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Polymers in the Formulation of Drug Dosage Forms with Modified Release

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Abstract—New polymer-based dosage forms with specified biopharmaceutical properties, including dosage forms with modified release, are described. The mechanism and character of release of active pharmaceutical ingredients from the dosage forms are discussed.

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INTRODUCTION

Solid drug forms with dosage release are produced using a large variety of auxiliary substances, including polymer products [1]. Auxiliary substances are either introduced into compositions or applied (film coatings) on intermediate products with the aim to endow them with required structural mechanical, physicochemical, and biopharmaceutical properties.

The introduction into the pharmaceutical practice of new polymers opens up the way to designing new drug dosage forms with preset biopharmaceutical properties, including those with modified release of the active substance [2–5]. Polymer auxiliary substances allow one to program the rate or site of release of the active substance from pills in the human body. Depending on the degree of control of the release process, controlled- and extended-release dosage forms are differentiated.

Drug dosage forms with controlled (programmed) release are characterized by a preset extended or accelerated delivery of an active substance to the biophase and the corresponding release time. The release process is considered controlled provided: (1) the form of mathematical equation relating the quantity of released substance on parameters controlling the process is known; (2) substances are released according to a pharmacokinetic program; (3) physiologic conditions (pH and enzyme composition of the contents of the gastrointestinal tract, etc.) do not or scarcely affect the rate of release, so that it is controlled by the properties of the drug itself and can be predicted with reasonable accuracy.

Controlled release is provided by multilayer tablets whose middle layer consists of microcapsules containing drug, whereas the outer layers contain auxiliary substances preventing the microcapsules from mechanical damage on tableting [6].

Extended dosage forms (matrix tablets, retard, multilayer, multiphase) provide slow release and extended action of drugs. They allow less frequent drug administrations and lower course doses, and, as a consequence, reduced side effects. The rate of drug release depends on such factors as the nature of auxiliary substances and the solubility of the drug, as well as on the porosity of the tablet and its production conditions.

Extended release can be provided by using matrix tablets or film coatings. In matrix tablets, the active substance is incorporated into a matrix of hydrophilic or gel-forming substances, or insoluble polymers. Such matrices create conditions for drugs to release sustainedly and evenly for a long time and to act sustainably [7, 8].

Matrix Tablets

There are different types of matrix tablets: carcass, skeleton, insoluble-carcass, and Durules. The matrices of carcass tablets are formed by network polymers with drugs incorporated into their structure [9].

Matrix tablets provide modified release of drugs in controlled regimens: extended (insoluble carcass, diffusion barrier), controlled (pH-dependent release), and accelerated (matrix tablets containing solid drug dispersions) [10, 11].

Matrices Providing Extended Drug Release

Tablet matrices can swell and slowly dissolve or preserve their geometric shape throughout the time they stay in the body and then be excreted intact, which makes possible extended drug release. When the matrix is preserved, the substance is washed out, and, therewith, the rate of release depends neither on the content of digestive enzymes nor on the pH of the medium of the body and scarcely varies as the tablet travels through the digestive tract [12].

In terms of the nature of interaction with the liquid medium of the body, polymer auxiliary substances are divided into hydrophilic and hydrophobic [4], whereas in terms of the capacity to release drug depending on the pH of the medium, into pH-dependent and pH-independent (inert matrices).

Hydrophilic matrices are made of swelling polymers: derivatives of cellulose, acrylic acid, polyvinyl acohol, etc. [13]. Inert matrices are made of water-insoluble polymers: polyvinyl chloride, polyethylene, polyurethanes, co-polymers of vinyl acetate and vinyl chloride, and ethyl cellulose. To make channels in a layer of a water-insoluble polymer, water-soluble components (polyethylene glycol, polyvinylpyrrolidone, lactose, pectin, etc.) are introduced into the matrix; these components are washed out from the tablet carcass, thereby creating conditions for gradual drug release [11].

The action of drugs can be extended by precipitating them on an ion-exchange resin. The advantage of extended-action drugs obtained by sorption of the active substance on ion-exchangers consists in that the rate of release is independent of the pH of the medium, activity of digestive enzymes, peristalsis and other physiologic factors and depends exclusively on the concentration of counter ions and the rate of diffusion of exchanging ions, which depends on the properties of the ion-exchanger (pK_a, cross-linking degree, dispersity). Diffusion of substances through the network of polymer chains of the ion-exchanger the slower, the larger the size of their particles. Extended-action drugs with ion-exchange matrices are known by the names ionexiten, resinates (drug resins), ion-exchange salts, and ion-exchange complexes. They form the base of such commercial medicines as Bephetamine, Spastipax, and Dexten.

Among hydrophilic polymers, cellulose derivatives are widely used as matrices for extended-action tablets. In particular, the efficiency of hydroxypropyl methyl cellulose which creates a diffusion barrier was confirmed with a great variety of active ingredients [14]. The wide range of molecular weight of this polymer makes it possible to obtain gels with a preset viscosity, which is quite important for the production of soluble matrix tablets.

Hydroxypropyl methyl cellulose (HPMC) as an auxiliary medical substance is produced under the trademark Methocel. There are several Methocel products differing from each other by the number of methyl and hydroxypropyl groups and polymerization degree, and, as a consequence, by the viscosity of a 2% aqueous solution.

For extended release of active drugs from dosage forms with a high drug content, an HPMC which is capable of rapidly forming viscous gels is required. Thus, Methocel K100M CR (viscosity ~100000 cP) and Methocel K 15M CR (viscosity ~15000 cP) form virtually insoluble gels, thus allowing gradual release of the substance into the solution medium due to diffusion through the gel layer. A combination of high- and medium-viscosity Methocels, for example, K4M CR (viscosity ~4000 cP) и K100 LV CR Fine can be used to provide a finer control of release of active substances. By combining various-viscosity HMPC one can obtain a controlled-release drug dosage form.

Other cellulose derivatives, such as hydroxypropel cellulose (Clucel) and hydroxyethyl cellulose (Natrosol 250 Pharm), are applied as binders for extended-action drugs or film-formers in water-based film coatings. Cellulose derivatives are pH-independent matrices.

Another group of polymers used in matrix tablets is formed by cross-linked carboxyacryl (carboxyvinyl) polymers [15]. They are produced under the trademark Carbopol (Noveon, USA). Carbopols 71G, 971P, and

974P are cross-linked with allyl pentaerythritol and polymerized in ethylacetate and neutralized by 1–3% potassium chloride [16, 17].

Carbopols strongly swell in water (1000 times) to form a gel layer. The gel layer forms within 10 min at pH 4.0−6.0. Since the pK_a of these polymers varies from 6.0 to 0.5, the hydroxyls of the carboxy groups in the polymer backbone are ionized, which results in electrostatic repulsion of the polymer chains and enhances swelling. This property is used in drug dosage forms with modified release. Carbopols exhibit adhesive activity with respect to mucous membranes [18, 19].

Carbopol 71G NF is a granular excipient for controlled-release drug dosage forms. It is manufactured by the direct pressing technology [18, 20].

Copolymers of acrylic and methacrylic acids have found wide application as tablet matrices. They are produced under the trademark Eudragit (Evonik Industries). There are a number of Eudragit polymer families which differ from each other by dissolution rate: Eudragit S family polymers dissolve slower than representatives of the Eudragit L family [21]. Oral extended- and pH-independent dosage forms are produced using Eudragit RL, RS, and NE. Drug release from the Eudragit E matrix occurs in stomach, from Eudragit L in intestine, from Eudragit L 100-55 and Eudragit L 30-D-55 in duodenum at pH > 5.5–6.0, from Eudragit L 100 in the segment from the small to twister intestine at pH 6.0−6.5, and from Eudragit S 100 near the large intestine at pH 6.0−7.5.

Polyvinyl alcohol derivatives, too, are used as tablet matrices.

The Kollidon VA 64 (Copovidone) matrix is used for lipophilic or water-insoluble substances. Kollidon VA 64 forms with polyacrylic acid an insoluble matrix complex. As the hydrophilic component, Kollidon VA64 controls release of drug if the latter is incurporated into a lipophilic matrix (stearyl or cetyl alcohol).

Kollicoat IR (copolymer of vinyl alcohol and ethylene glycol) is used for instant release tablets and granules, as well rapid release forms.

Among domestic polymers used as matrix-forming components of particular interest are interpolymer complexes formed by reactions of complementary macromolecules (polyanions and polycations or proton acceptors and donors). Drug release from the matrix tablets on the basis of a composite polymer carrier which is an interpolymer complex of poly(methacrylic acid) and poly(ethylene glycol) occurs by several mechanisms: dissolution of drug not bound to the matrix from the tablet surface; release from the polymer complex (when drug is bound to the composite polymer carrier); diffusion through the hydrogel layer; and diffusion in the polymer matrix. This composite polymer carrier shows pH-dependent release, which suggests the possibility of preparation of controlled-release dosage forms.

Controlled Drug Release Matrices

Pulsed (multiple, intermittent) release dosage forms release drugs in portions to mimic circadian drug intake. The group of pulsed release dosage forms includes two-layer (duplex) and multilayer tablets. In such forms, drug doses are separated with a barrier layer which can be film, pressed, or even pelleted; the time course of drug action depends on the number of layers in the tablet. Drug doses are released in preset intervals (irrespective of where the tablet resides in the gastrointestinal tract) or in a preset site of the digestive tract. Thus, if a dosage form contains an acid-resistant layer, the first drug portion can be released in stomach and the second, in intestine.

Drug dosage forms with sustained controlled release are produced using special auxiliary substances. In this case the initial drug dose is released immediately after intake, and further (maintaining) doses are released gradually at a constant rate corresponding to the excretion rate [1, 7]. Such drug forms are more efficient than pulsed release forms, since they provide a constant therapeutic drug concentration, with no expressed extremes and high toxic loads on the organism. Sustained release drug dosage forms include matrix tablets, tablets and capsules with microforms, etc. Multiphase tablets are produced by pressing granules showing different rates of release of the same drug. An example is provided by two-phase tablets (rapid retard) Adalat CL (Bayer) comprising a mixture of microgranules with instant and extended release of Nifedipine, due to which the drug combines a fast therapeutic effect and an extended action. Therewith, the therapeutic concentration of Nifedipine is maintained for 8−10 h. Individual, not mixed, granulates are used to produce two-layer tablets which provide separate delivery to organs of incompatible drugs (differently colored).

Retard tablets with pulsatile drug release are produced by pressing granules containing drug

encapsulated in a polymer matrix which dissolves layer-by-layer to release a further portion of drug. A number of excipient substances are used in retard tablets with different release mechanisms: delayed, sustained, or sustained extended. One group of retard tablets is formed by duplexes.

In multilayer tablets, drug layers alternate with polymer layers which prevent drug release until the polymer has been destroyed completely under the action of various factors of the gastrointestinal tract (pH, enzymes, temperature, etc.). Tablets with multilayer coating provide repetitive effect of a drug substance; they consist of a core containing a therapeutic dose of drug and having a limited-permeability coating, as well as an external layer designed for instant drug release.

A group of layered extended-release dosage forms are tablets which are pressed of granules with varied-thickness coatings. Such tablets are pressed of drug particles encapsulated in shells of either polymer materials or lipids with different melting points. Layered extended-release tablets contain in their middle layer drug capsules and in the external layer, polymer materials which protect microcapsules from damage on pressing [20, 22].

Special polymer excipients are used for production of hydrodynamically balanced tablets which float in the gastric juice and preserve this property until drug has been released completely. The tablets float in the stomach content for 2–3 h and gradually degrade, releasing the drug substance.

For a tablet to float, its density should be lower than that of the gastric juice [19]. Floating tablets can fulfill the function of drug delivery. Floating delivery systems are produced using swelling polymer matrices, such as Methocel or polysaccharides (for example, chitosan), with inclusion of effervescent components (sodium hydrocarbonate, citric or tartaric acid) or matrices containing a liquid which evolves gas (CO_2) on contact with the gastric juice.

Hydrocarbonates, along with that they impart floatability to tablets, create immediate alkaline environment of gel-forming polymers. Moreover, CO_2 evolution accelerates hydration of the floating tablet, which is quite important for forming a bioadhesive hydrogel due to triggering an additional mechanism of bioadhesion, which favors drug retention in the stomach.

Matrices Providing Accelerated Drug Release

Promising is the technology of production of carcass tablets with the use of solid disperse systems which represent highly dispersed drugs immobilized in a solid polymer matrix [8]. The high drug dispersion degree considerably accelerates tablet dissolution.

The advantages of solid disperse systems for pharmaceutics are as follow: (1) enhanced bio-availablity of hardly soluble and extended action of readily soluble substances; (2) accelerated initiation of therapeutic action; (3) decreased therapeutic dose at the same therapeutic effect; and (4) less frequent side effects.

Solid drug dispersions are produced by various technologies, including direct extrusion [23] or hot-melt extrusion. Polymers feasible for extrusion should exhibit a series of properties: They should be stable, nontoxic, and moisture-insensitive, and their glass transition point should fall in the range 50–180°C. For hot-melt extrusion, BASF has developed an amphiphilic polymer solubilizer Soluplus. This is a copolymer of vinylcaprolactam, vinyl acetate, and ethylene glycol. The glass transition point of Soluplus is 70°C. The copolymer forms a solid dispersion at 120−180°C. After extrusion at 180°C no polymer degradation was revealed.

Certain characteristic features, such as lipophilicity, proton donor or acceptor ability, and presence of an amido group enhance the solubilizing capacity of matrices for solid dispersions [24]. Thus, Povidone (*N*-vinylpyrrolidone monopolymer) and Copovidone (copolymer of *N*-vinylpyrrolidone and vinyl acetate) are lipiphilic substances [25], and they are quite appropriate for the production of solid dispersions by the extrusion process. Of the Kollidon family products, Kollidon VA 64, Kollidon 12 PF, Kollidon 30, and Kollidon SR [3] are used in the extrusion process.

The extrusion technology was also applied for the production of solid drug dosage forms with Eudragit RL and RS [26].

Biodegradable Polymers for Nano- and Microparticles

Production of nanoparticles and microspheres is an important direction in the development of pharmacy. Particle size affects drug release profile and action site. The pharmaceutical industry produces delivery systems containing extended release microspheres. The

preferable starting materials for such systems are polylactides and copolymers of lactic and glycolic acids with additional inclusion of other comonomers.

Most attention is focused on polylactide, polyglycolide, as well as copolymers of lactide (*L,D*-3,6-diisopropyl-1,4-dioxane-2,5-dione) and glycolide (1,4-dioxane-2,5-dione) with varied monomer ratio. Such materials are completely biocompatible, induce no inflammations, and their degradation products are excreted from the organism through normal metabolic processes. Of particular importance is the fact that the developed technology allows production of lactide–glycolide copolymer microparticles with the size ranging from 0.2 to 500 μm. Before injection such microparticles can be suspended in aqueous and nonaqueous solvents which do not dissolve the applied polymers.

Quite successful at the pharmaceutical market are Zoladex and Lupron Depot peptide-releasing systems. The implant Zoladex is obtained from a 50 : 50 lactide–glycolide copolymer which releases active substance over 28 days after subdermal injection. Lupron Depot microspheres release leuprolide acetate over a month.

Drug Dosage Forms with Polymer Film Coatings

Coating tablets with a shell of one or several layers of natural or synthetic excipients allows programming the rate or site of drug release [27].

Coatings are differentiated in terms of shell composition and coating procedure (encapsulating, film, and pressed) and in terms of the medium where the coating should dissolve (stomach-soluble and intestine-soluble) [28].

Tablets with a film coating have a thin shell (film thickness 0.05–0.2 mm) comprising less than 10 wt % of the tablet of membrane-forming materials. Film coatings are produced by applying on tablets a film-forming substance in aqueous or nonaqueous solvents. As a rule, film coatings are applied under pseudo-liquefaction conditions [12]. The film sticking to the tablet surface after evaporation of the solvent allows preserving the initial shape, breaking line, and identification label of the tablet.

The progress in the technology of production of tablets with film polymer coatings is favored by the advantages offered by such drug dosage forms. These include selective solubility of tablets in stomach or intestine; controlled rate of drug adsorption; possibility to combine incompatible active substances in a single dosage form; preservation of the physical, chemical, and mechanical properties of tablet core, as well as of the initial geometric parameters of tablets, their shape and specific marks and labels; lower weight compared with encapsulating coatings; and possibility of automation of the coating process.

Excipient substances used in tablet coatings are arbitrarily divided into two groups.

Water-soluble coatings protect from mechanical damage but do not protect from air moisture. Such coatings are produced from poly(vinylpyrrolidone), methylcellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose, and other polymers applied from aqueous ethanol or aqueous solutions.

Stomach-soluble coatings protect tablets from water but do not prevent their fast degradation in stomach (within 10–30 min).

Intestine-soluble tablets are stable in the stomach and release drugs in the intestine juice. They are obtained by coating drug core with an intestine-soluble shell, pressing granules and particles coated with intestine-soluble shells, or pressing drugs with acid-resistant fillers.

The permeability of water-insoluble films can be varies by varying the thickness of coating and using pore-forming additives (polyethylene glycol, hydroxypropyl methyl cellulose, or microcrystalline cellulose). The amount of additive is chosen so as to meet preset drug release conditions. Coatings soluble in the intestine juice localize drugs in the intestine, prolonging their action. Insoluble coatings represent microporous films obtained, for instance, from ethyl cellulose. The mechanism of drug release is as follows: Gastric juices rapidly penetrate through pores in the insoluble shell and dissolve the active substance or cause it to swell. In the first case the substance diffuses through the film in the reverse direction and in the second, the shell is broken, and the substance releases in a usual way [28].

At present more than 50 film-forming materials are used. Certain film-forming compositions are produced either as ready-to-use solutions comprising a film-former, plasticizer, colorant, and solvent in an optimal ratio or as half-products as granules (powders). In the last case the film-forming solution is prepared immediately before use.

Below we consider a series of film-forming compositions.

Water-soluble film coatings for tablets are produced with cellulose derivatives as film-forming materials.

Metolose is a nonionic water-soluble cellulose ester. The viscosity of metolose solutions, like with other water-soluble polymers, depends on their molecular weight. Transparent films obtained from metolose solutions are further plasticized by adding plasticizers like glycerol, propylene glycol, sorbitol, and citric acid esters.

CEKOL is a registered trademark of carboxymethyl cellulose. It is produced by Noviant (Sweden). CEKOL is produced as a film-former, binder, thickener, and stabilizer. After drying CEKOL solutions form strong and flexible films. Tablet coatings are recommended to be produced from CEKOL 30.

Aquacoat ECD (FMC, USA) is a 30% aqueous dispersion of ethyl cellulose. It is a hydrophobic film-forming system. It is used for protection of active substances of tablets from moisture and for masking their taste. Aquacoat ECD offers a number of advantages. It is a well-dispersed aqueous system featuring a low viscosity, short time of preparation, and high strength of the resulting coating which ensures sustainable pH-independent drug release. This product makes it possible to obtain a uniform, readily printable coating.

Surelease (Colorcon, Great Britain) is an optimally plasticized 25% aqueous suspension of ethyl cellulose. Coatings from this material make possible extended release of drugs from solid dosage forms. Surelease possesses taste-masking properties.

Intestine-soluble film coatings are produced from the following film-forming materials.

Hypromellose phthalate (hydroxypropyl methyl cellulose phthalate, HPMCP) is a powder with a 400–600-μm mean particle diameter. It is fairly easily dispersed in solution and readily soluble in organic solvents. This film-forming material under the trademark HP-55 is applied for production of a usual intestine-soluble coating. HP-55S has a higher polymerization degree than HP-55 and, naturally, a higher viscosity, and it forms a mechanically strong film resistant to the gastric juice. HP-50 dissolves at a lower pH, and, therefore, this film-forming material can be used for developing drugs soluble in upper intestine [9].

Aquacoat CPD (30% aqueous suspension of acetyl phthalyl cellulose) is a registered trademark of the FMC Corporation. This material is used for coating tablets of acetylsalicylic acid, sodium diclofenac, antibiotics, bromophenylamine maleate, and sodium fluoride. A functionally stable film can be prepared using 6−10 wt % of the coating material. In pellets and biologically active additives (BAA), the most common weight fraction of the coating material is 10−15%. Aquacoat CPD is also used for coating hard and soft gelatin capsules. To impart elasticity to brittle or hard polymer films of acetyl phthalyl cellulose, the starting film-forming agent should be doped with plasticizers, such as diethyl phthalate, triethyl citrate, and glycerol triacetate.

Pharmacoat Shin-Esti is a modified hydroxypropyl methyl cellulose. Pharmacoat 606G is a granulated product. It is designed for fast preparation of film-forming solutions. Pharmacoat 904 is used not only for preparing film-forming solutions, but also for fixing sugar coatings, as well as a binder for granulation. Tablets coated with Pharmacoat exhibit hardness, improved resistance to abrasion, uniform color, good taste, packing flowability, and printability. Unlike pH-dependent film-forming polymers, such as acrylic and vinyl polymers, Pharmacoat has no restrictions as to solubility, which makes it quite convenient to use.

OPADRY (Colorcon, Great Britain) is a ready-to-use mixture of excipients including 50−70% of hydroxypropyl methyl cellulose, 5−10% of polyethylene glycol 400, and 25−40% of a coloring pigment.

Sepifilm (the principal components are hypromellose, microcrystalline cellulose, and polyethylene stearate 400) allows preparation of high-quality uniform and stable tablet coatings due to its high dispersivity and the ability of the resulting dispersions to be evenly spread over tablet surface and strongly fixed on tablet core.

Let us consider to commercial film-forming materials for intestine-soluble coatings.

Sureteric (Colorcon, Great Britain) is a powdered mixture of excipients (polyvinyl acetate phthalate, titanium dioxide, talc, PEG 400, sodium hydrocarbonate, sodium alginate, triethyl citrate, stearic acid, silicon dioxide). It is prepared for use by dispersing in

water. The films applied on tablets are soluble in the thin intestine.

Kollicoat MAE 30 DP and Kollicoat MAE 100P (BASF, Germany) are copolymers of methacrylic acid and ethyl acrylate. They are designed for preparation of drugs resistant to the gastric juice.

There is a fairly wide range of film-formers for coatings for extended-release drug dosage forms.

Kollicoat SR30D is a polyvinyl acetate dispersion stabilized with povidone and sodium lauryl sulfate. It is used for production of dosage forms with controlled pH-independent drug release, as well as for masking unpleasant taste and odor. Moreover, the resulting coatings can serve for separation of drugs with the aim to prevent their interaction.

Kollicoat EMM30D is a copolymer of ethyl and methyl acrylates. It is used for production of dosage forms with controlled pH-independent drug release. The coating masks the odor and taste of the active substance and prevents it from moisture and interaction with other components.

Kollicoat MAE30DP and Kollicoat MAE100P, copolymers on the basis of methacrylic acid, are used in extended-release drug dosage forms.

Eudragit L30D is primarily used as a coating for oral dosage forms, particularly tablets or capsules. Such coatings are resistant to the gastric juice but dissolve in the intestinal juice.

Acryl-EZE (Colorcon, Great Britain) is a powdered mixture of excipients, which is ready for applying a film coating soluble in the thin intestine. This film-forming material is applied on solid dosage forms (tablets and pellets) as an aqueous solution. It is a fully optimized intestine-soluble powdered system on the water basis for coating drug dosage forms (sugar spheres, pellets, minitablets, etc.).

CONCLUSIONS

The industry of drugs with modified characteristics is based on the application of new polymer materials which make it possible to preset engineering and biopharmaceutical parameters. The above-described polymer materials stabilize drug dosage forms, including controlled-release forms, and improve their improve physical properties.

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