REVIEWS

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Solid dispersion in pharmaceutical technology. Part II. The methods of analysis of solid dispersions and examples of their application

Stałe rozproszenia w technologii postaci leku. Część II. Metody badania stałych rozproszeń i przykłady ich zastosowania

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Summary

In the first part of the article solid dispersions were classified the properties and methods of their preparation were described. This section presents methods of analysis of solid dispersions i.e.: thermoanalytical methods, XRPD, FTIR, microscopic methods, dissolution studies and examples of drug forms where solid dispersions were used **(Polim. Med. 2012, 42, 2, 97–107)**.

Key words: solid dispersions, XRPD, FTIR, thermoanalytical methods, microscopic methods, dissolution tests, drug dosage forms with incorporated solid dissolution.

Streszczenie

W pierwszej części artykułu dokonano klasyfikacji stałych rozproszeń, opisano właściwości i metody ich otrzymywania. W tej części przedstawiono metody badań stałych rozproszeń tj. metody termoanalityczne, XRPD, FTIR, metody mikroskopowe i testy rozpuszczania oraz przykłady postaci leku otrzymanych z ich wykorzystaniem (**Polim. Med. 2012, 42, 2, 97–107**).

Słowa kluczowe: stałe rozproszenia, XRPD, FTIR, metody termoanalityczne, metody mikroskopowe, testy rozpuszczania, postacie leku z inkorporowanym stałym rozproszeniem.

Methods that allow study of solid dispersions include dissolution testing, thermoanalytical methods, calorimetric analysis, X-ray diffraction, IR spectroscopy and microscopic methods. However, a clear differentiation and determination of a degree of order of individual system components poses a problem due to the complexity of their composition. The use of different analytical methods may lead to different results.

Methods of X-ray diffraction, IR spectroscopy, dissolution calorimetry or isothermal microcalorimetry are applied in order to identify crystalline forms of a substance or carrier in a solid dispersion. Detection of amorphous components requires several analytical methods, i.e. Confocal Raman Spectroscopy, IR and FTIR spectroscopy techniques, Temperature-Modulated Differential Scanning Calorimetry (TMDSC) [1]. For a complete characterization of the solid dispersions obtained two or more of these methods must be applied simultaneously. Techniques used to study solid dispersions are summarized in Table.

Table. Techniques applied to study solid dispersions [1]

Tabela. Techniki stosowane w badaniach stałych rozproszeń [1]

The purpose of application	Type of method
Drug-carrier miscibility	Hot stage microscopy DSC (Conventional modulated) XRPD NMR ^{1}H spin lattice relaxation time
Drug-carrier interactions	FT-IR spectroscopy Raman spectroscopy Solid state NMR
Physical structure	Scanning electron microscopy Surface area analysis
Surface properties	Dynamic vapor sorption Inverse gas chromatography Atomic force microscopy Raman microscopy
Amorphous content	Polarised light optical microscopy Hot stage microscopy DSC (MTDSC) XRPD Isothermal titration calorimetry (*ITC*)
Stability	Dynamic vapor sorption Isothermal calorimetry Humidity studies DSC Saturated solubility study
Dissolution enhacement	Dissolution Intrinsic dissolution Dynamic solubility Dissolution in bio-relevant media

Thermoanalytical methods: Differential Thermal Analysis (DTA), Hot Stage Microscopy, Differential Scanning Calorimetry (DSC)

Thermal analysis consists in measurement of changes in selected physical parameters of a substance when heated under conditions of a linear temperature increase. These changes are recorded as a function of time or temperature. The most important thermoanalytical methods include differential thermal analysis that records temperature difference between the sample and a reference substance, and thermogravimetry (TG) measuring change in the sample mass upon heating [2]. Hot stage microscopy, in turn, is an analytical technique that combines advantages of microscopy and thermal analysis, allowing to learn the physical properties of a substance as a function of temperature. The principle of the method is to monitor sample behaviour during exposure to low or high temperature [3]. These techniques are used to estimate content of crystalline forms and hydrates, as well as to determine phase transitions (polymorphic transformations) in the analysed solid dispersions [4].

Differential Scanning Calorimetry is considered to be a modern and accurate technique used in solid dispersion analysis [5]. It allows to explore the process of melting, crystallization, evaporation, phase equilibria, sublimation, glassy and polymorphic transformations, dehydration, isomerization, adsorption and substance degradation [6]. It detects metastable forms and eutectic mixtures through heating and cooling cycling [5]. When the sample is heated peaks indicating changes in enthalpy and specific heat (Fig.) are recorded. Each peak refers to the specific thermal effect resulting from the process, such as crystallization or melting. The sample crystallization is confirmed by a sharp peak on the thermogram, indicating the exothermic nature of the transformation. On the other hand, the process of melting characteristic for samples with the crystalline structure only is detected as the endothermic peak on the thermogram. Peaks of the DSC curve associated with melting cannot be found for the amorphous forms [7]. Glass transition temperature, Tg is a particularly important parameter read from the DSC thermogram. This is the temperature when the amorphous bodies (non-crystalline) are transformed from brittle, breakable, glass-like to elastic and rubber-like forms. Chain mobility decreases below Tg while the relaxation time, resulting from the movements, extends even until the end of the measurement. Tg is a characteristic parameter of each polymer indicating change in its heat capacity. On the DSC curve Tg is manifested as a change in the base line taking the form of a step (Fig.) [5, 7].

DSC method may be used for thermostability testing and T_g measurement in the analysed solid dispersions. Lack of a peak related to solid dispersion melting on DSC indicates that the substance predominates in the amorphous form in the formulation. In practice, such result is to be confirmed by a further study, described below, using X-ray powder diffraction.

X-ray powder diffraction (XRPD)

In the X-ray diffractometer an X-ray beam is directed onto the tested sample where it is dispersed. The intensity of radiation is recorded, for example, on the photographic membrane. In the course of the study an interaction between the electrons surrounding the atomic nuclei of the substance and the X-ray radiation photons is identified. The X-ray diffraction by the space lattice of a crystal results in diffraction patterns unique

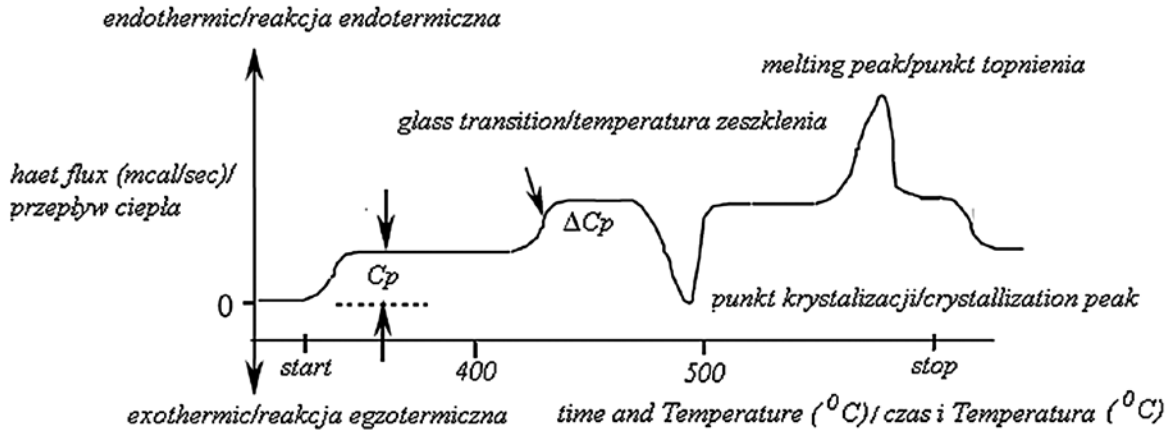

Fig. Typical DSC scan [6]

Ryc. Typowy wykres DSC [6]

to a specific substance. Analysis of the X-ray diffraction spectra allows to determine, for example, molecular structure, crystal structure, spatial distribution of atoms, crystal lattice parameters and atom locations within the unit cells [8–10]. X-ray powder diffraction (XRPD) is used to identify amorphous varieties and polymorphic forms of a substance, while the sharper peaks in the registered image indicate a more crystalline material [10]. This technique is considered to be the only one when the phase composition of simple mixtures or the ratio of amorphous to crystalline form are to be determined. In solid dispersion studies XRPD analysis allows identification of crystal forms and determination of crystal size. Due to uniqueness of diffraction patterns received, crystalline state can be confirmed for both the drug substance and the carrier. Diffraction methods allow for the differentiation between solid solutions containing drug in the amorphous form and solid dispersions with the active substance present partly in the crystalline form and the carrier in the amorphous or crystalline form. It should be noted that crystals in the amount of 5–10% of the sample weight are not determined [11].

Infrared (IR) spectroscopy

IR spectroscopic analysis provides information on chemical bonding, functional groups, presence or absence of changes in the crystal structure of a compound. Spectra obtained using infrared spectroscopy allow to determine physical and chemical properties of the material by recording frequency of vibrations that correlate with common atomic bonds. At the time of exposure to infrared radiation the sample absorbs radiation energy in a selective manner, resulting in changes in the molecular vibrational energy. Radiation of a certain energy level is absorbed due to energy quantization. The amount of the absorbed energy corresponds to the energy states of specific functional groups that perform vibrations [12]. Interactions between the active compounds and between API and the carrier provide the relevant information through infrared spectroscopy technique. In effect, they affect substance release mechanism from these systems [13]. Changes in the IR spectrum confirm presence of these interactions and are recorded as new bands, bands disappearing, a shift or widening of the existing bands as well as a change in their intensity. Interactions observed between the solid dispersion components such as physical adsorption phenomenon, an effect of electrostatic forces, hydrogen bond and van der Waals interactions are in general reversible, while the chemical interactions, including ion exchange, protonation, complexation are irreversible changes. The research shows that the degree of physical adsorption depends to similar extent on physicochemical properties of both solid dispersion components, i.e. both drug substance and excipients [14].

Microscopic Methods: Polarizing Microscopy, Scanning Electron Microscopy

Scanning electron microscope (SEM) allows viewing and surface analysis of solid dispersions as well as spatial pattern formation for the scanned object. This is very important for the qualitative assessment of their properties such as particle size, their shape, morphology, porosity, presence of crystalline forms, as well as tested powders texture monitoring. The information obtained may be helpful when confirming crystal structure of the analysed sample, comparing the solubility of the incorporated substance and in the impact assessment of the performed modification on its bioavailability. Images obtained by SEM help verifying if particles of the tested

substance have not lost the desired physical properties as a result of technological process, e.g. powder mass compression in tablet machine [15].

Polarizing microscope is a tool to study solid dispersions of substances that show optical activity. It provides much information on the physical properties of the sample, which include: shape of the observed particles, their size, surface appearance, hardness, colour, transparency, refractive index, pleochroism (multicolourness, polychroism), polymorphism, birefringence, fluorescence, interference, or the melting point [16].

Dissolution Testing

Literature data indicate that for drug substances with intrinsic dissolution rate of <0.1 mg/cm^2/min, the dissolution rate is an absorption limiting factor [17]. The dissolution profile of the active substance is affected by the substance physical form characterised based on the assessment of dispersed particle size and their crystalline form. However, it is also affected by the qualitative composition of the formulation prepared, i.e. amount of the active substance, type and amount of the excipients, technological process and storage conditions, i.e. temperature, humidity [18]. Application of solid dispersions for hydrophobic substances, in comparison to standard formulations, increases absorption of poorly soluble substances from given pharmaceutical form to body fluids. This is undoubtedly a result of an increase in their solubility and dissolution rate. Mutual spatial arrangement of the constituents plays a decisive role in the dissolution of these forms as well as the form of their components. Correlation between interposition of solid dispersion components and dissolution rate of the formulation ingredients has been confirmed. When individual components of a solid dispersion form separate phases, the physical interaction between them is inhibited and the components are exposed to dissolution medium. This accelerates the dissolution process and simultaneously inhibits agglomeration of particles of the hydrophobic drug substance within the carrier. It has been proven that the solubility of the solid dispersion is affected by the carrier applied. It may increase the solubility by improving the ability to wet the substance and by extension of the surface of dissolution [19]. Solid dispersions of ingredients present in the crystalline form of high energy show lower solubility when compared to the amorphous form.

The correctness of the performed solubility test depends on appropriately selected test method and a number of parameters, including: type and volume of the fluid used for analysis, temperature, rotation speed, medium flow rate, duration of test and of the acceptor fluid sampling as well as the amount of formulation required. 0.1 mole/l hydrochloric acid (pH 1.2) or phosphate buffer, pH 6.8 are most commonly used. Other fluids used in the study are: water, phosphate buffer, pH 7.6, acid solutions such as acetic acid, tartaric acid, liquids with the surface active agents added. Studying of sparingly soluble substances due to their low solubility in water requires a medium with surfactant addition. Commonly used mediums for this purpose are: sodium lauryl sulphate (SLS), polyoxyethylene sorbitan (Tween), cetyltrimethylammonium bromide (CTAB), cremophor – castor oil-derived polyether, hexadecyltrimethylammonium bromide (HTAB), polyethylene glycol p-1,1,3,3-tetramethylbutylphenyl ether (Triton), cyclodextrins and lecithin [20].

Dosage forms with incorporated solid dispersion

Multiple advantages of solid dispersion usage have been identified in pharmaceutical technology field. They include ability to obtain a uniform dispersion of a small amount of drug substance in a solid phase, possibility to obtain a solid drug form for labile, liquid (up to 10%) substances or gaseous compounds, prospects for development of a sustained-action dosage form, promptly releasing initial dose and dosage form of an extended-release of easily soluble substances, using poorly soluble or insoluble carriers. Their use can allow reduction in the presystemic drug metabolism, i.e. morphine or progesterone, and changes in the substance polymorph ratio in a given system (transition to solid solutions, eutectics, and etc.) [21].

Solid dispersions and oral forms with incorporated solid dispersion

The advantages of solid dispersion preparation using low solubility substances are widely described in the literature. The below-mentioned study characterizes only a few examples of dispersions of drugs from different pharmacological groups, with the main focus on oral forms.

Ibolya et al. used the melting method to obtain solid dispersions of NSAID, flufenamic acid, BCS class II representative, in polyoxyethylene glycol (PEG) 4000 and 6000 at a substance to polymer weight ratio 1:5 and 1:10, respectively. DSC and thermomicroscopic analyses of the received dispersions showed that flufenamic acid dissolves in molten polyethylene glycols, and measurements made by XRPD method confirmed formation of amorphous form in the formulation. The solubility study of solid dispersions obtained in artificial gastric juice gave, when compared to the pure API, 4.4-fold greater substance solubility in the system with PEG

4000 at a 1:10 substance to carrier weight ratio. During the solubility study of the derived forms a phenomenon of supersaturated solution formation was observed with the temporary crystallization of flufenamic acid. However, that was delayed by the addition of PEG as the process inhibitor. The authors point out that a substance with high permeability as flufenamic acid can be absorbed from thus obtained formulation to a greater extent from the gastrointestinal tract [22].

Venkates Kumar et al. studied solid dispersions of valsartan in the skimmed milk powder, obtained at the weight ratios of 1:1, 1:3, 1:5 and 1:9. Solid dispersions obtained by grinding of moistened with ethanol substance mixture improved the valsartan solubility and decreased participation of the substance in a crystalline form in this system. From thus obtained solid dispersion at a drug to polymer ratio of 1:9, 81.60% of the substance has been dissolved in phosphate buffer within 60 minutes, as compared to 34.91% and 69.88% for the pure drug product and the physical mixture of the analogical composition, respectively [23].

The aim of Madhavi et al. study was to obtain solid dispersion of zafirlukast in β-cyclodextrins. Zafirlukast is an orally administered antileukotriene drug used for allergen-induced or irritating compound-induced asthma attack prevention. Poor solubility of zafirlukast in body fluids reduces its bioavailability. In this study solid dispersion was obtained by physical mixing of the two components: by grinding or solvent evaporation method. In the tests conducted the largest increase in drug solubility was observed for solid dispersions received by grinding ingredients in a mortar [24].

In other studies solid dispersions of paracetamol in PEG 4000, PEG 6000 and urea were developed. Formulation, obtained by the melting method, which contained the substance and PEG 6000 at a 1:5 ratio gave a 5-fold greater solubility of paracetamol in comparison to the pure substance [25].

Guedes et al. studied solid dispersion developed for imidazolidinedione (LPSF/FZ4) derivative in polyvinylpyrrolidone (PVP) and PEG. Pyrazolidinedione derivatives show cestocidal activity, however the effect is limited due to their poor solubility in water (less than 1 mg/l). In the 60th minute solid dispersion of LPSF/FZ4 in PEG, obtained by solvent evaporation method, had 4.8-fold higher solubility in water and 5.8-fold higher in formulation based on PVP, compared to the pure substance. The studies confirmed that increase in the degree of dissolution of (5Z)-3-(4-chloro-benzyl)-5-(4-nitro-benzylidene)-imidazolidine-2,4-dione from solid dispersions is associated with the existence of intermolecular interactions such as hydrogen bond (> NH-H ···O <) between the amide group (> N-H) of LPSF/FZ4 and the ether group (-O-) of polyoxyethylene glycol or the carbonyl (C=O) of polyvinylpyrrolidone. The intensity of these interactions was directly reflected in the studies with the use of scanning electron microscopy, X-ray and DSC diffraction, where the substance amorphous aggregates of irregular sizes were identified [26].

Gill et al. studied the release of glimepiride, hypoglycemic drug, from tablets prepared by direct compression. The tablets contained solid dispersion (produced by melting method) of the substance in poloxamer 188 (1:4) and different contents of croscarmellose sodium and microcrystalline cellulose (Avicel PH10), talc and magnesium stearate. Within 60 minutes the forms developed released 3 times more glimepiride when compared to the form with the pure substance. The glimepiride release rate increased in proportion to the increase in the amount of croscarmellose in the formulation [27]. The other group evaluated in vivo in rats bioavailability of gliclazide, another sulfonylurea derivative, from the solid dispersion in polyvinylpyrrolidone K-30 obtained by the solvent evaporation method (methanol: acetone 1:1) at a 1:1 substance: polymer ratio. Following the oral administration of 0.5% suspension of the developed formulation in carboxymethylcellulose solution, researchers used pharmacokinetic tests to compare the received forms with the pure substance and the commercial formulation. Cmax in plasma following administration of an equivalent amount of the pure API, solid dispersion and the commercial formulation was 8.76 ± 2.5, 16.04 ± 5.5 and 9.24 ± 3.6 mg/ml, respectively. The modification obtained is an effective method to improve solubility, dissolution rate and bioavailability of poorly soluble drugs. It was confirmed by the highest, among the studied forms, AUC value observed for a substance administered in the form of a solid dispersion [28].

Sturak and Cho patented the carrier that provides controlled release of flutamide, a drug used in hormone therapy for prostate cancer. This drug form was designed to achieve rapid release of initial dose of flutamide and to sustain that release in the gastrointestinal tract for two days. The carrier has been designed as a core tablet, where the appropriate enteric coating separating the drug reservoir from its initial dose was applied to a core constituting the substance maintenance dose. The invention subject matter is a core incorporated solid dispersion in an amount from 20 to 80 % [w] of total flutamide dose present in the designed form [29].

Chaulang et al. compared furosemide release from the two commercial formulations to the developed solid form incorporating the dispersion of this substance. Solid dispersion of furosemide in crospovidone was obtained by kneading at a 1:2 substance to polymer ratio using water and ethanol mixture (1:1) as a solvent. Confirmation of a 5-fold increase in the substance solubility from the said solid dispersion, when compared to the pure substance, was a step to develop a form (direct tabletting) containing 80 mg of the said dispersion, 89 mg of Avicel PH102, 40 mg of croscarmellose sodium and 1 mg of magnesium stearate. Tablets containing solid dispersion had better profile of API release to the

artificial gastric juice of pH 1.2, compared to commercial forms. Over 84% of the substance was released in 60 minutes from the proposed form, while it was over 25% and over 37% for the commercial formulations, i.e. Salinex and Lasix, respectively. Such a release profile indicates potential use of the preparation technique for solid dispersions of substances, i.e. furosemide, BCS Class IV drug, of low solubility and permeability, to improve their availability in vivo [30].

Another group studied solid dispersion obtained by solvent evaporation technique, consisting of practically water insoluble celecoxib in polyvinylpyrrolidone K30 at a 1:2 substance to polymer weight ratio. Development of a quickly soluble tablet with 100 mg of celecoxib incorporated as a solid dispersion, based on croscarmellose sodium as disintegrant and mannitol (Pearlitol 200 SD) as a pore forming agent, improved solubility of the active substance present in the amorphous form as well as its release. Tablets containing 4% of croscarmellose and 10% of Pearlitol were considered optimal compositions to obtain quickly soluble solid dosage forms. They got wet in about 70 seconds and released 85.92% of the drug into 1% sodium lauryl sulfate solution in 20 minutes [31].

Padmapriya et al. studied solid dispersions of hydrochlorothiazide with captopril, drugs used in hypertension combination therapy. Their synergistic effect is limited due to poor solubility of hydrochlorothiazide. Solid dispersions of these substances, prepared by kneading, in ratios [w] corresponding to the commercial formulations available in the market (hydrochlorothiazide: captopril – 1:1 and 1:1.7) allowed to obtain formulations giving the hydrochlorothiazide dissolution rate higher than the value recorded for the pure substance or for physical mixtures of the corresponding composition. An example of such a solid dispersion where a poorly soluble substance is combined in one application form with a more soluble drug offers a new alternative way to increasing the bioavailability of poorly soluble API (*Active Pharmaceutical Ingredients*) by linking them to other co-administered drugs in combination therapy [32].

As a result of melting, Gorajana et al. received solid dispersion of nimodipine in PEG 4000 and PVP K30 at a substance to polymer ratio of 1:1. Compared to the pure substance, formulations developed in this fashion gave an about 80% increase in solubility of nimodipine in acetate buffer (pH 4.5) supplemented with 0.3% sodium lauryl sulfate [33]. Sun et al. produced other dispersions of nimodipine using Eudragit-E100 and Plasdon-S630 by melting and extrusion method. In relation to the pure substance and the physical mixture of the corresponding qualitative composition, the nimodipine solubility from these forms also increased by about 80% in 30 minutes. In the next stage of work an additional increase in pharmaceutical availability by about 95% in 20 min was noted following mixing of the prepared solid dispersions with Plasdone-S630 (copolymer of N-vinyl-2-pyrrolidone with vinyl acetate) and PEG400, and their confinement in hard gelatin capsules. The relative bioavailability of the substance from this final form was studied following administration of a single dose to beagle dogs in comparison to the reference formulation, Nimotop. The results suggest that there was no significant difference between the compared forms. AUC(0-∞) for the form containing the solid dispersion was 2488±433 ng/hmL and Cmax was 321±78 ng/ml, while for Nimotop AUC (0-∞) was 2272±398 ng/hmL and Cmax was 293±73 ng/mL. However, the apparent rate of absorption from the capsules containing solid dispersion (tmax = 1.3h) was higher than for Nimotop (tmax = 3.1h), which indicates an increase in solubility related to the addition of the substance in this modified form [34].

Laitinen et al. received solid dispersions of perphenazine in PVP K30 and PEG 8000 at 5:1, 1:5 and 1:20 ratios [w] of substance to polymer. In preliminary studies the authors concluded that the solid dispersion prepared at a 1:5 ratio of substance to PEG was most stable at elevated temperature and high humidity. The chosen dispersion was incorporated into rapidly disintegrating tablet prepared with mannitol (60%), crospovidone (15%) and calcium silicate (15%), obtained by direct tabletting. The tablet containing 10% of formulation had fast disintegration time (37 ± 3 min), adequate hardness (1.28±0.06 MPa) and quickly released the drug. 34% of the administered perphenazine dose was released within 4 minutes. Such release time allows for development of fast-dissolving solid dosage forms used by persons finding it difficult to swallow a tablet, i.e. children and the elderly. Research by Laitinen et al. confirmed that appropriate choice of solid dispersion composition and of tablet formulation allows to obtain fast disintegrating form with a satisfactory substance release rate and an adequate mechanical strength, allowing for normal packing and transport [35].

Krasnyuk et al. obtained solid dispersion of phenazepam in PEG 1500 and PVP 10000. Solid dispersion of phenazepam in PVP (1:2) obtained by the evaporation method, when compared to the pure substance, had a 44-fold higher solubility after 5 minutes and 13-fold after 60 minutes from the start of the study [36]. Kalia et al. developed mouth dissolving tablets with the incorporated solid dispersion of oxcarbazepine in polyvinylpyrrolidone K-30 and polyethylene glycol 6000, obtained by the solvent evaporation method. Oxcarbazepine is the first-line anticonvulsant used in adults and children. However, due to the need for rapid administration in sudden onsets of the disease, it is necessary to develop the form allowing for a rapid release of the substance. Mouth dissolving tablets were prepared using the solid dispersion of oxcarbazepine with polyvinylpyrrolidone K-30 at a 1:2 ratio, mannitol, crospovidone, magnesium stearate and aspartame. These forms released up to 95% of the substance within 60 minutes,

which allows to use such dispersions in the development of fast dissolving dosage forms [37].

Khabriev et al. obtained solid dispersions of erythromycin in PVP 10000, PEG 1500 by the solvent evaporation method and solid dispersions in β-cyclodextrin using a high-shear mixer. Solid dispersion of erythromycin in PVP had 1.77-fold higher solubility after 60 minutes, when compared to the pure substance, and approximately 4.65-fold higher in the first 20 minutes. On the other hand, dispersions of erythromycin in PEG and in β-cyclodextrins obtained by the same method showed 1.5-2-fold higher solubility within 10–15 minutes and 1.34-1.38-fold higher within 60 minutes. Analysis of the results collected from studying the proposed solid dispersion properties leads to a conclusion that an increase in the incorporated erythromycin release was due to the decrease in substance crystallinity and in formation of intermolecular complexes of the substance with the polymer [38]. Another antibiotic, roxithromycin, was administered in fast dissolving tablets containing solid dispersion of a substance in mannitol at a 1:4 ratio received by fusion. The tablets prepared with 10% starch, microcrystalline cellulose, aerosil and magnesium stearate released over 89% of the substance within 60 minutes [39].

Another example of utilization of solid dispersions in pharmaceutical technology is development of microparticles that contained piroxicam dispersion in Eudragit S100 by Maghsoodi and Sadeghpoor. Piroxicam, a nonspecific cyclooxygenase inhibitor, in addition to the low solubility in water, irritates stomach lining. The development of solid dispersion of piroxicam in Eudragit S100, obtained by spherical crystallization with use of Aerosil 200 as an anti-adhesive agent, made it possible to receive a form of a drug soluble to a small extent in gastric juice pH 1.2 and quickly releasing the substance in the intestinal juice, pH 7.4. Administration of a drug form prepared in this fashion is preferred mainly due to limitation of adverse drug effects on the gastric mucosa as well as due to its rapid release in the intestines. Stability test run at 40°C and humidity of 75% for 3 months did not show any changes in solubility of the substance prepared in this form [40].

Varshosaz et al. developed a solid drug form with the incorporated solid dispersion of budesonide in dextran, prepared by the solvent evaporation method. It was ground and mixed with magnesium stearate to give a matrix tablet. Such form designed, containing solid dispersion of budesonide in dextran 10 000 (1:7), released 25% of the drug substance in the first 6 hours and the entire administered dose was released at the target site, i.e. in the cecum and colon. This carrier allowed a significant reduction in colon inflammation as compared to the oral administration of budesonide suspension at the same dose in rats, and releasing the full dose at the target site it reduced systemic side effects [41].

Other dosage forms with incorporated solid dispersion

Onoue et al. developed solid dispersion of tranilast with the intention to administer the drug via a dry powder inhaler. Application of tranilast in the asthma therapy is limited by its poor solubility in body fluids and the occurrence of systemic side effects. Solid dispersion was obtained by wet grinding of the crystalline tranilast and the aqueous suspension of hydroxypropylcellulose SL with addition of sodium lauryl sulfate using Nano-Mill device. The resulting mixture was lyophilized and the product, mixed with lactose as a carrier, was ground in a jet mill. Following inhalation of 100 μg of thus obtained formulation using the DPI system, the resulting Cmax increased 2.5-fold, $T_{0.5}$ decreased 11.25-fold and 11-fold decreased the area under the curve compared to the oral drug administration at a dose of 1.67 mg/kg bw. By using this approach it is possible to improve effectiveness of asthma treatment, while limiting the number of the reported side effects following the oral drug administration [42].

Zijlstra et al. studied solid dispersion containing cyclosporine with inulin in order to administer this substance via inhalation as an alternative method to nebulisation in patients after lung transplantation. Solid dispersions were obtained by mixing solutions of cyclosporine in tert-butyl alcohol and inulin in water at a 40:60 volume ratio. Immediately after mixing the resulting solution was sprayed into the liquid nitrogen through the heated nozzle and, following the evaporation of liquid nitrogen, the atomised frozen droplets were lyophilised. The resulting powder following atomisation (at relative humidity of 30% and temperature of 25°C) had large specific surface area ~ 160 m^2/g (for pure substance ~ 40 m^2/g) and perfect dispersion, compared to the pure atomised substance. The described carriers were obtained in the form of large porous particles ($x_{50} \approx 7$ μm) of low density ≈ 0.2 g/cm^3, yet quickly dissolving even at high drug contents. This may be particularly beneficial because of the possibility to reduce the amount of powder inhaled by the patient. Studies have confirmed that the prepared solid dispersions dissolve faster than the corresponding physical mixtures (80% compared to 50% of physical mixtures in 30 min) or the pure substance, while the introduction of inulin resulted in an increase in specific surface area and cyclosporin wettability. Increase in dissolution of the solid dispersions containing 10 and 20% of the substance was caused by faster inulin dissolution in comparison to cyclosporine. Further research will confirm whether this method is an alternative to administration of nebulised cyclosporine in lung transplant patients [43].

Perioli et al. developed and studied solid dispersions of benzydamine in hydroxypropyl methylocellulose and Carbopol at different weight ratios. Obtained formulations subject to direct compression resulted in

mucoadhesive tablets for vaginal use. All the proposed compositions were found suitable for this route of administration, showing good bioadhesive properties and mechanical strength. However, the tablet containing solid dispersion of benzydamine in HPMC had a very good wettability and formed the homogeneous gel with the improved adhesion to the mucosa and the extended drug release (over 40 h). Using benzydamine, an anti-inflammatory and anti-swelling drug, in the form of a solid dispersion in the mucoadhesive tablet, it is possible to obtain a higher concentration of the drug substance at the site of administration, which improves the effectiveness of therapy [44].

Pignatello et al. proposed usage of the solid dispersion of miconazole in chitosan obtained by spray-drying and freeze-drying methods. It was in the form of mucoadhesive microparticles for treatment of fungal infections of the mouth and vagina. Studies of an *in vitro* release of the substance in the environment of pH 5.0 (physiological vagina pH) and 6.6 (physiological saliva pH) confirmed the release of 60 to 85% of miconazole in the first 30 minutes in both environments. There was no further increase in the release within the next 4 hours. The solid dispersion of miconazole in chitozan prepared by the freeze-drying technique showed higher cidal activity against various Candida strains in comparison to the pure substance. This can be explained by the increase in the dissolution rate and therefore, local increase in the drug substance concentration [45].

The objective of Dobaria et al. work was development and in vitro, ex vivo and in vivo evaluation of bioadhesive vaginal films with the incorporated solid dispersion of itraconazole in hydroxypropyl methylocellulose E15. The solid dispersions were prepared by spray-drying after dissolving both substances in a mixture of dichloromethane and methanol (80:20). The dry polymer film was obtained by the introduction of hydroxypropylcellulose and PEG 400 in the aqueous suspension of solid dispersion and by solvent evaporation. In vitro studies revealed that these carriers improved antibacterial activity of itraconazole. In the ex vivo tests it was observed that the bioadhesive polymers used to obtain this form ensured that the carrier was maintained on the vaginal mucosa for up to 7 hours. Fungicidal activity of the films developed was tested in vivo against Candida albicans in vaginal inflammation in female rats. In the group of animals where the films were used significant therapeutic benefits were reported following their application. After 6 days of dosing Candida albicans c.f.u. was at least 10^3-fold lower without affecting the vaginal mucosa morphology. These studies suggest that the bioadhesive films with solid dispersion incorporated can be successfully used to treat vaginal candidiasis [46].

Saleem and Bala obtained solid dispersions of meloxicam in cyclodextrins, polyvinyl pyrrolidone and urea at different weight ratios by the kneading method, and incorporated them into 1% Carbopol gel. Release of meloxicam from thus obtained formulations, in comparison to the pure substance, increased about 6-fold in 120 min, while the*in vitro* permeation of meloxicam through the rat skin increased 9.5-fold [47]. Aejaz et al. obtained higher pharmaceutical availability, compared to the physical mixtures and the pure substance, of aceclofenac from the incorporated into hydroxypropylmethylcellulose gel solid dispersions prepared by melting and solvent evaporation. In the developed solid dispersions PVP, PEG 6000, mannitol and urea were used as carriers at substance to carrier ratios of 1:1, 1:2 and 1:3, respectively. Following the preliminary studies of the aceclofenac release profile from the developed formulations it was found that the fastest solid dispersions to dissolve were these obtained at carrier to substance ratio of 1:3. These systems following wetting with ethanol were introduced in an amount of 1% into HPMC gel containing glycerol and DMSO. Incorporation of solid dispersions into gel improved substance solubility and its diffusion from gel [48].

Nobuhito et al. studied in vivo the pharmacokinetics of rifampicin in suppositories based on Witepsol H-32 following its rectal administration in rats. The rifampicin was added to the base in the form of amorphous solid dispersions with polyoxyethylene glycol 3000 or 6000 at a 1:3 substance to polymer ratio. Pharmaceutical availability of substances from the suppositories tested was compared to standard formulations obtained based on Witepsol H-15. Comparison of the release profile of the rifampicin from suppositories obtained using solid dispersion with PEG 3000 and 6000 allowed to conclude that the substance was better released from the forms containing PEG 3000. AUC obtained following administration of suppositories containing the rifampicin dispersion in PEG 3000 to rats was approximately 2.8-fold higher than that of standard suppositories. Introduction of permeation enhancers such as sodium deoxycholate, sodium ursodeoxycholate, gall powder to the formulation resulted in an additional increase in the AUC value of rifampicin by a factor of 1.2, 1.5 and 1.6, respectively. In the *in vivo* studies the AUC of rifampicin administered as the solid dispersion with PEG 3000 in suppositories based on Witepsol H-32 with the addition of yellow amounted to 80% of the AUC value obtained after oral administration of the substance [49].

Jachowicz and Czech studied solid dispersions of piroxicam in hydroxypropyl methylcellulose acetate succinate (HPMCAS-LF,-HF) considering their potential use as ophthalmic dosage forms. Binary (piroxicam-HPMCAS 1:5 and 1:1) and ternary (piroxicam-HPMCAS-Carbopol 940 1:5:1 and 1:1:1) solid dispersions were prepared by the spray-drying technique after dissolving the substance in acetone and introducing it into the polymer solution for the binary systems or adding Carbopol to the solution containing the substance and HPMCAS for the ternary systems. The piroxicam in vit-

ro release from the forms developed was analysed with the flow-through method into the artificial tear solution and compared to the corresponding physical mixtures. Use of HPMCAS increased the API dissolution rate from the binary solid dispersions. Carbopol addition in the ternary systems made it possible to receive forms of extended piroxicam release. In both types of dispersion the dissolution profile depended on the type of HPMCAS used as well as on the substance to polymer ratio. Presence of the substance in the amorphous form in the said solid dispersions was confirmed by the DSC and X-ray diffraction studies. Application of the formulation containing piroxicam: HPMCAS in a 1:1 ratio resulted in spherical microparticles of a smooth surface [50].

Nabekura et al. studied solid dispersions of disulfiram, diethyldithiocarbamate dimer (DDC), a potent radical scavenger used in the cataract prevention. It is hardly absorbed from the cornea and its bioavailability is very low when administered via this route. Solid dispersions of disulfiram were prepared by solvent evaporation or the spray-drying techniques using polyvinylpyrrolidone as a carrier at 1:1, 1:2 and 1:5.7 substance to polymer ratios. The particle size of solid dispersions prepared by spray-drying and determined using SEM was smaller than of those prepared using solvent evaporation technique (spray-drying: 3.3±0.04μm, evaporation: 34.3±18.0μm). The in vivo substance absorption was studied following suspension of solid dispersions in the solution containing sodium dihydrogen phosphate, disodium hydrogen phosphate and parabens M and P, from thus prepared 1% suspension administered in an amount of 50μl per rabbit eyeball. The highest Cmax (44.7±4.5μm) and AUC values (1.56±0.05mMmin) were obtained for the formulations prepared by spray-drying with a 1:2 substance to polymer ratio. On the other hand, following instillation of a physical mixture suspension obtained at a 1:1 substance: polymer ratio, disulfiram was not detected in the aqueous humor of the anterior chamber of the eye. Nabekury's study confirmed that the prepared solid dispersions following suspension in a solution might become a new API carrier applied to the eyeball in the cataract treatment [51].

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