Use of Solid Dispersion Systems in Pharmacy


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Abstract

An overview of the use of solid dispersion systems in pharmacy is presented. The main techniques of obtaining solid dispersions were considered. The simplest one is the solvent removal technique: the medicinal drug and the carrier are dissolved in the solvent that is then evaporated. The fusion method involves heating the mixture of the medicinal drug with the carrier above the fusion temperature with further hardening under quick cooling. The co-milling method is based on the co-use of compression, fracture, and friction energy for the transition of the solid-state drug and carrier into the amorphous state. The kneading method is a variation of the co-milling method. In this case, the solvent performs several functions at the same time: it dissolves one of the components and enters the micro-fissures of crystals of another component, producing a wedge effect and contributing to the milling and interpenetration of one substance into the pores of another. The method of using the agents stabilising the amorphous state of the medicinal drug involves mixing the following components: a sparingly soluble medicinal drug, an agent inducing the transition of the system into the amorphous state, and an agent stabilising its amorphous state. The obtained mixture is subjected to thermal or mechanochemical treatment. Combinations of these methods are also used to obtain solid dispersion systems. Examples of polymers and non-polymer substances used as carriers in solid dispersion systems are given. The works of authors were studied that are dedicated to the creation and study of solid dispersions of various active pharmaceutical ingredients as well as dosage forms produced from these solid dispersions.

Keywords: solid dispersion systems, carriers, medicinal drugs.


The term “solid dispersions” was suggested by Japanese scientists Sekiguchi and Obi in 1961. “Solid dispersions (SDs) are bi- or multicomponent systems consisting of a pharmaceutical substance and a carrier, which are highly dispersed solid phases of pharmaceutical substance or solid solutions that form complexes with the carrier material [1]”. The use of SDs allows solving a number of problems that occur while creating different medicinal drugs:

– regulation of release time of the medicinal drug from the dosage form;
– elimination of undesirable properties of the pharmaceutical substance (adverse reactions, unpleasant organoleptic properties);
– increasing the stability of medicinal drugs in storage and their resistance to environmental influences;
– optimisation of the production technology of the dosage form.

Various techniques are used to obtain SDs:

1) solvent removal technique. It is the simplest technique of obtaining SDs. The medicinal drug and the carrier are dissolved in the solvent that is further evaporated under low pressure.
Chloroform, dichloromethane, methanol, ethanol, acetone, methylene chloride, and others are used as solvents. The role of the solvent is to ensure the disintegration and homogenisation of the system components at the molecular level and better interaction between the medicinal drug and the carrier.

2) The fusion method involves heating the mixture of the medicinal drug with the carrier above the fusion temperature with further hardening under quick cooling.

3) The co-milling method (mechanochemical method) is based on the co-use of compression, fracture, and friction energy for transition of the solid-state medicinal drug and carrier into the amorphous state. The original substances are mixed and milled using special equipment: a ball mill, a planetary mill, pressure treatment, etc. This method ensures a higher quality of disperse distribution of the amorphous medicinal drug in the carrier.

4) The kneading method is a variation of the co-milling method. The components are placed in a mortar with ethanol and then the mixture is ground until the ethanol is completely removed. In this case, the solvent performs several functions at the same time: it dissolves one of the components; enters the micro-fissures of crystals of another component, producing a wedge effect and contributing to the milling and interpenetration of one substance into the pores of another.

5) The method of using the agents stabilising the amorphous state of the medicinal drug. The idea of the method is based on mixing the following components: a sparingly soluble medicinal drug, an agent inducing the transition of the system into the amorphous state, and an agent stabilising its amorphous state. The agent inducing the transition into the amorphous state can be a crystalline compound that is able to lower the fusion temperature of the mixture with the medicinal drug. Such a compound can change the energy of the crystal lattice of the sparingly soluble medicinal drug decreasing it and increasing the vibrations of the crystal lattice at the same temperature in the presence of a source of thermal or mechanical energy. Examples of such substances are organic acids and their sodium and potassium salts, urea derivatives, creatinin, aluminium hydroxide, nicotinamide, maltol, mannitol, methyl glucamine, sodium deoxycholate, phosphatidyl-choline, etc. A thermally-stable compound containing a functional group interacting with the sparingly soluble medicinal drug acts as an agent stabilising the amorphous state. For this purpose the following are used: cellulose derivatives, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), polyvinyl acetate (PVAC), copolymer of vinyl alcohol and vinyl acetate, copolymer of ethylene and vinyl acetate, derivatives of polyethylene oxides (PEO), tweens, polysaccharides, cyclodextrins, derivatives of alginic acid, acrylic polymers, aerosil, aluminium hydroxide, and others. The process is completed with the thermal or mechanochemical treatment of the obtained mixture.

6) Finally, combinations of the above-mentioned techniques can be used to obtain solid dispersion systems [2].

Various polymers, copolymers or their combinations as well as non-polymer substances are used as carriers for the formation of SDs. For example, polyvinylpyrrolidone (PVP) with different molecular weights and its derivatives, polymers of acrylic and metacrylic acid and their copolymers, α-, β-, γ-cyclodextrins (CDs) and their derivatives, chitosan, cellulose and its derivatives, starch, alginic acid, polyethylene glycols (PEGs) or polyethylene oxides (PEOs) with different molecular weights, carbomers, trisamine, lactose, fructose, maltose, urea, saccharose, alkaline carbonates and other compounds [3].

Medicinal drugs of different pharmacotherapeutic groups are often used among active pharmaceutical ingredients introduced into dosage forms as SDs.

M.K. Sarangi and N. Singh obtained an SD based on aceclofenac using PEO 6000, β-cyclodextrin (β-CD), and carboxymethylcellulose sodium (Na-CMC) using the solvent removal technique. The results of their research showed that aceclofenac can exist in the amorphous state in solid dispersion. The SD produced with the ratio of 1:2 (aceclofenac: PEO 6000) showed the fastest dissolution among all solid dispersion systems. Basing on this SD, pills were formed that showed the best solution profiles as compared to dosage forms available on the market [4].
S. Muralidhar et al. obtained an SD of etoricoxib using the co-milling method, the kneading method, and solvent removal technique with PEO 6000 as the carrier with the ratios 1:1, 1:3, 1:6, 1:9. While studying the solution profile of solid dispersion system in 0.1 N HCl containing 1% of sodium lauryl sulphate, it was shown that the maximum dissolution rate is observed in the solid dispersion system of etoricoxib with PEO 6000 with the ratio of 1:6 produced by the solvent removal technique [5].

While studying the solid dispersion system of ibuprofen with hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), powdered sugar, dextrose, mannitol, and lactose obtained by the fusion method, N. Saffoon et al. showed that the rate of ibuprofen dissolution was considerably improved when prepared in the solid dispersion system with HPMC and HPC. Solid dispersion systems with powdered sugar, dextrose, mannitol, and lactose release the drug considerably slower in the dissolution test [6].

A system was developed that includes indomethacin and a composition consisting of a hydrophilic hydroxypropylmethylcellulose polymer and stearoyl macrogol-32 glycerides, Gelucire 50/13. The studies of this solid dispersion system using X-ray diffraction analysis, differential scanning calorimetry, and hot stage microscopy showed the presence of amorphous indomethacin in polymer/lipid matrices. Near-infrared spectroscopy allowed detecting the shifts of the peaks indicating possible interaction and formation of H-bonds between the drug and the polymer/lipid carrier. Studies of the dissolution in vitro showed a synergetic effect of the polymer/lipid carrier with the delay time of 2 hours in acid environment but with further increase of the rate of indomethacin dissolution at pH > 5.5 [7].

M. Ochi et al. developed an amorphous solid dispersion system of meloxicam with PVP K-30, hydroxypropylmethylcellulose SSL, and Eudragit EPO. The morphology, crystallinity, dissolution properties, stability, and interactions between meloxicam and polymers are described. The solid dispersion system of meloxicam with Eudragit EPO is characterised by physicochemical stability after being stored at 40 °C with a relative humidity of 75 % for 30 days. IR spectroscopy and 1H NMR analysis showed that Eudragit EPO interacts with meloxicam and reduces the intramolecular binding between its molecules, which may lead to inhibition of the growth of meloxicam crystals. The solid dispersion system of meloxicam with Eudragit EPO showed the highest improvement in dissolution among all the prepared SDs of meloxicam.

B. Karolewicz et al. developed a solid dispersion system for imatinib using the kneading method with Pluronic F127 from 10 to 90 % (copolymer of polyoxyethylene and polyoxypropylene). The studies were conducted using X-ray diffraction analysis, differential scanning calorimetry, FTIR spectroscopy, and scanning electron microscopy which showed that there was no chemical interaction between imatinib and Pluronic F127 in a solid state, and they form a simple eutectic phase diagram. When studying the dissolution of solid dispersion systems in 0.1 M HCl and phosphate buffer (pH 6.8), it was shown that the dynamics of release of the imatinib base from the solid dispersion system with Pluronic F127 depends on the pH of the dissolution medium. With pH 1.2, the presence of polymer in the solid dispersion causes a delay in the drug release due to the formation of a viscous gel layer, while with pH 6.8 a considerable increase in the dissolution rate of the drug from solid dispersions, as compared to a pure substance, is observed. In the view of solubility, solid dispersion systems containing 20 % and 30 % of the polymer were the most appropriate [9].

Pluronic F127 was also used for the formation of solid dispersion systems with fenofibrate using the fusion method. Studies of the obtained SD using FTIR spectroscopy, X-ray diffraction analysis, and differential scanning calorimetry did not identify any interaction between fenofibrate and Pluronic F127 but showed that these substances form a simple eutectic system. In this solid dispersion system the dissolution rate of fenofibrate was considerably higher as compared to the pure drug. The highest increase in the dissolution rate was observed in the solid dispersion system containing 20 % of fenofibrate and 70 % of Pluronic F127 [10].
The solid dispersion system of lovastatin obtained using the co-milling method is also described. Instead of a polymer, it uses a low-molecular substance, acetylsalicylic acid, as a carrier. Differential scanning calorimetry, FTIR spectroscopy, and X-ray diffraction (XRD) analysis showed that there is no interaction between the drugs. Lovastatin and acetylsalicylic acid form a simple eutectic phase diagram. Studies of the dissolution showed that the dissolution rate ofLovastatin in vitro released from the solid dispersion systems, containing 10, 20, 40, and 60 % ofLovastatin was improved, as compared to a separate medicinal drug [11].

C. C. C. Teixeira et al. developed an SD of curcumin containing Gelucire® 50/13-Aerosil® using the spray drying method. The solid dispersion system containing 40 % of curcumin was studied by DSC, IR spectroscopy, and XRD. Solubility and dissolution rate of curcumin in HCl or phosphate buffer improved by 3600 and 7.3 times respectively. The accelerated stability test showed that the SD was stable for 9 months [12].

An SD of glibenclamide with Neusilin® UFL2, an amorphous synthetic form of magnesium aluminum metasilicate, was developed in various proportions. Physicochemical and biopharmaceutical properties as well as the stability of four different batches were characterised. It was established that the complete dispersion of glibenclamide in the amorphous polymer was obtained with the ratio of the medicinal drug to Neusilin being 1:2.5. Completely amorphous dispersion was tested by thermal and X-ray diffraction analysis. Amorphous batches were physically and chemically stable for the duration of experiments. Physicochemical properties of four batches were compared to the properties of the original materials and physical mixtures Neusilin® UFL2 and glibenclamide. Studies of the solubility of four solid dispersion systems showed the very high dissolution rate of completely amorphous batches due to amorphous characteristics of these SDs, the very small size of the particles, and the presence of polysorbate 80 that improved the wettability of the solid substance [13].

K. Punčochová et al. used magnetic resonance imaging, ATR-FTIR spectroscopic imaging, and Raman mapping to study the mechanism of aprepronit release from multi-component amorphous solid dispersion systems. The SD was prepared on the basis of the combination of two polymers – Soluplus as a solubilising agent and PVP as a dissolution amplifier. The compositions were prepared with the ratio of Soluplus:PVP being 1:10, 1:5, 1:3, and 1:1. Crystallisation of aprepronit during the dissolution was observed to a variable extent with the polymer ratios of 1:10, 1:5, and 1:3, but the increase of the amount of Soluplus in the composition delayed the start of crystallisation. The best matrix for the SD was the composition of Soluplus:PVP (1:1). In this case, the dissolution rate of aprepronit was considerably increased [14].

An SD of valsartan was prepared and characterised using β-cyclodextrin with the ratios 1:1, 1:2, 1:3, 1:4 to improve its solubility in water and the dissolution rate using the solvent evaporation method. The compositions were studied using DSC, FTIR spectroscopy, and scanning electron microscopy. Solid dispersions showed a marked improvement of solubility characteristics and improved release of the drug. It was found that the composition valsartan:β-cyclodextrin (1:4) is the most appropriate based on the study of solubility characteristics and dissolution rate. The obtained results showed that solubility in water and dissolution rate were considerably higher in solid dispersion as compared to the pure drug. The increase of dissolution rate depends on the nature and amount of the carrier and increase with the higher concentration of cyclodextrin [15].

D. Akiladevi et al. prepared an SD of paracetamol using the co-milling and fusion methods with PEO 4000, PEO 6000, and urea with the ratio of drug:polymer being 1:1, 1:4, and 1:5. The SD was studied by the following parameters: appearance, solubility, and dissolution in vitro. The method of FTIR spectroscopy showed that paracetamol is stable in the SD. It was established that the content of the drug is high. The prepared SD showed a notable increase in the dissolution rate of paracetamol as compared to the pure substance. The solid dispersion system with PEO 6000 (1:5) prepared using the fusion method showed higher dissolution rate (107.26 %) as compared to PEO 4000 and urea (1:4 and 1:5) [16].
I. I. Krasnyuk (Jr.) et al. developed solid dispersion systems of erythromycin, synthomycin, amoxicillin trihydrate, ampicillin trihydrate, protonamide, rifampin, nozepam, benzonal, parmidinum, and chloramphenicol. PEO1500, PVP 10000, β-CD were used to obtain the solid dispersion systems. The solvent removal technique, the co-milling method, and the kneading method were used to prepare the SDs.

It was found that the introduction of the medicinal drug into a solid dispersion system with PEO leads to the increase of solubility and the rate of drug dissolution in water. The highest increase of solubility was shown for the SD with benzonal (by 3.50 times), rifampin (by 2.49 times), ampicillin trihydrate (by 1.73 times), and synthomycin (by 1.47 times). On average, the studied solid dispersion systems with PEO are dissolved 4 times faster.

The solubility of solid dispersion systems with PVP increased by 2.50–3.00 times. Increased solubility was found for solid dispersion systems of benzonal (by 5.46 times), rifampin (by 2.68 times), chloramphenicol (by 3.54 times), protonamide (by 2.56 times), synthomycin, erythromycin, and nozepam (approximately by 2.00 times), and amoxicillin trihydrate (by 1.63 times). No changes in solubility were found for the solid dispersion system of ampicillin trihydrate with PVP. The dissolution rate of the studied medicinal drugs from the SDs with PVP increases by 4 times on average.

The obtaining of the solid dispersion system with β-CD has a less obvious effect on solubility and dissolution rate of the drug. The solubility of the drugs obtained in the SD with β-CD increased by 1.70 times on average. The increase of solubility was observed for SDs of: benzonal (by 3.57 times), rifampin (by 2.11 times), nozepam (by 1.90 times), chloramphenicol (approximately by 1.50 times), ampicillin trihydrate, erythromycin, and protonamide (not more than 1.35 times). The dissolution rate of the studied medicinal drugs from the SDs with β-CD increases on average by 2.80 times.

The mechanisms that cause changes in the solubility and dissolution rate of the medicinal drugs from SDs were identified. A complex of physicochemical methods (X-ray diffraction analysis, crystalline microchemical analysis, IR spectroscopy, thermal analysis) proved the change in the crystal structure and amorphisation, formation of intramolecular complexes, products of interaction, and polymorphic modifications of the studied drugs in SDs.

Solid dosage forms (pills and capsules) with the solid dispersion systems of erythromycin, chloramphenicol, and rifampin were developed. PVP was used as a carrier for the SDs. The study of the medicinal drug release from model pills and capsules showed that the introduction of SDs of the studied medicinal drugs with PVP in pills and capsules increases the pharmaceutical availability of the medicinal drug.

L. P. Suntsova et al. obtained and studied the properties of the solid dispersion systems based on such flavonoids as genistein, dihydroquercetin, and rutin. Calcium and magnesium carbonates as well as natural polysaccharide arabinogalactan (AG) were used as carriers. The SDs were obtained using the mechanical treatment of the mixtures of powders. In mechanochemically treated mixtures the heat of fusion and intensity of XRD reflections are decreased while the crystallinity of solid phases of flavonoids is partially lost. The shift of equilibrium to ionised molecules increases the general concentration of flavonoids in the solution. As a result of the mechanical treatment of flavonoids with AG, their molecules were dispersed into the matrix of water-soluble polysaccharide, which contributed to their accelerated release into the solution and formation of intramolecular complexes during hydration [31-33].

I. V. Kovalevskaya et al. studied the properties of the solid dispersion systems of thioctic acid with water-soluble high-molecular substances obtained using the solvent removal technique. SD samples with polyethylene glycol 6000, polyvinlypyridoline, shellac, carbomers 934, 980, Ultere 21 were studied in terms of their form and size of particles, hygroscopy, values of dissolution of thioctic acid, and technological properties. It was established that the most promising carrier for the solid dispersion system of thioctic acid is PEG 6000 that ensures a 5 times better dissolution of the substance, has higher values of compressibility, flowability, and durability [34].
condensed system of ibuprofen with trisamine as well as the secondary system of the formed compound (ibutris) with trisamine. According to DSC and visual–polythermal analysis, a phase diagram was created. In terms of physicochemical interaction, this is a simple eutectic system which is achieved with the ibutris:trisamine ratio of 53:47 % by weight with a fusion temperature of 134°C. It has been shown that, as compared to the parameters of the pure substance, the extreme solubility (more than by 200 times) and dissolution rate (approximately by 8 times) of ibuprofen is typical for the eutectic composition of the ibutris — trisamine system.

Phase equilibria of the solid system of butadionum with trisamine was studied using DSC and visual–polythermal analysis. It was established that with the ratio of butadionum with trisamine being 71.8:28.2 % by weight, a compound butatris is formed that interacts with the original substances (butadionum and trisamine) similarly to simple eutectics. When studying the solubility of the prepared binary samples with trisamine, it was established that the solubility of butadionum from the butatris sample at the temperature of 37 °C is almost 100 times higher than typical solubility of butadionum substance in similar conditions, while for the eutectic composition butatris—trisamine it is 170 times higher, reaching the value of 1.2 g per 100 g of water expressed as butadionum. It is shown that the release rate of butadionum from the butatris samples is 10 times higher and 20 times higher from the butatris — trisamine eutectic sample, as compared to the release rate of butadionum from the sample of the pure substance [37, 38].

V. V. Grikh studied the effect of solid dispersion systems on the process of nifedipine dissolution. PVP 10000 with the ratio of 1:1–2 as well as PEG 400 and PEG 1500 with the ratio of 1:3 were used as polymer carriers. Solid dispersion systems were obtained using the solvent removal technique. Compositions of nifedipine ointments with hydrophilic and diphilic bases as well as hydrogels based on carbomer gelation agent were developed [39–49].

Therefore, the use of the drugs included in solid dispersion systems in pharmaceutical technology allows increasing the solubility and dissolution rate of active pharmaceutical ingredients, optimise technological properties and improve biopharmaceutical parameters of a drug ensuring its optimal stability. The use of solid dispersions in medicine and pharmacy is driven by the possibility of optimising medicinal drug release from the dosage form, the increase of bioavailability and pharmacological activity of the medicinal drug due to the increase of its solubility, and the release rate from the dosage form.

Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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