WATER-SOLUBLE POLY(2-OXAZOLINES) AND THEIR SELECTED PHARMACEUTICAL APPLICATIONS

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Abstract

Poly(2-oxazolines) were first synthesized in the 1960s by polymerisation of cyclic imino ethers. Now these polymers attract significant attention of researchers because of the possibilities to prepare various functionalised macromolecules of different architecture and their high biocompatibility. Methyl, ethyl, n-propyl and isopropyl derivatives of poly(2-oxazolines) are soluble in water. Some pharmaceutical applications of water-soluble poly(2-oxazolines) are considered in this mini-review. Attention is paid to the application of poly(2-oxazolines) for the preparation of solid dosage forms (tablets and films), mucus-penetrating nanoparticles, mucoadhesive derivatives, as well as solid drug dispersions and iodophors with antimicrobial properties.

Keywords: poly(2-oxazolines), water-soluble polymers, drug delivery, mucoadhesion, nanoparticles, solid dispersions, iodophors

Introduction

Poly(2-oxazolines) were first synthesized in the 1960s by several groups of researchers [1-4]. However, for several decades there has been no significant interest in this class of polymers in the world. Such interest appeared only from the beginning of the 1990s, which was marked by the emergence of many new studies on poly(2-oxazolines). The growth of interest in the study of these polymers can be clearly seen in the analysis of publications in the Web of Knowledge database (Fig. 1).

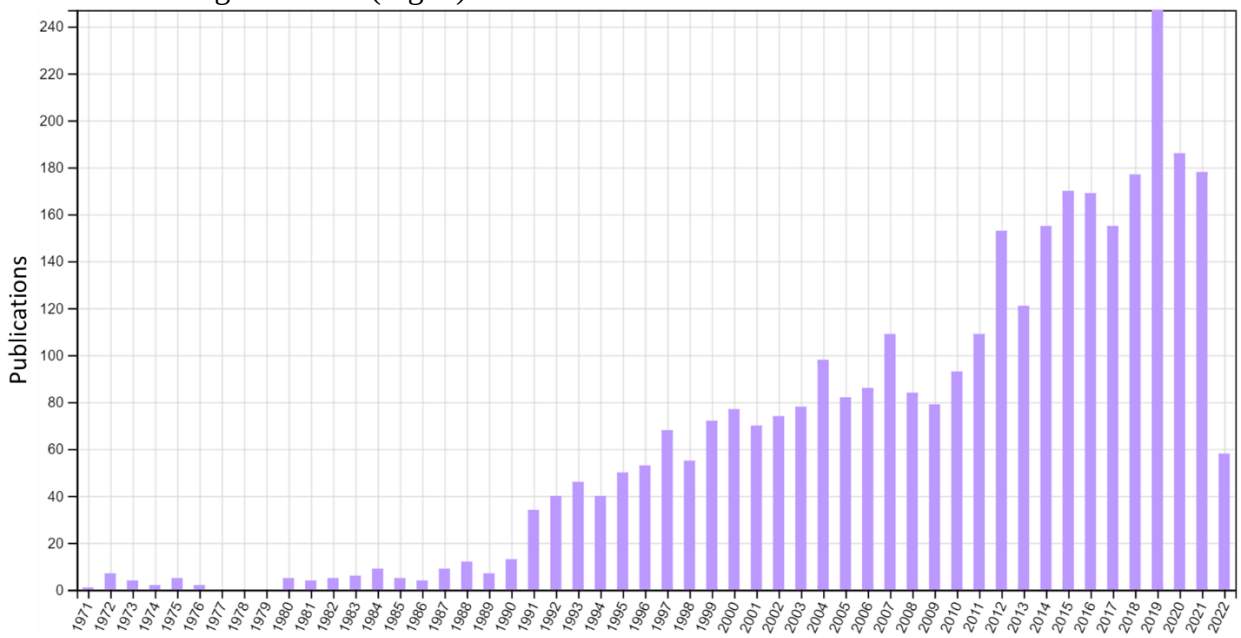


Figure 1. Publications on poly(2-oxazolines) according to the Web of Knowledge database. Data retrieved June 10, 2022 using a combination of the keywords "poly*" and "oxazoline*". A total of 3366 publications were found.

Currently, poly(2-oxazolines) are synthesized by controlled ring-opening polymerization[5], which leads to the formation of well-characterized polymers with narrow molecular weight distributions (Fig. 2).

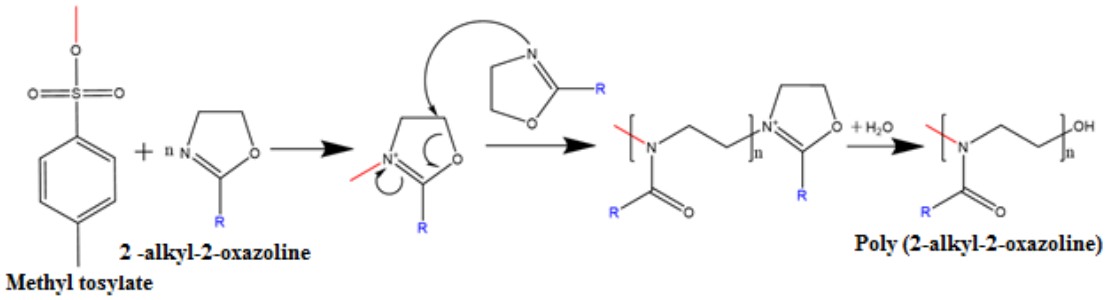


Figure 2. Mechanism of polymerization of 2-alkyl-2-oxazolines.

Due to the live and controlled nature of this polymerization, it allows obtaining not only homopolymers, but also block copolymers of various architectures.

It is also possible to synthesize poly(2-oxazolines) by polymer-analogous transformations from one derivative to another. While the original poly(2-ethyl-2-oxazoline) is subjected to complete or partial hydrolysis. Complete hydrolysis yields linear polyethyleneimine (lPEI). LPEI can then be modified by reaction with various anhydrides, resulting in the formation of new poly(2-oxazolines) (Fig. 3)[6,7].

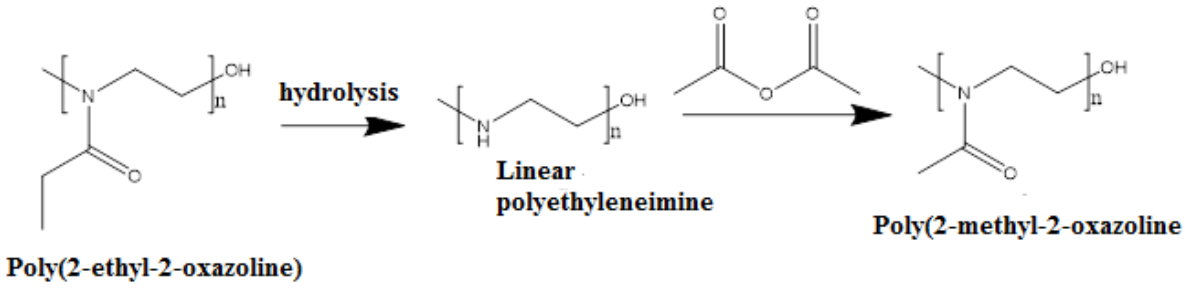


Figure 3. Synthesis of poly(2-oxazolines) by polymer analogous transformations.

Advances in the synthesis, research and applications of various poly(2-oxazolines) have been reviewed in a number of well-known reviews [8-10]. It should be noted that the methyl, ethyl, n-propyl and isopropyl derivatives of poly(2-oxazolines) are water soluble and some of these are already commercially available, for example through Sigma-Aldrich. These polymers are non-toxic and therefore find many new applications in pharmaceutical technology and biomedicine. To date, poly(2-ethyl-2-oxazoline) has already been approved by the US Food and Drug Administration (FDA) as an adhesive for use in packaging materials in the food industry, and the conjugate polymer with a medicinal substance passes the first phase of clinical trials [9].

This mini-review is devoted to some of the author's works on the use of water-soluble poly(2-oxazolines) in pharmaceutical technologies.

Interpolymer complexes of polyoxazolines

In aqueous solutions, these polymers behave like typical non-ionic macromolecules, for example, in slightly acidic environments they are capable of interacting with polycarboxylic acids, leading to the formation of interpolymer complexes (IPCs) through hydrogen bonds (Fig. 4). Complexes of this kind are used in various pharmaceutical technologies, for example, for the production of mucoadhesive dosage forms, the production of solid dispersions with poorly soluble drugs, encapsulation processes, the production of various nano-drug carriers, hydrogels, and gel-forming systems [11].

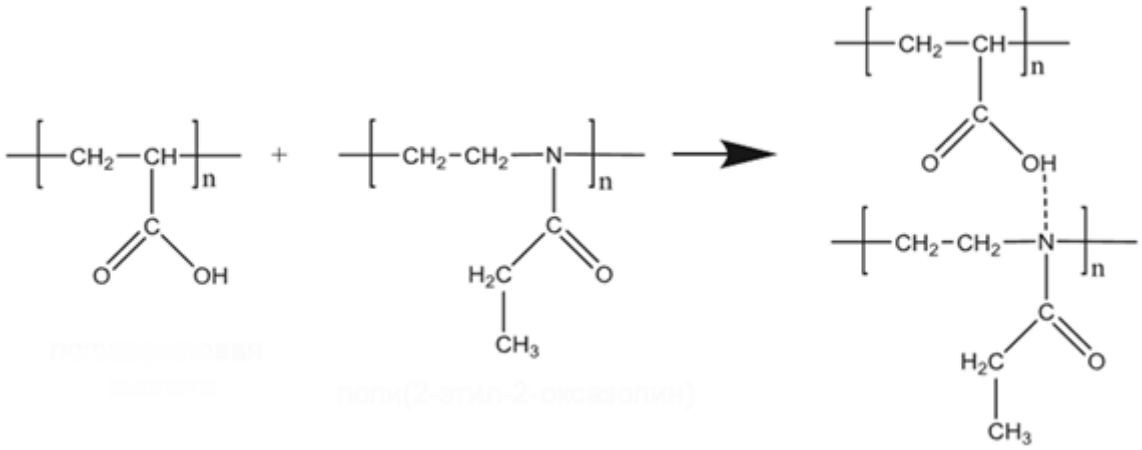
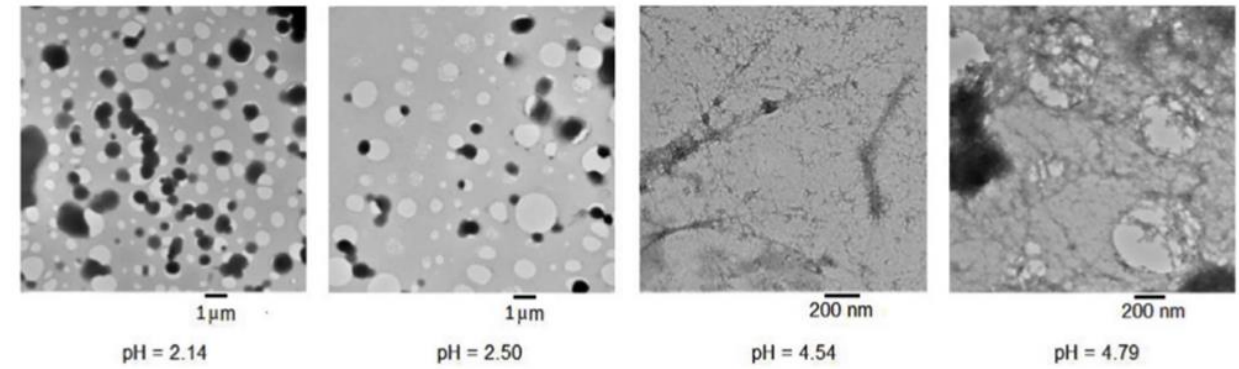
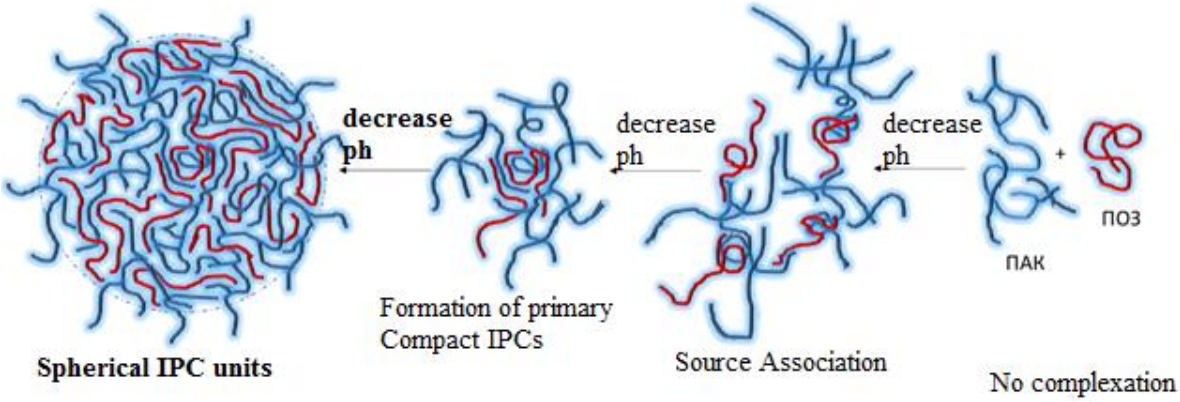


Figure 4. Scheme of the formation of an interpolymer complex in the interaction of polyacrylic acid and poly(2-ethyl-2-oxazoline).

The structure of the resulting IPCs in such systems will largely depend on a number of factors, such as pH and ionic strength of the solution, temperature, nature of the solvent, etc. Using transmission electron microscopy (TEM), we studied interpolymer interactions and the formation of IPC in aqueous solutions of poly(2-ethyl-2-oxazoline) (POZ) and weakly cross-linked polyacrylic acid (various brands of Carbopol®) at different pH values (Fig. 5a) [12]. As a result of the research, we proposed the following scheme of transformations observed during the formation of IPC at various pH values (Fig. 5b).



(a)



(b)

Figure 5. TEM micrographs of the products of the interaction of weakly cross-linked PAA and POZ in aqueous solutions with different pH values (a); Scheme of the formation of IPC particles at different pH values (b). Reprinted from [12] with permission from Elsevier.

These interpolymer interactions were used by us to obtain tablets based on complexes and mixtures of poly(2-ethyl-2-oxazoline) and weakly cross-linked polyacrylic acid with the model drug mesalazine, which made it possible to regulate its release in the gastrointestinal tract[12]. In another work, based on these interpolymer complexes, we obtained mucoadhesive tablets with hydrocortisone and investigated the possibility of their use for buccal delivery [13]. Tablets based on pure POZ showed a rather low adhesiveness to buccal tissues, however, mixing POZ with weakly crosslinked PAA can significantly enhance the mucoadhesive properties of the dosage form. The formation of IPA also significantly affects the mucoadhesive properties and gives materials different from compositions obtained by simple mixing of powdered polymers.

Mucoadhesive films based on mixtures of chitosan and poly(2-ethyl-2-oxazoline)

Chitosan is a cationic polysaccharide derived from chitin, a material found in the shells of crustaceans, some insects, and fungi.[14]. Chitosan has a number of unique physical and chemical properties. It is non-toxic, biocompatible, biodegradable, and exhibits mucoadhesive, wound healing, and antimicrobial properties [15-17].

Obtaining mixtures of chitosan with other water-soluble polymers seems to be an opportunity for preparing films with desired mechanical and mucoadhesive characteristics. In work[eighteen]we studied mixtures and films based on chitosan and poly(2-ethyl-2-oxazoline). It has been established that films obtained by casting from weakly acidic aqueous solutions exhibit full compatibility due to the formation of weak hydrogen bonds between dissimilar macromolecules. We prepared films saturated with a fluorescent dye and carried out experiments on their adhesion and retention on the surface of the eyes of a cow in vitro, as well as on rabbits in vivo. It has been established that the introduction of poly(2-ethyl-2-oxazoline) into chitosan makes it possible to control its mechanical and mucoadhesive properties of films (Fig. 6).

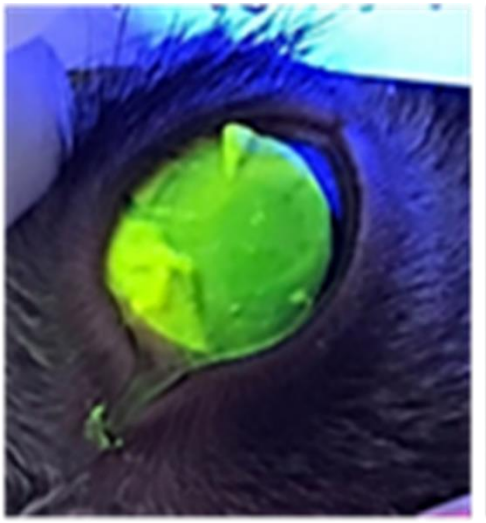


Figure 6. Photograph of a film with fluorescein on the eye of a rabbit under ultraviolet light.

In subsequent work[19]we also obtained similar films saturated with the antibiotic ciprofloxacin and investigated the possibility of their use for intravaginal delivery.

Chemical modification of poly(2-ethyl-2-oxazoline) to give it mucoadhesive properties

The non-ionic nature of poly(2-oxazolines) is the reason for their low adhesion to mucous membranes [20]. However, if there is a need to enhance the mucoadhesive properties of such polymers, one of the promising approaches is the introduction of special functional groups. Thiol, acryloyl, methacryloyl, maleimide, phenylboronic, catechol and others can be used as such groups [21]. These groups enhance mucoadhesive properties by forming covalent bonds with the functional constituents of mucins.

In work [22] we have shown the possibility of obtaining a polymer with enhanced mucoadhesive properties based on poly(2-ethyl-2-polyoxazoline) by introducing methacryloyl groups into its structure. Such a polymer was synthesized by us in two stages. At the first stage, poly(2-ethyl-2-oxazoline) was subjected to partial hydrolysis in an HCl medium, which led to the formation of a copolymer of 2-ethyl-2-oxazoline and ethyleneimine. Then, in the second stage, this copolymer reacted with methacrylic anhydride, which led to the formation of a terpolymer with methacryloyl groups (Fig. 7).

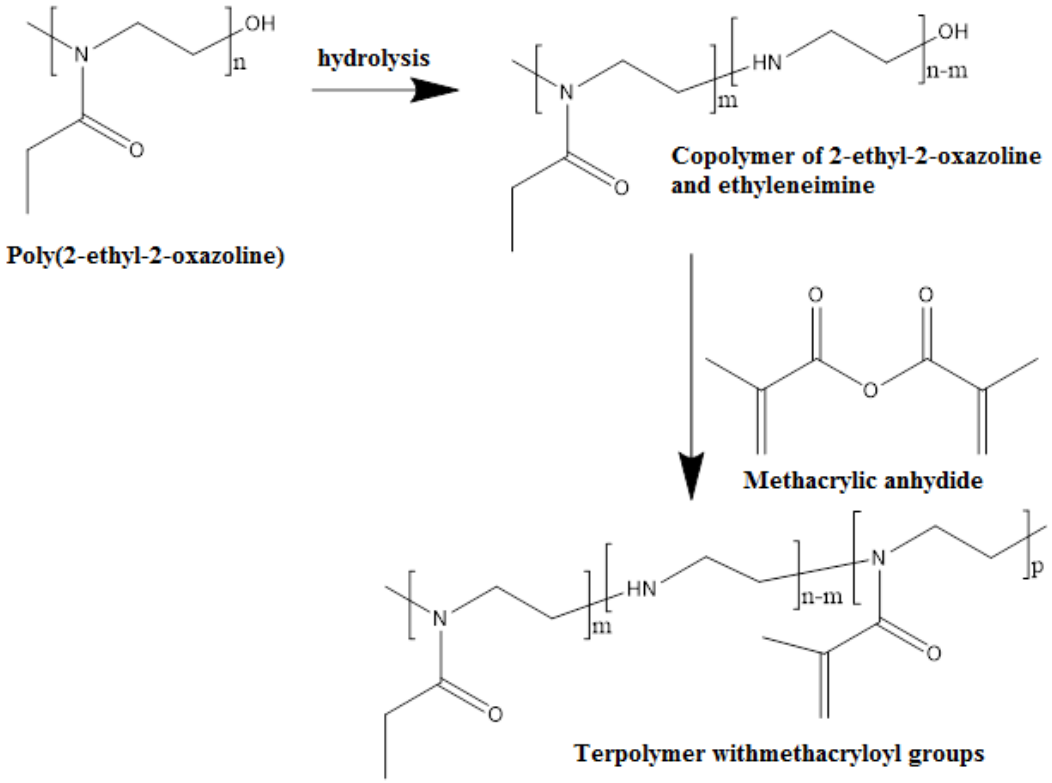


Figure 7. Scheme for the synthesis of a terpolymer with methacryloyl groups.

The mucoadhesive properties of this terpolymer were examined in combination with sodium fluorescein on the surface of the nasal mucosa of sheep using fluorescence microscopy. It has been shown that with an increase in the content of methacryloyl groups in the polymer structure, an increase in mucoadhesive properties is observed. This is due to the ability of methacryloyl groups to form a covalent bond with thiols present in the cysteine fragments of mucin.

Low-adhesive and mucus-penetrating nanoparticles

Previously, Hanes et al. [23,24] it was shown that coating the surface of nanoparticles with polyethylene glycol (PEG) macromolecules with a small molecular weight makes it possible to create carriers with enhanced mucosal permeability. Poly(2-oxazolines) are considered in the literature as an opportunity to replace PEG in some pharmaceutical technologies due to a number of their advantages.

The weak ability of poly(2-oxazolines) to mucoadhesion can also be used to create nanoparticles with mucus-penetrating properties. In this regard, we obtained model nanoparticles based on 3-mercaptopropyltrimethoxysilane, and their surface was functionalized by adding either 5 kDa PEG or poly(2-oxazolines). These particles were further labeled by attaching a fluorescent dye. Comparative experiments on the retention of thiolated nanoparticles, as well as nanoparticles with polymeric surfaces, were carried out on a model of the rat gastrointestinal tract [25]. It has been established that nanoparticles with a thiolated surface exhibit a high ability to adhere to the mucosa. At the same time, the

particles, on the surface of which short-chain fragments of PEG or POS were attached, showed a low ability to mucoadhesion. In separate works [26,27] we also studied the diffusion properties of such particles in mucin solutions by the method of tracking analysis, as well as their penetration through the gastric mucosa. It has been established that the mucus-penetrating ability of nanoparticles strongly depends on the nature of the poly(2-oxazoline) present on the surface. The transition from poly(n-propyl-2-oxazoline) (PnPOZ) to poly(2-ethyl-2-oxazoline) (PEOZ) and to poly(2-methyl-2-polyoxazoline) (PMOZ) promotes an increase in the permeability of nanoparticles through mucus (Fig. 8), which is most likely due to an increase in the hydrophobicity of poly(2-oxazolines).

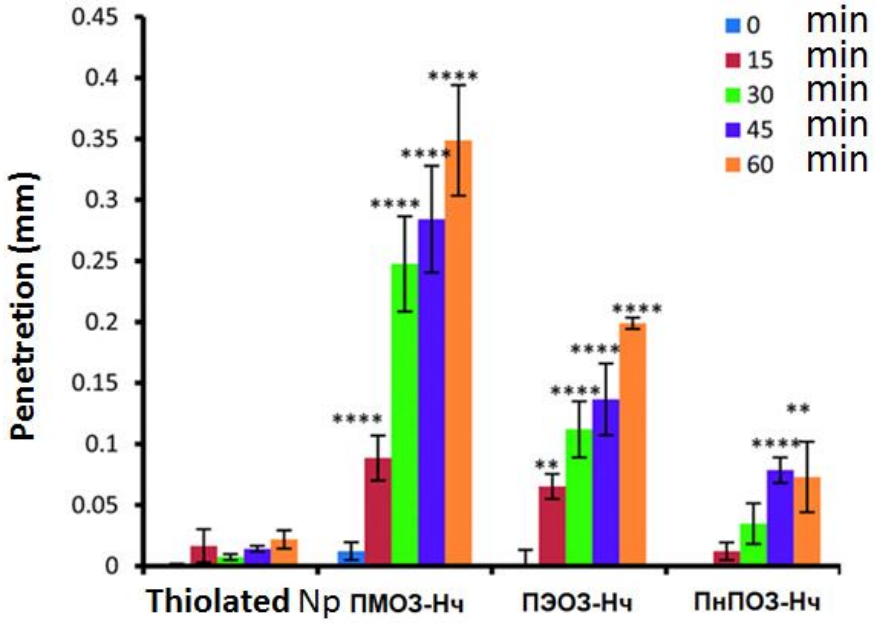


Figure 8. Penetration of thiolated nanoparticles (NPs), as well as nanoparticles containing methyl, ethyl and n-propyl chains of poly(2-oxazolines) on the surface into the layer of gastric mucus. Reprinted from[27]Courtesy of the Royal Society of Chemistry.

Similar mucus-penetrating particles with a surface containing poly(2-ethyl-2-oxazoline) were obtained by us on the basis of gold nanoparticles and the possibility of their functionalization with fluorescein was shown [28]. However, it should be noted that the above nanoparticles based on 3-mercaptopropyltrimethoxysilane and gold can only be used as model objects for research, but cannot in any way be drug carriers due to their non-porous nature. In this regard, we are currently working on obtaining water-soluble polysaccharides containing grafted short-chain macromolecules of poly(2-oxazolines). For example, poly(2-ethyl-2-oxazoline) grafted onto gellan was obtained and its biocompatibility was established [29]. Such a polymer can be used to obtain nanoparticles with included protein molecules, and our work in this regard is ongoing. In another recent study, we obtained lipid nanoparticles, the surface of which is coated with either chitosan or poly(2-ethyl-2-oxazoline) [30]. It has been shown that nanoparticles coated with chitosan have a high retention on the surface of the mucous membrane of the eye. At the same time, nanoparticles with surface poly(2-ethyl-2-oxazoline) have a much lower retention. The possibility of including the antibiotic ciprofloxacin in such particles for delivery to the eye has been shown.

Solid dispersions with poorly soluble drugs

In recent years, about 40% of all approved drugs and about 90% of drugs that are under development are poorly soluble [31]. Given that most drugs are taken orally, there is a problem of too slow release of poorly soluble drugs from tablets. When a poorly soluble drug is present in the dosage form in the form of crystals, then its release will also be slowed down. In this regard, so-called solid dispersions are used in pharmaceutical technologies, in which the drug is present in an amorphous form. This promotes faster release of the drug in the gastrointestinal tract. Amorphization of a drug in a dosage form, as a rule, can be achieved by mixing it with water-soluble polymers, the macromolecules of which prevent recrystallization. Poly(N-vinylpyrrolidone), polyethylene glycol, and some cellulose ethers are often used as such polymers [32,33].

Water-soluble poly(2-oxazolines) are also foundyat applications for the stabilization of amorphous dispersions of poorly soluble drugs [34,35]. We have obtained various water-soluble poly(2-oxazolines) by polymer-analogous transformations of poly(2-ethyl-2-oxazoline) and studied their ability to stabilize haloperidol dispersions [7] and ibuprofen [36]. It has been established that the nature of the polymer has a significant effect on the ability to stabilize the amorphous structure of the drug and, accordingly, on the kinetics of its release (Fig. 9). As expected, the crystalline haloperidol is released into solution rather slowly. At the same time, the release of haloperidol (HP) from a solid dispersion stabilized with poly(N-vinylpyrrolidone) (PVP), poly(2-ethyl-2-oxazoline) (PEOZ), poly(isopropyl-2-oxazoline) (PIPOZ) and poly(2-methyl-2-oxazoline) (PMOS), occurs much faster. Moreover, according to the ability to accelerate the release of the drug, the polymers can be arranged in the following order: PVP > PEOS > PiPOS = PMOS. However, the dispersion of haloperidol, obtained with poly(n-propyl-2-polyoxazoline) (PnPOZ) showed the effect of slowing down the release of the drug, even compared with crystalline haloperidol. We attribute this unusual slowdown to the presence of a lower critical dissolution temperature in PnPOZ. Under the conditions of experiments on dissolution at 37° this polymer becomes insoluble in water and slows down the release of haloperidol into solution.

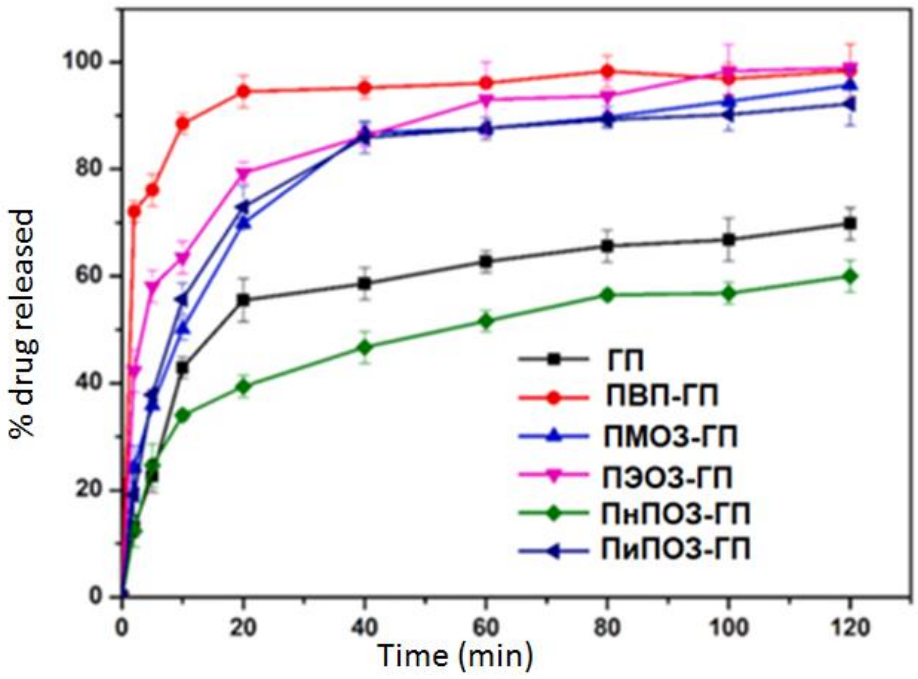


Figure 9. Dissolution of haloperidol (HP) from solid dispersions based on different polymers at 37°C. Reprinted from [7] with permission from Elsevier.

In subsequent work on the study of solid dispersions with ibuprofen, we found the effect of the formation of hydrogen bonds between polymer macromolecules and drug molecules on the nature of the resulting solid dispersions and dissolution of the drug [36]. The significant difference in drug structure between haloperidol and ibuprofen results in a difference in the formation of solid dispersions.

Iodophors

Many water-soluble polymers are capable of forming complexes with molecular iodine. The best known complexes of this type are complexes of iodine with starch, PVP and polyvinyl alcohol (PVA) [37]. Such complexes are called iodophors due to their slow release of iodine and antimicrobial properties. Iodophors most commonly used in medicine are prepared on the basis of PVP and PVA.

In work [38] we have shown for the first time the possibility of the formation of iodine complexes with poly(2-ethyl-2-oxazoline) and carried out their study in comparison with PVP. The optical, hydrodynamic, thermodynamic, and antimicrobial properties of such complexes have been studied. It has been established that poly(2-ethyl-2-oxazoline) has a stronger ability to bind iodine compared to PVP, however, the antimicrobial properties of iodophors based on these polymers are very similar.

Conclusions

This mini-review is devoted to a rapidly developing and fashionable area of polymer chemistry - the synthesis of poly(2-oxazolines) and their applications in pharmaceuticals. The author's works in this area are mainly considered. The use of water-soluble poly(2-oxazolines) for the creation of dosage forms for transmucosal delivery, including tablets and films based on interpolymer complexes and physical mixtures of poly(2-oxazolines) with other polymers, has been shown. The possibility of enhancing the mucoadhesive properties of poly(2-oxazolines) by introducing methacryloyl groups into them has been demonstrated. Obtaining nanoparticles, the surface of which is coated with short-chain poly(2-oxazolines) makes it possible to create mucus-penetrating drug delivery systems. Water-soluble poly(2-oxazolines) also find applications in the preparation of solid drug dispersions and iodophors.

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