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POLIMERY

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Polymers in pharmaceutical taste masking applications

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Abstract: Taste masking is an important factor in the development of dosage forms containing active pharmaceutical ingredients with unacceptable taste. Film coating has been found as the most effective and commonly used approach for taste masking. Depending on the taste masking technology, shell material should be selected from a wide variety of water soluble or insoluble polymers. The present article provides an overview of the commonly used polymers and ready-to-use polymer mixtures employed for taste masking.

Keywords: taste masking, hypromellose, methyl cellulose, ethyl cellulose, methacrylate copolymers, ready-to-use polymer mixtures.

Polimery stosowane w technologiach farmaceutycznych do maskowania smaku substancji czynnych

Streszczenie: Maskowanie smaku jest ważnym czynnikiem w projektowaniu postaci leków zawierających substancje czynne o nieakceptowalnym smaku. Najskuteczniejszą i powszechnie stosowaną metodą maskowania smaku jest powlekanie opracowywanej postaci leku. Materiał otoczki stanowią rozpuszczalne lub nierozpuszczalne w wodzie polimery odpowiednio dobrane w zależności od metody maskowania smaku. W niniejszym artykule dokonano przeglądu polimerów oraz ich gotowych mieszanin, powszechnie używanych w celu zamaskowania smaku leku.

Słowa kluczowe: maskowanie smaku, hypromeloza, metyloceluloza, etyloceluloza, kopolimery metakrylanów, gotowe mieszaniny polimerów.

Undesirable taste is one of the most important problems that are encountered during designing new dosage forms [1–4]. The increased industrial interest in new taste-masking technologies indicates that palatability plays an important role in the commercial success of finished dosage forms. Taste masking can be carried out by using various techniques depending on the type of active ingredients and type of the dosage form, like: addition of flavors, film coating, complexation with cyclodextrins, melting and liquid extrusion, encapsulation, pH modification of active pharmaceutical ingredient (API), and ion-exchange resins. Moreover, the type of taste masking method suitable for final formulation is also influenced by the manufacturing process. Figure 1 illustrates drug properties that have to be considered while selecting an appropriate taste masking technique.

For instance, extremely bitter taste cannot be masked with sweeteners or flavorants alone, and intermediary techniques like coating or matrix entrapment should be

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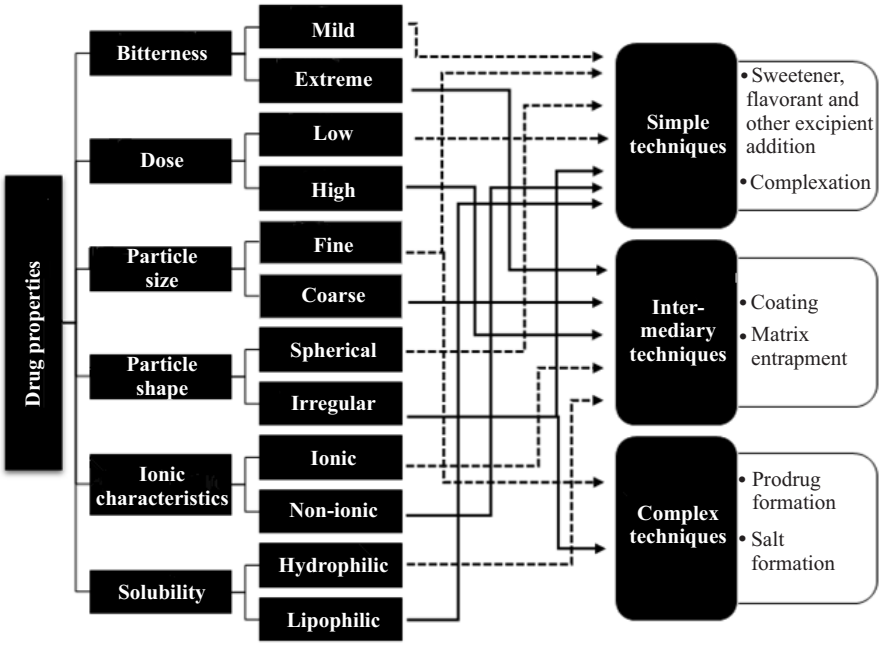


Fig. 1. Selection of the taste masking method, depending on the properties of the active substance [3–5]

considered. An unpleasant taste of ionic drugs can be masked with ion exchange resins and of lipophilic drugs – by entrapping them into a lipoidal matrix. An appropriate taste masking technique can affect both product quality and process effectiveness [6–10]. Recent trends of use of bitter taste blockers such as hydroxyflavanones, adenosine monophosphate and gamma-aminobutanoic acid were found to be effective to achieve the taste masking of bitter drugs [11–13]. However, one of the most effective method of taste masking is to form a barrier between the drug and the tongue buds by using polymers. Among these taste masking methods, it can be distinguished: spray drying (formation of microcapsules or microspheres), coacervation phase separation, spray congealing, coating of granules, pellets or tablets with suitable polymers [14]. The mostly used technique for taste masking is microencapsulation. Microencapsulation is a process in which API is coated with a polymeric material or embedded in a homogeneous or heterogeneous polymer matrix. Polymer layer ensures a protective environment around the drug thus avoiding its contact with the tongue [15–17]. High efficiency and effectiveness of the microencapsulation process is the reason of development of various platform technologies based on coating process [18–22] (Table 1).

T a b l e 1. Microencapsulation patented technologies for taste masking [18–22]

Patent	Company	Commercial products/API
Camouflage®	SPJ Pharma (USA)	Ambroxol (ambroxol hydrochloride), Dextromethorphan (dextromethorphan hydrobromide)
Microcaps™	Aptalis (USA)	Lamictal® ODT (lamotrigine)
Micromask™	Particle Dynamics International (USA)	MicroMask® Ibuprofen (ibuprofen)
Fastmelt®	Athena Pharmaceutiques (France)	Domperidone® ODT (domperidone)

Polymer selection is a crucial factor to be considered for taste masking by coating. Physical, chemical, and biological properties of the polymer, such as film forming capacity, non-toxicity, and biodegradability are important parameters in the final product performance.

A large number of natural and synthetic polymers are available [22, 23]. Polymers commonly used in taste masking applications can be divided into two groups: soluble and insoluble in water. Taste-masking layer can be prepared by combining the water insoluble and water soluble polymers with different ratio (for example ethyl cellulose and hypromellose). Water soluble polymers are substances that dissolve, disperse or swell in water and thus modify the physical properties of aqueous systems in the form of gellation or thickening. Traditionally, water soluble polymers used for taste masking are cellulose ethers (hydroxypropylmethyl cellulose and methyl cellulose) and synthetic vinyl polymers. The most effective taste masking results are obtained by using polymers or their mixtures which are insoluble at neutral pH. For taste masking applications, methacrylic copolymers and ethyl cellulose are widely used. Insoluble at the neutral pH of saliva, they provide an effective barrier against the movement of drug molecules to the surface and water molecules to the core – thus providing taste masking effect [22–26]. However, it should be noted that using organic solvents for insoluble in water polymers is not recommended for taste masking applications. Therefore, in order to limit the use of organic solvents in the coating process, some polymers from this group are obtained in the form of latex or pseudo-latex. Copolymers of

acrylic and methacrylic acid, copolymers of methyl methacrylate, ethyl acrylate and ethyl cellulose occur in the latex dispersion or pseudo-latex form [26, 27]. The term latex is a colloidal dispersion of the polymer and its name is derived from the natural rubber. Synthetic latex is a dispersion obtained by emulsion polymerization and is formed by direct dispersing of the polymer in the form of powder. Additionally, the pseudo-latex term defines a mixture obtained by emulsification of polymer organic solution in water with subsequent evaporation of the solvent in vacuum. Both latex and pseudo-latex should be characterized by the ability to the formation of appropriate coating film. Selection of a compatible plasticizer, its particle size (typically 10–1000 nm), concentration in the dispersion, mechanical properties, permeability, the glass transition temperature, and a minimum film-forming temperature are critical parameters which decide on their utility [26–28].

In addition to traditional polymers used in taste masking techniques, polymer mixtures have been developed such as: Eudragit® E PO ReadyMix [29], Kollicoat SmartSeal® 30 D [30], Aquacoat® ECD [31], Sepifilm® TMLP [32], Opadry® AMB [33], and Surelease® [34]. They have been commercialized in order to facilitate process of the taste masking. The composition of ready-to-use polymer mixtures is presented in Table 2.

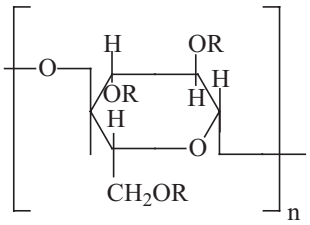
T a b l e 2. Composition of ready-to-use polymer mixtures

Ready-to-use mixture	Composition	Company
Eudragit® E PO ReadyMix	Eudragit® E PO, sodium lauryl sulfate, talc, silicon dioxide, stearic acid	Evonik
Kollicoat SmartSeal® 30 D	Copolymer methyl methacrylate and diethylaminoethyl methacrylate, sodium lauryl sulfate and macrogol cetostearyl ether	BASF
Aquacoat® ECD	Ethyl cellulose, sodium lauryl sulfate, cetyl alcohol	FMC BioPolymer
Sepifilm® TMLP	Hypromellose, cellulose, stearic acid	SEPPIC S.A.
Opadry® AMB	Polyvinyl alcohol, titanium dioxide, talc, lecithin, xanthan gum	Colorcon
Surelease®	Ethyl cellulose, dibutyl sebacate, oleic acid, ammonia and colloidal silica	Colorcon

WATER SOLUBLE POLYMERS

This group contains derivatives of cellulose: hypromellose – HPMC (Sepifilm® LP, Pharmacoat®, AnyCoat® C, Spectracel®), methylcellulose – MC (Metolose® SM-4 and Methocel®).

Cellulose occurs as a white, odorless, water insoluble crystalline powder. It is manufactured by hydrolysis with dilute mineral acid solutions of alpha-cellulose, obtained as a pulp from fibrous plant materials. Next, hydrocellulose is purified by filtration and obtained aqueous dispersion is spray-dried to form dry, porous particles. Cellulose is commercially available in different particle size, viscosity, and moisture grades. Pure cellulose as such is insoluble in hot or cold water due to strong intramolecular hydrogen bonding. In this reason, cellulose is converted to cellulose esters or cellulose ethers derivatives which are water soluble. A very wide range of products can be prepared using different cellulose ethers [27, 35, 36]. They differ from each other with respect to the type of substituents, substitution level, molecular weight (viscosity), and particle size. Water soluble cellulose ethers are: hydroxypropylmethyl cellulose (HPMC), methyl cellulose (MC), hydroxyethyl cellulose (HEC), and sodium carboxymethyl cellulose (Na-CMC) [36, 37]. For taste masking and odor sealing applications, HPMC and MC are mainly used (Scheme A).



Scheme A. Chemical structure of HPMC [R – CH_3, $CH_2CH(OH)CH_3$], or MC (R – CH_3) [35, 36]

European Pharmacopoeia describes HPMC as partly *O*-methylated and *O*-(2-hydroxypropylated) cellulose with an average molecular weight of 10 to 150 kDa [38]. Examples of commercially available film-coating materials containing HPMC for taste masking applications include: Pharmacoat®, AnyCoat® C, Spectracel® and ready-to-use mixture Sepifilm®. The effectiveness of taste masking depends on the viscosity of the polymer dispersion used. Among many viscosity types of HPMC, the 15, 6 and 4.5 mPa · s grades are the most often applied. The maximum acceptable viscosity of taste masking film forming is 500 mPa · s, which corresponds to 11 % dispersion of HPMC 6 mPa · s. Sepifilm® can be dispersed up to 15 % and Spectracel® up to 20 % [35–38]. Mwesigwa *et al*. have reported that Sepifilm® was successfully applied for creating taste and moisture barrier in solid dosage form containing acetylsalicylic acid [39].

MC is a long-chain substituted cellulose in which approximately 27–32 % of the hydroxyl groups are in the form of the methyl ether. MC solutions are stable over a wide range of pH (2–12) with no apparent change in viscosity. Commercially products of MC are Metolose® SM-4 and Methocel® [40–43].

POLY(ETHYLENE OXIDE)

Poly(ethylene glycol), PG = [poly(ethylene oxide), PEO] is synthesized by the interaction of ethylene oxide with

water, ethylene glycol, or ethylene glycol oligomers. It is suitable for pharmaceutical applications, because it is soluble in water and is characterized by low intrinsic toxicity. Commercially available products based on poly(ethylene glycol) designed especially for taste masking process are Kollicoat® IR and Kollicoat Protect®. Kollicoat® IR is a poly(vinyl alcohol)/poly(ethylene glycol) graft copolymer (75/25) with the addition of colloidal silica. Kollicoat Protect® is co-processed product of Kollicoat® IR (55–65 %) and poly(vinyl alcohol) (35–45 %). They are water soluble film forming agents, for taste masking and instant release coatings for solid dosage forms. They are characterized by low viscosity of the polymer solution, outstanding flexibility of the film coating without the addition of plasticizers and rapid coating dissolution [44]. It was shown that effective taste masking with polyethylene copolymers was achieved for ibuprofen and cetirizine dihydrochloride by different methods [45, 46]. Kollicoat Protect® has been successfully used for taste masking of extremely bitter cetirizine dihydrochloride. *In vivo* assessment of the taste masking of cetirizine dihydrochloride microparticles formulated with drug : polymer ratio (0.5 : 1.0) by the spray drying technique has revealed that polymer created efficient taste masking barrier [47]. Moreover, obtained microparticles were characterized by smooth surface and regular shape (Fig. 2).

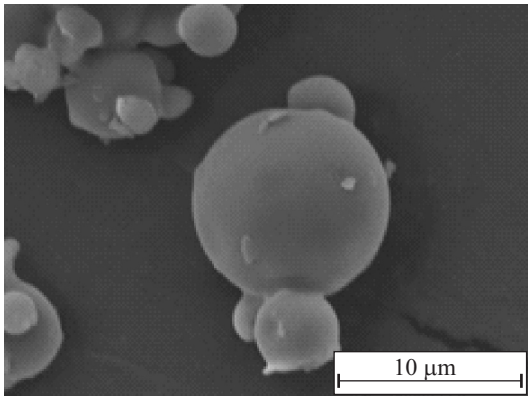
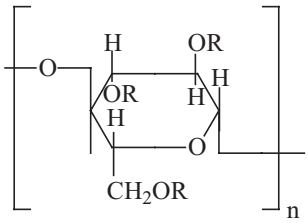


Fig. 2. Scanning electron microscopy image (SEM S-400, Hitachi, Japan) of Kollicoat Protect® microparticles with cetirizine dihydrochloride obtained by the spray drying method; magnification 20 000x (author's unpublished image)

POLYMERS INSOLUBLE IN WATER OR INSOLUBLE AT NEUTRAL PH

Ethyl cellulose – EC (Ethocel®, Aquacoat®, Surelease®) – is a cellulose ether obtained by the reaction of ethyl chloride with alkali cellulose (Scheme B). Ethyl cellulose is available in form of organic and aqueous dispersions [48].

EC is white to light tan odorless and tasteless powder or granular substance with melting point ranged from 240 to 255 °C. It is stable against light, heat, oxygen and chemicals and is mainly used in oral formulations. The molecular weight of EC affects the release rate of the drug. Polymers with higher molecular weights form solutions of



Scheme B. Chemical structure of ethyl cellulose (R – C_2H_5)

higher viscosity and provide coatings characterized by a higher mechanical strength. EC has ability to absorb pressure and hence protects the coating from fracture during compression process. When the content of ethoxyl groups is estimated at 48.0–49.5 %, the coatings have lower melting point and are more soluble in a range of organic solvents, such as: ethyl alcohol, methylene chloride, acetone, isopropyl alcohol, toluene, and ethyl acetate. EC is extensively used in microencapsulation process not only as taste masking, but also as modified release polymer [48]. Commercially available product of EC is Ethocel®. It dissolves in a wide range of solvents such as aliphatic alcohols, chlorinated solvents, and natural oils. It is practically insoluble in glycerin, propylene glycol, and water. Films made from Ethocel® are tough, with high tensile strength and high flexibility even at low temperatures. EC can be combined with water soluble polymers such as MC and HPMC in aqueous coating liquids [35, 49].

Aquacoat® ECD and Surelease® are aqueous dispersions of ethyl cellulose. Aquacoat® ECD contains ethyl cellulose (24.5–29.5 %), cetyl alcohol (1.7–3.3 %) and sodium lauryl sulfate (SLS) (0.9–1.7 %). Ethyl cellulose is present in the dispersion as spherical particles in the size range of 0.1 to 0.3 μm. It exists as a milky white liquid with the characteristic odor of ethyl cellulose. In order to obtain aqueous dispersion, ethyl cellulose is dissolved in a water-immiscible organic solvent and cetyl alcohol (cetanol) is added as a dispersion stabilizer. Then, obtained solution is emulsified into an aqueous SLS solution. The resulting crude emulsion is passed through a homoge-

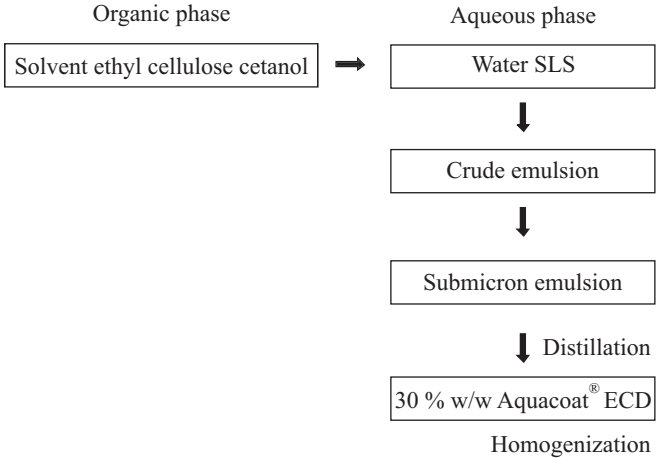


Fig. 3. Manufacturing process of Aquacoat® ECD pseudo-latex dispersion [50]

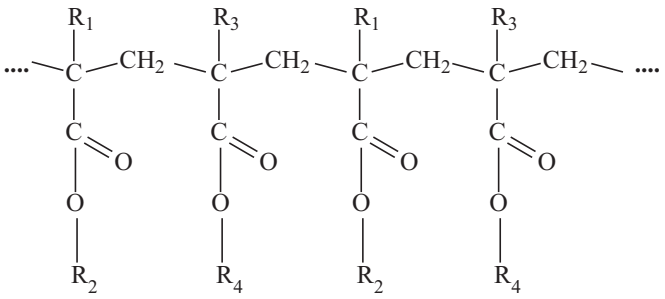
nizer to yield a submicron emulsion, which is distilled to remove the organic solvent and water to yield 30 % of solids dispersion (Fig. 3). Product does not contain plasticizer, therefore it should be added to the coating final mixture. Recommended plasticizers include dibutyl sebacate, acetylated monoglycerides, triacetin or glyceryl triacetate, acetyltriethyl citrate and triethyl citrate. The plasticizer level in a modified-release formulation is typically 20 % to 30 %, expressed as a percentage of Aquacoat® ECD solids [50], and 15 % to 24 % (w/w) – for taste masking by encapsulation method [51, 52].

Surelease® has a solid content of 25 % and it is plasticized with dibutyl sebacate (3.5 %) and oleic acid (1.9 %). Surelease® is produced by the emulsification of an extrusion melt (ethyl cellulose, plasticizer, and oleic acid) into ammoniated water. Ammonium oleate produced during the emulsification process stabilizes the colloidal EC particles. Before dilution, Surelease® should be agitated to ensure homogenization of solids in the dispersion [53, 54]. Obtained dispersion is further diluted by adding two parts of purified water to three parts of Surelease® and stirred with a low shear mixer for approximately 15 min. It is advisable to continue gentle agitation throughout the coating process to prevent any sedimentation of solid particles. The composition of various types of Surelease® is summarized in Table 3.

T a b l e 3. Composition of different types of Surelease® [54, 55]

Ingredient	Function	Type of Surelease®			
		E-7--19029	E-7--19030	E-7--19040	E-7--19050
Ethyl cellulose	Polymer	+	+	+	+
Coconut oil	Plasticizer	–	–	+	–
Dibutyl sebacate		+	+	–	–
Ammonium hydroxide	Stabilizer	+	+	+	+
Hypromellose		–	–	–	+
Acid oleic	Stabilizer/ Plasticizer	–	–	+	–
Colloidal SiO_2	Flow aid	–	+	–	–
Water	Vehicle	+	+	+	+

Methacrylic acid copolymers – (Eudragit® E 12.5, Eudragit® E 100, Eudragit® E PO, Eudragit® E PO ReadyMix, Kollicoat SmartSeal® 30 D) – based on methacrylic and acrylic acid, which physicochemical properties are governed by functional group R (Scheme C). They are manufactured by polymerization of acrylic and methacrylic acids or their esters.



Scheme C. Chemical structure of Eudragit, where R:
for Eudragit E:
R_1, R_3 – CH_3
R_2 – $CH_2CH_2N(CH_3)_2$
R_4 – CH_3, C_4H_9

for Eudragit L and Eudragit S:
R_1, R_3 – CH_3
R_2 – H
R_4 – CH_3

for Eudragit RL and Eudragit RS:
R_1 – H, CH_3
R_2 – CH_3, C_2H_5
R_3 – CH_3

for Eudragit NE 30 D and Eudragit NE 40 D:
R_1, R_3 – H, CH_3
R_2, R_4 – CH_3, H
R_4 – CH_3, C_2H_5

Solubility, swellability, and pH dependent properties of Eudragit polymers can be modified by incorporating anionic and cationic monomers such as methacrylic acid and dimethylaminoethyl acrylate. Poly(meth)acrylates that are soluble in digestive fluids by salt formation: Eudragit® L, S and E polymers with acidic or alkaline groups, enable pH-dependent release of the active ingredient. They are applied for simple taste masking through gastric resistance to controlled drug release in all sections of the intestine. Despite the different solubility and swellability across digestive tract, the drug release from these matrices occurs through a diffusion process. Based on the chemical structure, Eudragits can be divided into the different groups: cationic, anionic, and neutral (non-ionic) polymers. The cationic Eudragit series E is commonly used to mask bitter taste and moisture protect. Coating with dimethylaminoethyl methacrylate is possible using organic polymer solution in a mixture (60/40 isopropyl alcohol/acetone for Eudragit® E 12.5) or using aqueous colloidal dispersion prepared from Eudragit® E PO or Eudragit® E 100 present in the form of powder (Table 4).

Eudragit® E coating is insoluble at neutral and alkaline pH (pH of saliva 6.8–7.2), therefore it constitutes an effective barrier between the taste receptors and encapsulated substances (Fig. 4).

T a b l e 4. Characteristics of different types of Eudragit® E [29, 55]

Type of Eudragit® E	Physical form	Physical properties	Chemical name
Eudragit® E 100	Granules	Colorless to yellow tinged granules with a characteristic amine odor	Poly[butyl methacrylate-*co*-(2-dimethylaminoethyl) methacrylate-*co*-methyl methacrylate] 1 : 2 : 1
Eudragit® E 12.5	12.5 % organic solution	Yellow liquid of low viscosity, clear to slightly cloudy, characteristic odor of the solvents	
Eudragit® E PO	Powder	White powder with characteristic amine odor	

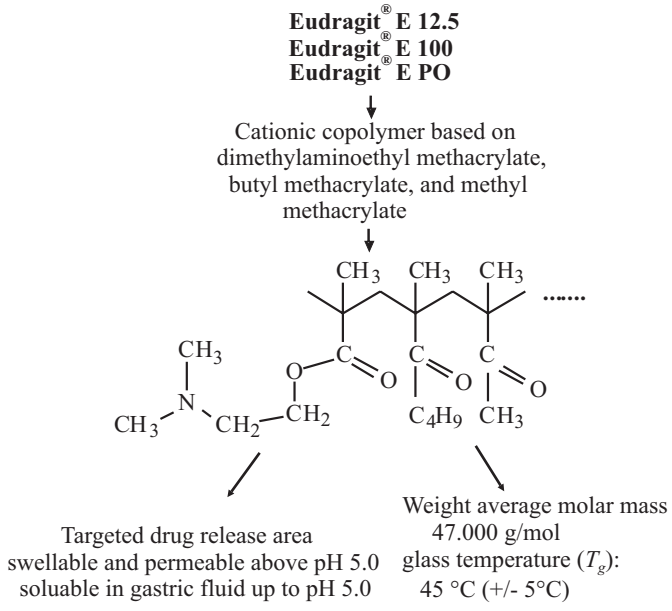


Fig. 4. Characteristics of Eudragit® E

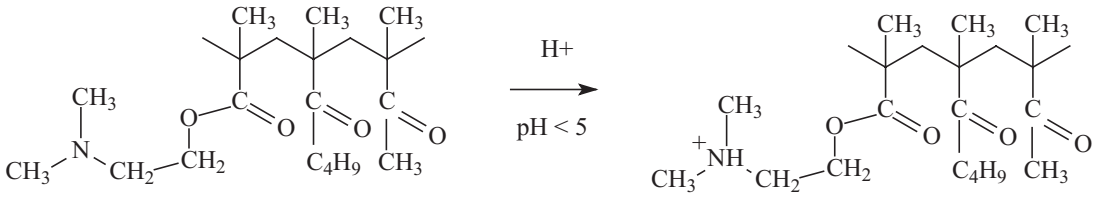
In acidic environment (pH < 5), dimethylaminoethyl functional groups in copolymers transform the polymer into soluble salt (Scheme D), and in the consequence drug release occurs in the stomach.

It was shown that effective taste masking with Eudragit® E was achieved for different active substances such as: paracetamol, ibuprofen, diclofenac sodium, famotidine or metoclopramide with various techniques [57–61]. Randale *et al*. have designed fast disintegrating tablets containing metoclopramide and Eudragit® E PO. 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 [57]. Fast-disintegrating tablets containing microparticles with taste masking effect have been described in a patent by Dobetti. Designed microparticles were prepared by a phase separation method and contained ibuprofen and Eudragit® E PO as a taste masking agent [58]. Al-Omran has reported that unpleasant taste of diclofenac sodium can by masked using Eudragit® E PO by solvent evaporation method [59], whereas Xu *et al.* successfully achieved taste masking of famotidine by the spray drying method [60]. The general composition of the coating mixture with Eudragit® E PO is presented in Table 5.

T a b l e 5. Composition of Eudragit® E PO coating mixture [29, 55]

Ingredient	Amount, g	Function
Eudragit® E PO	85.7	Polymer
Sodium lauryl sulfate	8.6	Surfactant
Stearic acid	12.9	Salt former
Talc	42.8	Anti-tacking
Water	850.0	Diluent

To prepare the aqueous coating mixture using Eudragit® E PO, several technological process stages should be applied. Based on a series of tests and preliminary experiments, the process of preparing a mixture of Eudragit® E PO was optimized. According to our protocol, water should be divided into two equal parts. Using the first part of water, sodium lauryl sulfate should be dissolved followed by the addition of the magnesium stearate gently stirring using a magnetic stirrer. Particle size of stearic acid is crucial parameter – to obtain homogeneous dispersion, optimal particles size should be below 600 μm. If using stearic acid with a particle size above 600 μm, in order to obtain a homogeneous solution, the temperature should be raised to 70–80 °C, which results in the formation of oil in water emulsion. Next, prepared mixture is cooled prior to addition of the polymer to prevent its precipitation. Portions of polymer should be added, and then stirred for 6–10 h at room temperature in order to obtain clear, light yellow solution. In the second part of water, talc should be dispersed followed by mixing the solution of polymer and dispersed talc [61]. Using



Scheme D. Transition of Eudragit® E into soluble salt at acidic pH [55–56]

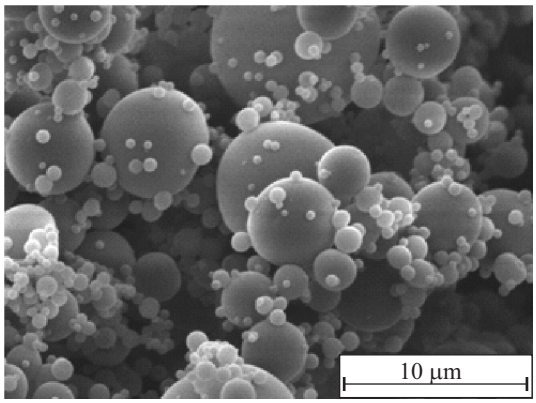


Fig. 5. Scanning electron microscopy image (SEM S-400, Hitachi, Japan) of Eudragit® E PO microparticles with cetirizine dihydrochloride obtained by the spray drying method; magnification 5 000x (author's unpublished image)

this procedure, smooth and regular microparticles with Eudragit® E PO containing cetirizine dihydrochloride by the spray drying technique were successfully obtained (Fig. 5).

To facilitate the preparation of coating mixture, new pharmaceutical product Eudragit® E PO ReadyMix was introduced. It is the coating suspension (Eudragit® E PO, sodium lauryl sulfate, talc, silicon dioxide, and stearic acid), which can be easily prepared by simple adding suitable amount of water [55].

It is also possible to mix several polymers in order to mask the taste, which was demonstrated by Cantor *et al*. They have shown that bitter taste of clindamycin hydrochloride was masked by using mixture of microcrystalline cellulose and Eudragit® E PO [62].

Kollicoat® SmartSeal 30 D is commercially available aqueous ready-to-use methacrylate copolymer dispersion. It contains methyl methacrylate and diethylaminoethyl methacrylate copolymer (6 : 4) stabilized with 0.6 % macrogol cetostearyl ether and 0.8 % sodium lauryl sulfate. The solids concentration is approximately 30 %. It is a milky white liquid with a faint characteristic odor [63]. Chivate *et al*. have found that Kollicoat® SmartSeal 30 D was effective polymer for taste masking of bitter ornidazole. Efficiently taste masking was achieved by using both top spray and bottom spray techniques with fluid bed processor. The taste masking was evaluated in human test panel by comparison of tested samples with standard solutions containing ornidazole at various concentrations [64]. It was also shown that Kollicoat® SmartSeal 30 D could be successfully used to mask bitter taste of cetirizine dihydrochloride [47]. The cross-section of microparticle with Kollicoat® SmartSeal 30 D and cetirizine dihydrochloride (drug : polymer ratio 0.5 : 1.0) is presented in Fig. 6.

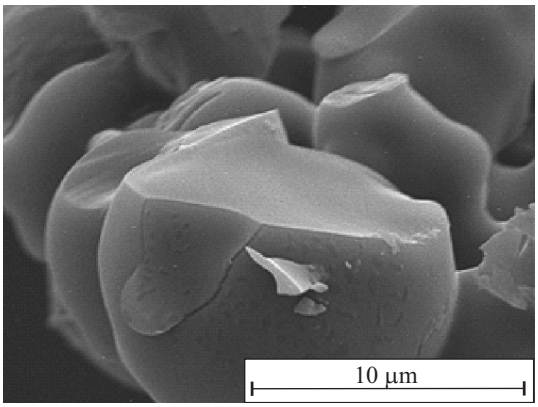


Fig. 6. Scanning electron microscopy image (SEM S-400, Hitachi, Japan) of cross-section of Kollicoat® SmartSeal 30 D microparticle with cetirizine dihydrochloride obtained by the spray drying method; magnification 15 000x (author's unpublished image)

CONCLUSIONS

Unacceptable taste of the active ingredient is often reason for the refusal of the drug or even discontinuation of treatment. Taste masking can be carried out using various techniques depending on the type of drug and type of the dosage form. The common method used to mask the unpleasant sensation is microencapsulation. This technique provides physical barrier between drug molecules and taste buds. Hydrophobic or hydrophilic polymers can be used as coating materials, alone or in combination to produce a layer coat depending on the drug bitterness. Hypromellose, methyl cellulose, methacrylic copolymers and ethyl cellulose possess appropriate properties to be used for effectively taste masking. Selection of taste masking polymer needs to be done on a case-by-case basis. New pharmaceutical excipients used for taste masking are ready-to-use mixture such as: Kollicoat® Protect, Aquacoat® ECD, Surelease®, Eudragit® E PO ReadyMix, Kollicoat SmartSeal® 30 D, which were designed to facilitate taste masking process.

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