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Role of Macromolecular Interactions of Pharmaceutically Acceptable Polymers in Functioning Oral Drug Delivery Systems

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Abstract—Research on polymer–polymer combinations of chemically complementary Eudragit types together with complex physicochemical and pharmaceutical assessments of (meth)acrylate polycomplexes is a new direction in assessing the prospects for their use as a modern tool to design modified-release oral drug delivery systems.

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The search for polymers suitable for use as drug carriers capable of controlling drug action time and localization and meeting medical and pharmaceutical requirements is complicated by the unpredictable toxicity of synthesized homopolymers and block copolymers, which restricts the practical application of the latter. The progress in macromolecular chemistry and pharmaceutical science led to a discovery of a new class of carriers — interpolymer (polymer–polymer) complexes whose unique physicochemical properties offer considerable scope for their use in modern drug formulations [1].

Interpolymer complexes are complexes formed by the reaction of chemically complementary macromolecules (proton donors and acceptors) with oppositely charged polyions [2–6]. The resulting interpolyelectrolyte complexes are less toxic that the corresponding individual polymers. At the same time, interpolyelectrolyte complexes are characterized by expressed pH value and ionic sensitivity, which adversely affects their stability in the body and may lead to their degradation into individual, not unlikely toxic macromolecular components [7–9].

Polymer–polymer complexes on the basis of copolymers widely used in pharmacy and well understood in terms of behavior in the body and safety, thus making possible to develop drug delivery systems without a risk to increase their toxicity which can be further reduced by combining synthetic (co)polymers. It should be noted that such composition "cooperation" cardinally alters the individual properties of the components in a controlled direction.

Already, for about half a century (meth)acrylic copolymers produced by the German concern Evonik Röhm (Degussa, Röhm Pharma) under the trade name Eudragit® have been used in the pharmaceutical technology in formulations for targeted oral drug delivery [10, 11]. Eudragits are used in the production of tablets, granules, and micro- and nanosized particles as coating or binding agents, as well as granulation agents in the production of matrix agents.

Eudragit copolymers are divided into two main groups: pH-dependent or pH-sensitive and pH-independent or time-dependent. The first group includes copolymers with ionogentic monomer units which ensure solution of the copolymers in corresponding compartments of the digestive tract: gastric-soluble polycations (Eudragit E) and acid-resistant or intestine-soluble polyanions (Eudragit L, S, FS). The local solubility is provided by acid-soluble diethylaminoethylmethacrylate units of type E and methacrylic acid monomer units in types L, S, and FS. The solubility of polyanionic copolymers depends on the content of carboxyl groups in the methacrylic acid monomer units: from 10% (FS) and 30% (S) to 50% (L), to ensure controlled solubility in different intestine region (at pH 7.2; 7.0, and 6.0, respectively). The replacement of methyl methacrylate units in subtype L100 by ethyl acrylate units in subtype L100-55 results in that the latter, while containing the same percentage of

methacrylate units, becomes soluble at pH > 5.5. Thus, the solubility range of the commercial copolymers Eudragit embraces the entire digestive tract: stomach (pH 1–1.2) and intestine, beginning with duodenum (pH > 5.5) and small bowels (pH 6–7) to colon (pH 7) and ileum (pH 7.5).

The second group of Eudragit copolymers includes eudragits insoluble in the gastrointestinal tract, which were given the name retarded eudragits. The permeability of coatings made of such copolymers is varied by introducing in them a small fraction of groups ionizable over the entire pH range. Thus, polycationic types Eudragit RS and Eudragit RL contain, 5 and 10% of quarternary (quarternized, zwitter-ion) groups, respectively. The same group also includes two other, N-neutral Eufragits which contain no ionizable groups at all, because their methacrylic acid units are fully esterified (Eudragit NE, NM). In view of a much higher average molecular weight, these types are primarily intended for use in delayed-release delivery systems. They are made permeable by hydrophilic ethyl ethacrylate units, unlike ionogenic but low-charge-density type RL and RS copolymers.

The issues of combining (meth)acrylic copolymers of different types, including oppositely charged Eudragit types, have been considered in a number of reviews [10, 12–14], but a comprehensive analysis of the physicochemical principles of macromolecular interactions, which clarifies the mechanism which controls the rate of drug release from the oral drug formulations on the basis of chemically complementary Eudragit types, was presented fairly recently in our review [15].

The first research on combining two oppositely charged types of Eudragit investigated by [16] on an example of matrix tablets prepared by direct compression of theophylline with a mixture of equal quantities of Eudragits L100 and RSPO. It was shown that the matrix tablets containing a physical mixture of copolymers slightly slower release theophylline into an acid medium mimicking the stomach conditions compared to Eudragit RS.

Quite successful proved to be an oral system registered under the trademark CODES. This system provides drug targeting to colon region. It is formulated by consecutive coating of a core tablet containing a drug and synthetic disaccharide lactulose by two outer layers of Eudragits E100 and L100 [17]. The copolymer ration in the bilayer coating applied from aqueous-ethanolic solutions (1 : 9 with E100 and 5 : 13 with L100) is 2 : 1 by weight. The positive results obtained with this system were confirmed by a scintigraphic analysis of the gastrointestinal tract in volunteer experiments.

Thus, film coatings, both monolayer obtained by combining intestine-soluble polyanions L/S with polycations RL/RS and bilayer obtained by combining with type E, ensure the desired profile of drug release from delivery systems.

Joint effort of researchers of the Univerity of Georgia (USA) and the Röhm Pharma (Germany) resulted in the development of an oral system for local delivery of drugs to the colon [18, 19]. The pellets comprise a central sugar core coated with a drug matrix layer. The localized action of this formulation is provided by its bilayer coating. The inner layer consists of a combination of two copolymers Eudragit RL and RS (ratio 2 : 8), which are similar to each other by chemical structure and properties. The outer layer is made of an Eudragit copolymer of the newest type FS30D which is designed for delivery systems targeted specifically to the colon. It was suggested that if copolymers of these types are combined in an oral formulation, the outer coating will ensure localization of drug release in the colon. Therewith, the outer layer consists of two insoluble copolymers RL and RS, and the permeability of the shell is controlled by the copolymer ratio. The researchers expected that the required copolymer ratio would ensure the required rate of drug release. However, the drug-release profiles in the tests on 5-aminosalicylic acid–loaded systems revealed an unexpected release slow down. In view of the fact that the copolymers used in the tested system bear opposite changed, intermacromolecular interactions of reactive groups of the polymer chains located at layer interfaces was suggested. Bilayer systems were prepared by applying one, preliminarily dried coating, on another in a sequence similar to that in the pellets. The researchers were highly surprised when detected, using IR and NMR spectroscopy and differential scanning calorimetry, no polymer–polymer interaction in the resulting bilayer films [20].

Even though a negative result was obtained, the researchers did not rule out the possibility of ionic binding between oppositely charged Eudragit copolymers. They suggested that the reason why intermacromolecular interactions were not detected lied in an insufficient sensitivity of the analytical techniques.

In view of the results obtained in [21], we suggested that evidence for intermacromolecular interaction is reasonable to search for in experiments on drug release in media mimicking the medium of the gastrointestinal tract, which proved to be the case [21].

The developed formulation of an oral system for local drug delivery to the colon, registered by Evonik Pharma by the trademark EUDRACOL, is the first and unique commercial product for the targeted delivery of drugs whose functioning is underlain by polymer–polymer interactions of oppositely charged Eudragit copolymers.

Attempts were undertaken to explain the unexpected deceleration of drug release from pellets with bilayer and monolayer coatings made of a mixture of oppositely charged Eudragit copolymers, but they failed. Taking into account that the interaction of oppositely charged polyelectrolytes are electrostatic in nature, which is only possible in aqueous salt solutions with a definite pH value, we suggested that researchers failed because they did not pay due attention to the effect of consecutive dwelling of an oral delivery system in different media during its pasiing through the gastrointenstinal tract.

Considering the structure of Eudragit copolymers, we can conclude that their chemically complementary pairs, having oppositely charged groups, will interact with each other to form interpolyelectrolyte complexes.

The possibility of interaction between Eudragits, both at the stage of preparation and at the stage of drug release from formulation, was either suggested or disputed, or even rejected a priori. The reason for such contradictory opinions of researchers can be explained as follows. The intestine-soluble (gastro-resistant) copolymers used in the pharmaceutical technology are polyanions soluble only in weakly acidic, neutral, and weakly alkaline media (pH > 5.5); at the same time, gastric-soluble Eudragit types copolymers are polycations, and they are soluble exclusively in acidic media (pH < 5.5). From this it follows that a pair of oppositely charged Eudragit copolymers are theoretically impossible to interact with each other, because the main condition for such an interaction to occur is their solubility at the same pH. However, in our experiment both oppositely charged copolymers dissolved at the same pH, and out attempt to observe polymer–polymer interaction met with success. The obtained polycomplex formed by a stomach-soluble Eudragit E100 (polycation) and an intestine-soluble L100 (polyanion) was characterized to find out whether it is feasible as a drug carrier in pelleted drug dosage forms [22–24]. Later we synthesized polycomplexes using other Eudragit copolymers (L100-55, L100, S100, EPO) [25–30], as well as combined methacrylic copolymers with oppositely charged polysaccharides (chitosan, sodium alginate) [31–33] to obtain matrix drug carriers.

Synthesis was performed by mixing polyelectrolyte solutions at a fixed pH value and varied ratios of copolymers, whereas their charge density, and, consequently, the reactivity of macromolecular components, was invariable. As a result, polycomplexes with equimolar compositions were obtained. These products are designed for delayed-release delivery systems [25]. Their chemical homogeneity and individuality, as well as composition were established by means of differential scanning calorimetry, IR spectroscopy, and elemental analysis [25, 27]. The synthesized interpolyelectrolyte complexes have only one glass transition temperature (Tg), and, therewith, all the polycomplexes had higher Tg's that the thermally more plastic copolymer Eudragit E. The experimental Tg of the copolymer EPO/L100-55 strongly deviated from that calculated the Gordon–Taylor equation, providing evidence for essential electrostatic interactions between the component copolymers (i.e. much more heat is required for the polymer chains in polycomplexes to acquire mobility required for glass formation [25, 27, 29]).

Thus, the first systematic research on the synthesis and physicochemical and pharmaceutical characteristics of interpolyelectrolyte complexes synthesized on the basis of a cationic Eudragit copolymer (E100/EPO) and polyanionic Eudragit copolymers (L100-55/L100/S100) resulted in the selection of therapeutically efficient carriers for drug delivery systems.

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