotransporters responsible for glucose absorption in the gastrointestinal tract and its renal reabsorption. Due to toxicity, these substances are not administered orally. However, the γ-PGA-PRZ conjugate, because of its high molecular weight, is not absorbed in the small intestine and may be administered via this route. Moreover, the spatial structure of the polymer chain also protects the drug from hydrolysis. After the oral administration of conjugates, a significant improvement in pharmacological effects and drug toxicity reduction were obtained in comparison with unmodified substance (Sanchis et al., 2010).

In order to improve the solubility in water of 4-amino-6-hydroxypyrazolo[3,4-d]pyrimidine (AHPP), an inhibitor of the xanthine oxidase enzyme, it was conjugated with biocompatible amphiphilic polymer – a styrene maleic acid copolymer (SMA), thus enabling it to obtain connections that are highly soluble in water. The SMA-AHPP conjugate in in vivo studies conducted on animals exhibited a longer action than that of free AHPP. After oral administration of the modified drug, blood pressure in the examined group remained low compared to the control group for up to 168 h. Considering the action mechanism of SMA-AHPP towards the xanthine oxidase enzyme, there is a possibility of employing this conjugate in the therapy of other diseases involving the presence of peroxides, e.g. viral infections, ulcers, inflammatory diseases and ischaemia/reperfusion injuries, as well as in pathological states connected with the forming of peroxynitrite anion (ONOO–), which mediates the cytotoxic effect (Sanchis et al., 2010).

Other antiviral HIV-1 protease inhibitor conjugates – saquinavir (SQV) and polymer – were obtained by forming ester bond between them, due to which the drug solubility improved and its half-life time was extended. Vlieghe et al. conjugated azidothymidine (AZT) with κ-carrageenan, confirming in in vitro studies on MT-4 cells an enhanced antiviral activity of obtained conjugates compared with the free drug (Vlieghe et al., 2002). After administrating other conjugates of azidothymidine with dextran, the drug concentration in blood plasma remained on the level of inhibiting concentration, IC_{50}, for up to 30 h, whereas for free drug this concentration fell to an undetectable level after just 5 h. To sum up, employing conjugates limits the fluctuations of AZT plasma concentrations, thus decreasing its toxicity, or, as in the case of conjugates of AZT with α,β poly(N-hydroxyethyl)-DL-aspartamide (PHEA), enables controlled drug release (Giammona et al., 1999).

Using amphotericin B (AMB) in mycoses therapy is limited due to its poor solubility in water and high nephrotoxicity. In order to take advantage of the acid environment which accompanies the fungal infections, PEG-AMB conjugates which selectively release the drug in an infection area in acid pH were used in the therapy (Sanchis et al., 2010).

PEG-naloxone (NKTR-118) conjugates have also been researched – they are currently in Phase II of clinical trials and are intended for the therapy of opioid-induced constipation or for the treatment of other intestinal dysfunctions resulting from administering these substances. The purpose of forming NKTR-118 conjugates was to decrease the side effects of opioid therapy and to enhance the activity of peripheral opioid receptors, while simultaneously avoiding drug permeability across the blood–brain barrier and side effects on the central nervous system (CNS). Phase I of clinical trials confirmed good tolerance of the drug, its fast absorption and longer half-life time compared with free naloxone (Pasut and Veronese, 2009).

In order to improve the effectiveness of ulcerative colitis treatment with the use of corticosteroids, Varshosaz et al. synthesized dextran-budesonide conjugates. The in vitro studies on the stability of obtained conjugates in an acid environment and in phosphate buffers of different pH values, as well as in in vivo studies, confirmed that less than 10% of conjugates were subjected to pH hydrolysis in the stomach and first

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intestinal segment, and a double increase of the drug concentration was achieved as a result of microflora activity in the caecum and colonic (Varshosaz et al., 2009).

Employing polymeric conjugates in the process of tissue repair, wound healing, bone resorption or ischaemia/reperfusion injuries also seems very promising (Sanchis et al., 2010).

12. Conclusion

Polymers in pharmaceutical technology constitute an important class of excipients of constantly increasing significance; therefore, discovering their properties becomes vital. Multifunctional polymers constitute a group of compounds which, apart from their basic functions, may additionally play an important role in formulating intelligent drug delivery systems, thus contributing to the improvement of achieved therapeutic effect. The use of polymer properties described in this review should be considered when selecting desired excipients for new formulations.

Founding source

Nil.

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