REVIEWS

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Solid dispersions in pharmaceutical technology. Part I. Classification and methods to obtain solid dispersions

Stałe rozproszenia w technologii postaci leku. Część I. Klasyfikacja i metody otrzymywania stałych rozproszeń

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Summary

There are many methods to increase solubility of a substance. These include, inter alia, preparation of solid dispersions, i.e. eutectic mixtures, solid solutions, glassy solutions and suspensions. When compared to the individual constituents prior to dispersion formation solid dispersion components are better soluble in water. Therefore, solid solutions became one of the most promising ways to modify solubility, ensuring improved bioavailability and consequently therapeutic efficacy of a substance.

In this part of the publication solid dispersions were classified and described in regard to their properties and preparation methods, i.e. melting method, melt evaporation and melt extrusion methods, lyophilisation technique, melt agglomeration process as well as SCF technology and electrospinning (**Polim. Med. 2012, 42, 1, 17–27**).

Key words: solid dispersion, improving drug solubility, solubilization techniques.

Streszczenie

Istnieje wiele metod umożliwiających zwiększenie rozpuszczalności substancji. Zalicza się do nich między innymi sporządzanie stałych rozproszeń tj. mieszaniny eutektyczne, stałe roztwory, roztwory i zawiesiny szkliste. Ze względu na fakt, iż poszczególne składniki stałych rozproszeń w porównaniu do ich pojedynczych składowych są lepiej rozpuszczalne w wodzie, stały się one jednym z najbardziej obiecujących sposobów modyfikacji rozpuszczalności, gwarantujących poprawę dostępności biologicznej i w konsekwencji skuteczności terapeutycznej substancji.

W tej części publikacji dokonano klasyfikacji stałych rozproszeń, opisano ich właściwości oraz metody otrzymywania tj. metoda stapiania, stapiania i odparowania, topienia i ekstruzji, liofilizacji, topienia i aglomeracji oraz technologia SCF i wytwarzania nanowłókien (**Polim. Med. 2012, 42, 1, 17–27**).

Słowa kluczowe: stałe rozproszenia, metody otrzymywania, nośniki.

Classification of solid dispersions

Ghaste et. al. wrote: "solid dispersion" refers to a group of solid mixtures of at least two different components", which basic elements are: hydrophilic carrier in a crystalline or amorphous form and hydrophobic drug substance [1]. In solid dispersions the role of a carrier play compounds of varied chemical structure. These include acids such as cholic, deoxycholic, citric, succinic, nitrogen compounds, i.e. urea, nicotinamide, sugars, i.e. dextrose, mannitol, sorbitol, xylitol, polymers, i.e. macrogol, polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA) crospovidone (PVA-CL), copolymer of polyvinylpyrrolidone and polyvinyl acetate (PVP-PVA), cellulose derivatives, i.e. ethyl cellulose, hydroxypropyl methylcellulose (HPMC), hydroxypropylcellulose (HPC) and Gelita Collagel (product of collagen hydrolysis) [2].

When choosing a carrier for preparation of solid dispersion the following properties must be taken into account:

(A) solubility in water – high, improves wettability and solubility,

(B) glass transition point – high, improves stability,

(C) water absorption – low, reduces Tg,

(D) solubility in the same solvent as a substance,

(E) melting point – should be relatively low [3].

Considering a carrier form, solid dispersions are divided into three generations. The substances, i.e. urea, sugars, organic acids, which form the so-called crystalline carriers, the second generation comprises of amorphous carriers, i.e. polyethylene glycols, polyvinylpyrrolidone, polyvinyl acetate, cellulose derivatives, while the third includes surfactants, self-emulsifying carriers such as poloxamer 188, tween 80 and Gelucire 44/14. Use of polymer carriers is considered particularly useful in preparation of solid dispersions, as they may fulfill many functions in the end product [3, 4]. They are solvents, solubilizers, may moisten and spatially stabilise the incorporated substance molecules. Also, they affect thermoplastic parameters and intermolecular interactions between solid dispersion constituents as well as determine mechanism of the prepared formulation dissolution [5, 6].

Drug in a carrier may also be found in a form of molecular dispersion, in amorphous or crystalline state [7]. Mutual spatial arrangement, the so-called interposition of component molecules in the prepared solid dispersion, is shown in Figure 1. Another meaning for "solid dispersion" was introduced in the 90's. They have been defined as two-or three-component systems, which consist of an easily soluble drug substance and a sparingly soluble carrier lacking separate pharmacological activity (Figure 1) [4].

Considering mutual spatial arrangement of individual components and their state, the following types of solid dispersions were defined: eutectic mixtures, solid solutions, glass solutions, glass suspensions and amorphous precipitates (Table 1). Knowledge of particle distribution and of their character allows better understanding of properties of a given solid dispersion type and of the mutual interactions between its components. Additionally, such knowledge facilitates selection of desired physico-chemical characteristics and enables to determine stability in relation to the application (Table 1) [8].

In addition to the types described above, it is possible to obtain certain combinations of solid dispersions, coexisting in the same product, where some particles are in form of agglomerates, while other form the molecular dispersion. Although properties of solid dispersions are primarily determined by distribution of component particles, their classification is also based on the preparation method. Different methods to obtain solid dispersion may give the same product or similar methods of preparation finally lead to different products [8].

Many studies indicate an increase in dissolution rate of hydrophobic substances when prepared in form of solid dispersion [4]. The mechanism of this phenomenon is still under studies and explained with increased wettability of hydrophobic drug, reduction in particle size and distortion in crystal structure arrangement as well as

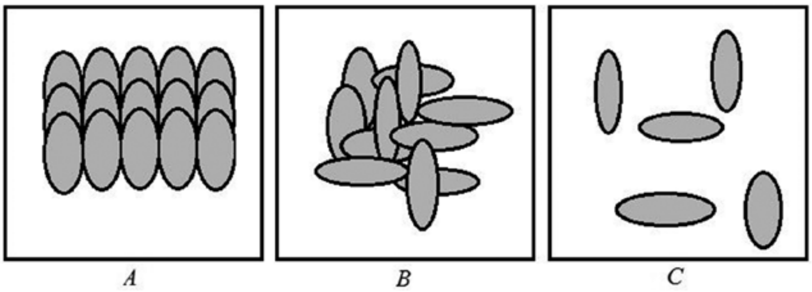

Fig. 1. Spatial arrangement (interposition) of component molecules in solid dispersion, A – in crystalline state, B – in amorphous state, C – molecular dispersion [8]

Ryc. 1. Uporządkowanie (interpozycja) cząsteczek składników w wytworzonym stałym rozproszeniu, A – w stanie krystalicznym, B – w stanie amorficznym, C – rozproszenie molekularne [8]

Table 1. Classification of solid dispersions in relation to the state of component molecules in produced dispersion

Tabela 1. Podział stałych rozproszeń uwzględniający postać, w której występują cząsteczki składowych wytworzonego rozproszenia

	glass solution	solid solutions	eutectics	glass suspension	amorphous precipitations		another's
					crystalline matrix	amorphous matrix	
phases	1	1	2	2	2	2	1
drug	molecularly dispersed	molecularly dispersed	crystalline	crystalline	amorphous	amorphous	amorphous or crystalline
matrix	amorphous	crystalline	crystalline	amorphous	crystalline	amorphous	amorphous or crystalline

Table 2. Advantages and disadvantages of solid dispersions [3, 10]

Tabela 2. Zalety i wady stałych rozproszeń [3, 10]

Advantages	Disadvanteges
reduction of drug particle size	possible low stability – changes occurring during the processing (mechanical stress) or storage (temperature and humidity stress) leading to the crystallization of amorphous forms
increase drug wettability	limitations in the case of industrial scale production – laborious and expensive methods of preparation – limitations of reproducibility of physicochemical characteristics – difficulty in incorporating into formulation of dosage forms – limitations of scale up of solid dispersion systems
increase solid dispersion particle porosity – porosity depends on the type of carrier, the use of linear polymers allows for a more porous particles than crosslinked	
substance in an amorphous state	
more acceptable to patients than solubilization products – allow to obtain a solid oral dosage form instead of liquid form, where the substance is solubilized	

by preventing agglomeration of hydrophobic drug substance molecules within the carrier [5]. Reduction in size of drug substance crystals and increase in their number leads to increase in the contact area between solubilized molecules and a solvent. It was shown that the surface of the solubilized substances directly affects solubility and dissolution rate and, consequently, determines the extent of absorption [9]. The dissolution coefficient of solid dispersion results to a great extent from the carrier dissolution coefficient. By a thorough selection of a carrier, drug dissolution coefficient may be increased by several orders of magnitude. Use of solid dispersions allows for an increase in the extent of absorption of sparingly soluble substances from a given dosage form to physiological fluids and for improvement in bioavailability and pharmacokinetic parameters [6]. In addition, preparation of solid dispersions of easily soluble in water drug substances in sparingly soluble carrier enables receiving extended-release dosage form (Table 2) [4].

Properties of solid dispersions should not alter during storage. It has been demonstrated however, that their solubility may decrease upon storage. Moreover, physical state of matrix should be monitored, because changes that may occur therein affect physical form of a substance and its release. Content of amorphous substance molecules in solid dispersions should be relatively low, since systems they form are thermodynamically unstable. In dispersions containing crystalline particles crystallization nuclei are formed, being the starting point for further crystallization. Systems containing amorphous substance molecules may crystallize following the stage of nucleation. In homogeneous solid dispersions, where the substance is present as molecular dispersion, the crystallization process requires an additional step, before nucleation drug molecules migrate (diffuse) through the matrix. Hence, physical stability of amorphous solid dispersions is associated not only with crystallization process of a substance, but also with any change in molecular structure, including substance distribution [3].

Solid dispersion characteristics

Eutectic mixtures

Simple eutectic mixture consists of at least two chemically inert ingredients, which are completely miscible with each other in liquid state while to a very small extent in solid state [10]. Substances, used in certain proportions as mixture components, form a system with melting point lower than melting point of individual constituents [11]. Solid eutectic mixtures are usually prepared by rapid cooling of the melted components in order to obtain physical mixture of very fine crystals of individual components [1]. Ghaste et al. wrote: "solid eutectic mixtures are usually prepared by rapid cooling of the melted components in order to obtain physical mixture of very fine crystals of individual components" [1]. In case of eutectic mixtures consisting of substances X and Y, both components crystallize simultaneously during cooling process, while in a system other than eutectic components crystallize at different times during the same process. An example phase diagram of eutectic mixture consisting of components X and Y is shown in Figure 2. AB and BC lines show temperature at which homogeneous liquid mixtures of specific proportions of X and Y components begin to crystallize. System is liquid above these lines and described as *liquidus*. DBE line indicates temperature at which mixture of X and Y components begins to melt. Below that temperature system is in solid state. Below the DBE line mixture components are in so called *solidus* state. The area ABD indicates existence of liquid X and Y component mixture being in equilibrium with solid component Y, while the area CBE indicates presence of liquid X and Y component mixture in equilibrium with solid component X. Point B where the ABC line specified as *liquidus* meets the DBE line specified as *solidus*, defines the eutectic mixture composition [11].

A polymer, which similarly to the substance is pres-

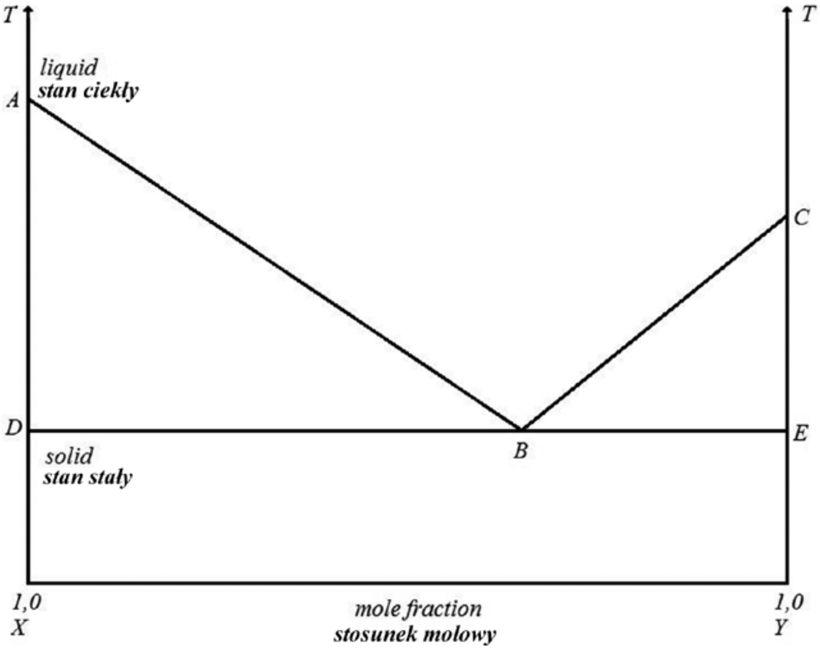

Fig. 2. Phase diagram of eutectic mixture [11]

Ryc. 2. Diagram fazowy dla mieszaniny eutektycznej [11]

ent in the prepared mixture in crystalline form, may be a eutectic mixture component as well as a carrier. In that case, to form the eutectic mixture a drug is required to dissolve in molten polymer at temperature equal to its melting point or, the opposite, the polymer must dissolve in molten drug substance [12]. Usually however, the drug substance has higher melting point than macromolecular compound used.

An advantage of creating complex eutectic mixtures of poorly soluble drug and well soluble in water, chemically inert carrier is a possibility to increase drug solubility in water medium. In addition to the said rapid dissolution of the carrier, Sekiguchi et al. proposed explaining the phenomenon of improved solubility of eutectic mixtures in gastrointestinal environment with influence of digestive juices on formulation and fast dissolving of the carrier. Sparingly soluble drug in the well-soluble carrier environment is gaining favorable physico-chemical properties for further disintegration into smaller particles. This phenomenon is known as microenvironmental solubilization [13]. An additional advantage of creating a drug dosage form based on eutectic mixture is lowered temperature of the technological process [12].

Solid solutions

Similarly to liquid solutions, solid solutions form a single phase system, regardless of the number of their components. However, such a system is not formed unless both solid components mix together. Simultaneously, particle size of a drug product in solid solutions is reduced to an absolute minimum, i.e., to molecular dimensions [11]. Goldberg et al. proposed that the term "solid solutions" should be used when mutual solubility of both components exceeds 5%. Ghaste et al. wrote: "assuming that the solubility of the drug substance in the carrier is 5%" and the upper limit of tablet or capsule weight is 1 g, there would be no possibility to develop dosage form containing that substance in amount over 50 mg. This becomes possible, however, owing to solid solution preparation, where solubility of the substance in the carrier is significantly higher [12].

Two methods of solid solution classification are available. The former takes into account mutual miscibility of components and differentiates continuous solid solutions and discontinuous solid solutions. The latter, takes into account dispersion of particles in a carrier (solvent) [12]. In the continuous solid solution the components mix in all proportions. This in theory means that the bond strength between the two components is greater than the bond strength between molecules of a single component. This kind of solid dispersions has not been widely described in pharmaceutical literature to date [13]. On the other hand, in the discontinuous solid solution solubility of each component in the other component is limited. Figure 3. shows the phase diagram of a discontinuous solid solution. Area α indicates solid solution of component Y in X, while the area β indicates solid solution of a component X in Y. In these areas, one of the solid components is completely dissolved in the second solid component. Below certain temperature level the mutual solubility of both components decreases.

The latter solid solution classification method, based on dispersion of particles in the carrier (solvent), differentiates substitutional crystalline solid solutions, interstitial crystalline solid solutions and amorphous solid solutions. [1]. As the name suggests, all molecules in

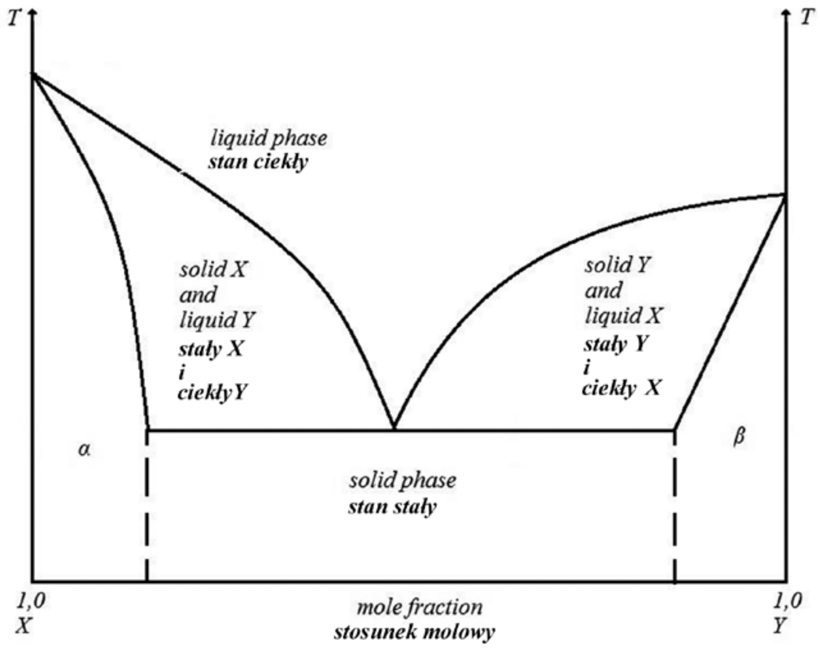

Fig. 3. Phase diagram of discontinuous solid solution [11]

Ryc. 3. Diagram fazowy dla nieciągłego roztworu stałego [11]

the substitutional crystalline solid solution have a crystalline structure formed by replacing solvent molecules with molecules of a substance in the crystal structure or, alternatively, by occupying the space between individual solvent molecules. This results in formation of mixed crystals. Both components of the solution are required to have similar charge and spatial dimensions [11]. Replacement is possible only when dimensions of the dissolved molecules differ by less than 15% compared to the size of solvent molecules [14].

In the interstitial crystalline solid solution, dissolved drug substance molecules are located in spaces between carrier molecules within its crystal structure. This type of solid solution is formed when one of the components can get incorporated between the neighboring molecules in the crystal structure of the second component [2]. This phenomenon occurs when there is a big difference in molecular weight between the carrier used and the drug substance [4]. Dissolved particles are required to have a diameter not exceeding 0.59 of solvent molecule diameter, while their volume is not lower than 20% of solvent volume [1]. Obtaining the interstitial crystalline solid solution guarantees improved wettability of the drug substance molecules and prevents agglomeration of hydrophobic molecules within the carrier.

In the amorphous dispersion, its components are arranged in erratic and random manner. This condition is known as topological disorder [15]. The amorphous state is unstable in terms of thermodynamics and has a natural tendency towards crystallization. This results in system energy reduction [8]. The crystallization process has been proven to adversely affect solubility of the drug substance. This state is thermodynamically stable and results in lower concentration of the drug incorporated in the carrier. Amorphous solid solution consists of the carrier in the amorphous state and the drug in molecular, random and irregular dispersion. In the early research works mainly sugars such as sucrose, dextrose, galactose and urea played the role of a carrier in this type of a solution [1]. Chiou and Riegelman were the first researchers to prepare an amorphous solid solution of sparingly soluble griseofulvin with the use of citric acid, the same improving its solubility [16]. An increase in the substance dissolution rate and in its pharmaceutical availability from the drug dosage form, received with the use of amorphous bodies, is explained with lack of necessity to expend energy for the breakdown of crystal structure of the prepared system [4].

Ghaste et al. wrote: “recently, to receive amorphous solid solutions organic polymers such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) and various cellulose derivatives were applied” [1]. The phenomenon of formation of amorphous solid solutions mentioned above occurs within the network formed by the polymer chains. Molecules dissolved in the amorphous carrier induce greater plasticity of the polymer and may cause lowering its glass transition temperature [1].

Glassy solid solutions and glass suspensions

Chiou and Riegelman first proposed the idea of creating glassy solid solution as a method to increase solubility and absorption of a substance [7]. Glassy state is seen as critical and decisive for durability and physical stability of the incorporated lipophilic substance.

Transformation into the glassy state is one of the most important phenomena occurring in the amorphous bodies and leading to changes in their properties. Glassy state is characterized by lack of a long-range order and molecules are able to perform oscillations around stationary positions. Exchange of molecules here occurs sporadicly in contrast with the liquid state, where self-diffusion occurs. In the glassy state possibility of particle rearrangement is inhibited and mobility, i.e. rotational and translational motion, ceases [15].

Glassy solid solution is a multi-ingredient, glassy system, which consists of one phase only. At the molecular level it is homogenous and uniform. The carrier in this system occurs in amorphous state, while the dissolved molecules are molecularly dispersed. When studying these systems by DSC method a single peak appears due to the presence of one phase, indicating glass transition temperature (Tg) [17]. Below Tg glassy solid solution is transparent and clear. During heating above Tg solid dispersion softens gradually without sharp melting point [1]. In order to produce this type of a system mutual miscibility/ solubility of its components is required. Glassy solution formation occurs upon rapid cooling/ evaporation of solvent. Sugars, i.e. dextrose, fructose, galactose, trehalose, inulin and polymers i.e. polyvinylpyrrolidone (PVP), copolimer of polyvinylpyrrolidone and polyvinyl acetate (PVP-PVA), hydroxypropyl methylcellulose (HPMC) [14] often are used as carriers for preparation of this form.

Glass suspension is a two-phase system consisting of a carrier in amorphous state with the incorporated drug substance in crystalline form. Method to obtain glass suspensions consists in crystallization of the drug substance in amorphous carrier, while particle size of dispersed phase is dependent on the rate of cooling/ evaporation of solvent [8].

Amorphous precipitation in solid carriers

Based on molecular structure two types of amorphous precipitations were distinguished. In the former, drug substance is dispersed in form of amorphous agglomerates in amorphous carrier. The latter, comprises a carrier in crystalline form and the drug substance in amorphous form. The solid dispersion sub-types listed consist of two phases and are characterized by lack of homogeneity at the molecular level. While studying these systems by DSC method glass transition Tg is observed for both components: drug substance and the carrier [17].

Methods to obtain solid dispersions

Literature describes many methods of solid dispersion preparation, i.e. melting method, solvent method, method of melt extrusion or lyophilisation technique, all based on linking drug with a carrier. The two components usually poorly mix together. During the solid dispersion preparation partial or total separation of phases mixed and formation of new ones is observed.

Melting method (fusion method)

Melting method is also referred to as a fusion method. For the first time this method was employed to form solid dispersions by Sekiguchi and Obi, who obtained physical mixture consisting of sulfathiazole and urea [18]. Formation of physical solution consisting of drug and a water-soluble carrier occurs upon heating of components until they melt. The molten mixture hardens rapidly while stirred vigorously at low temperature of an ice bath. Supersaturation with solute can be obtained by sudden cooling of the mixture formed. Under these conditions substance molecules become “trapped” in a matrix of a rapidly solidifying system. The solid mass formed is comminuted, pulverised and then sieved in order to standardize the size of grains obtained. This technique increases dispersion of crystals in the eutectic mixture [1]. Despite its widespread use fusion method has numerous limitations. It can be employed only if the drug substance and the carrier mix homogeneously while heated. If the substances used do not mix together, two separate phases and, consequently, a non-homogenous solid dispersion is formed. Use of surfactants can prevent this phenomenon [8]. Another important limitation of this method is degradation of both the drug substance and the carrier at high temperature. Heating may cause evaporation of a volatile drug or a carrier. One approach to solve this problem is heating the mixture or melting under vacuum. Also, the process may be conducted under an inert gas, such as nitrogen, atmosphere which prevents the oxygen initiated degradation of the drug or carrier [1]. Another unfavorable phenomenon which may occur during preparation of solid dispersion using this method, is a change in the mutual miscibility of the components during cooling, resulting in phase separation. Upon slow cooling of the mixture, appearance of the drug in a crystalline form was observed. On the other hand, rapid cooling promotes formation of amorphous solid dispersions [8].

Solvent method

Solvent method was first used by Tachibani and Nakamura. The method enabled formation of solid solution of liophilic β-carotene in a hydrophilic carrier – polyvinylpyrrolidone [19]. In this method, physical mixture of a drug and a carrier is dissolved in a volatile solvent, i.e. chloroform or dichloromethane. Then, solvent is completely evaporated at 23–65°C, and the dissolved solids form a layer of solid dispersion. The resulting film is dried and pulverized [8]. The solvent used and its removal rate are very important factors, determining dissolution rate of drug substance in the solid dispersion thus obtained. They affect crystallographic structure of the resulting system [4].

The main advantage of the described solid dispersion preparation method is preventing degradation of the drug substance or carrier by maintenance of low temperature needed to vaporize the organic solvent. The disadvantages include high cost of production, difficulties with selection of an easily volatile solvent and its complete removal, possible side effects caused by solvent residues affecting chemical stability of the substance, as well as problem with reconstruction of the crystalline form [1]. Difficulties with selection of a suitable solvent result from significant differences in polarity of both components, the drug and the carrier, which are not always possible to dissolve at the desired concentration in a chosen solvent. To improve solubility of the substances used size of their particles is minimised, and then, both substances are introduced to the solvent and dispersed [8]. Low concentrations of drug to be dissolved in the solvent, in the presence of a carrier, are also used. However, that requires evaporation of large amounts of solvent, making the method expensive and impractical. Solubilizers, i.e. cyclodextrins or surfactants such as Tween 80, are also applied, increasing drug solubility in water. However, the amounts of excipients in the product are often too high. Moreover, intolerance to substances used may develop and even their toxicity was observed. Presence of these substances results also in a change in the physical properties of the carrier leading, e.g. to decrease in Tg value, or reduction in the amount of drug used. According to classification of the International Conference on Harmonization (ICH), solvents used in production of solid dispersions belong mainly to group I, consisting of the most toxic volatile solvents [8]. Their usage gets limited as the residue left in the final product after drying is difficult to identify and remains below detection limit. An alternative method allowing dissolution of the drug and the carrier is to use solvent mixture. For this purpose mixtures of water and ethanol or dichloromethane and ethanol were used [8]. Another problem with the solvent method is prevention of phase separation, e.g. crystallization of the drug or carrier at the time of solvent removal by lyophilisation or spray drying. It should be remembered that even small variations in organic solvent removal process may result in large deviations in the product properties [2]. Drying at high temperature accelerates process of phase separation, which results from high mobility of drug and carrier molecules. In order to limit this phenomenon drying solution under vacuum, under reduced pressure and with moderate heating is applied [8]. Drying under vacuum with the use of elevated temperature may also pose a risk of phase separation, because when using this technique mobility of the drug and the carrier molecules decreases slowly. On the other hand, method of spray drying envolves dispersing solution into small droplets in hot air atmosphere. Due to the expanded droplet drying surface, solvent evaporates quickly and solid dispersion is formed within a few seconds. Short time required to obtain the product prevents phase separation. Moreover, solid dispersion formed using the presented method of drying consists of particles which size can be adjusted by size of aerosol droplets. The drug in that dispersion is mostly in an amorphous state, rarely in crystal form [8].

Melt evaporation method

Solid dispersions are created also by dissolving drug in relevant solvent and incorporating this solution in polyethylene glycol (PEG) melt below 70°C [20]. After combining the two solutions, the solvent is evaporated leaving the product layer. The resulting film is then dried to until a fixed weight is achieved. The difficulty in preparing solid dispersion using this method is limited mixing of the used solvents or of the dissolved drug with the molten PEG. Studies confirmed that 5 to 10% of liquid ingredients gets incorporated into PEG 6000 without any significant loss of solid features. In addition, liquid solvent used in this method is capable of initiating formation of polymorphic drug forms which then, as precipitates, appear in the resulting solid dispersion [1].

Method to obtain solid dispersions by melt evaporation has the advantages of both melting and solvent methods. Its unquestionable drawback is the limit of the amount of drug introduced into solid dispersion, equaling to 10% of the whole system [4].

Melt extrusion method

Melt extrusion method to prepare solid dispersions was introduced relatively recently [1]. It is considered particularly useful to obtain dispersions of drug substances occurring in various polymorphic forms of different bioavailability [21]. In the process of solid dispersion formation with the use of this technique drug substances dissolve in polymer and remain in form of molecular dispersion even as the polymer solidifies. Melt extrusion method is a variation of the previously discussed melting method.

Technological process of melt extrusion can be divided into several stages, including: introduction of substrates into extruder, mixing and reducing particle size, concentrating mass to be extruded into compact material of solid consistency, mass melting, homogenization and forcing the melt through extrusion tool.

Substance that fulfills role of a carrier, e.g. polymer, is introduced into the feeder part of extruder through dosing hopper. Due to the appropriate technical solutions, the material is easily transported inside a cylinder via a single or a double worm. Along the way it is premelt in the heat supplied from the outside source, produced by heating elements located on cylinder walls and by friction. Owing to the installed heating elements temperature in certain areas of the cylinder can be maintained at a constant, given level. As a result, the polymer melts and forms the gluey melt that reaches the drug substance dosing place. The introduced substrates are mixed together, kneaded and subjected to melting. In the subsequent extruder part deaerating takes place, then, homogenization of the material and eventually, the intermediate reaches degassing zone. Eventually, it reaches the dosing part as a homogeneous, malleable alloy ready for extrusion. The use of water and solvents in this process is unnecessary. In order to ensure the uniform product thickness, the mass flow through the cylinder into the receiver part must be constant. After cooling, the resulting products are collected and transported in the further process via belt conveyor. The final stage of the process is grinding of the obtained extrudate for one minute using laboratory mill and sieving to separate particles larger than 355 μm. After extrusion completion the product is formed into tablets, granules or pellets. Each of these forms contains solid dispersion of an active ingredient in a carrier [22]. Concentration of drug in so obtained solid dispersion usually equals 40% (w/w) [1].

Like in the traditional melting method, problem with use of the melt extrusion method may be mutual mixing of components and their sensitivity to temperature [8]. However, due to the short-term sample exposure to high temperatures (about one minute), this technique may be employed to receive solid dispersions even for heat labile substances [11]. Extrusion method allows production of solid dispersions on a larger scale than a laboratory method. Additionally, the product can easily be used in the subsequent steps, which does not delay the production process.

Lyophilisation technique

Lyophilisation technique has been proposed as an alternative to solvent method of solid dispersion preparation. The difference is, that the carrier and the drug are dissolved in a solvent and then, frozen in an atmosphere over, e.g. liquid nitrogen. This stage lasts a few minutes and is conducted in lyophilizer, which ensures that low pressure and sublimation temperature of –53°C are maintained. Sample introduced into the device sublimates to form a molecular dispersion, which is then placed in a vacuum desiccator over silica gel at room temperature for at least one day [1, 23].

Available literature describes this technique as promising and suitable for incorporating drug in a carrier. However, this method is not widely used to create solid dispersions. A factor significantly limiting its use is low freezing temperature of most organic solvents, while the process of sublimation may occur only when solvent remains in a frozen state. 2-methyl-2-propanol or tertiary butanol (TBA) can be used as solvents in this method, the latter characterized by high melting temperature and high pressure of evaporation. In addition, if sample is in glassy state, temperature should be maintained below the glass transition temperature Tg [8].

An important advantage of lyophilisation is reduction in time of sample exposure to thermal stress during formation of solid dispersion and minimal risk of phase separation. A more promising drying method than classic lyophilisation is spray drying at temperature of freezing. The solution is sprayed into liquid nitrogen or cold, dry air, and then the frozen droplets are lyophilised. A large surface and direct contact with the refrigerant accelerate process of glass transition and reduce the risk of phase separation to a minimum. Method with the use of aerosol allows adjustment of received dispersion particle size to required application, e.g. to receive aerosol dosage forms for delivery to lungs or nose [8].

Melt agglomeration process

This technique was used to create solid dispersions where a carrier acts also as a binding agent. In this case, solid dispersions may be prepared with simultaneous stirring of a heated carrier (binding agent), drug and excipients, using a high speed mixer above the melting point of the carrier. Also, solid dispersions may be prepared following addition of the dispersed drug together with the excipients to the already melted and heated carrier, or following adding of the molten carrier with the drug to preheated excipients [1, 24–26].

Type of a binding agent, method of preparation and particle size, are parameters considered as critical in preparation of solid dispersion using this technique. Particle size determines solubility of the created system, mechanism of agglomerate formation and their size, distribution and concentration. It was established that substance melting allows for greater mixture solubility than aerosol formation using PEG 3000, poloxamer 188 and gelucire 50/13 (surfactant, polyethylene glycol glycerides), because of a different mechanism of agglomerate formation. In addition, melting stage in the process allows to obtain a homogeneous dispersion of drug in the agglomerates [1].

Method with the use of surfactants

The use of surfactants in order to solubilize sparingly soluble substances is a common practice in pharmaceutical technology. Adsorption of surfactants on particle surface may modify particle hydrophobicity, electric charge and other properties, which in consequence leads to changes in behavior of the substance in a solution. Surfactants are attributed participation in solvation/ plasticization, which limits melting of the components and lowers their glass transition temperature [1]. Surfactants in solid dispersion may perform role of a carrier, as well as a dispersant, and emulsifying agent for the incorporated drug. Their presence in the formulation ensures increased solubility of a substance, due to the increased contact area between drug and the solvent. Also, it causes the substance molecules to disperse and emulsify, and as a result they get quickly dissolved. When a solid dispersion is prepared without surfactants, a layer rich in drug substance is formed on its surface. This layer restricts dissolution and extends drug release [27].

Parameter which must be noted when choosing a surfactant for a carrier in solid dispersion, is its melting temperature and solubility of the drug in the carrier. Filling of hard and soft gelatin capsules with solid dispersion requires that the mixture temperature does not exceed 70ºC and 40ºC, respectively. Besides, technological process requires the carrier to form a molten, liquid mass [28]. Also, a certain drug dose may be used only when solubilised by the carrier, and dissolves in that carrier in a satisfactory manner. When a sparingly soluble substance is used, its dispersion and dissolution often requires large amount of the carrier-surfactant [27].

Important problem associated with use of surfactants is uncontrolled crystallization of drug molecules outside of solid dispersion. This caused withdrawal of Norvir (Abbott) capsules, that contained ritonavir in supersaturated solid solution system, from the pharmaceutical market [29].

Electrospinning

Electrospinning is a technique that enables production of long polymer fibres of 40–2000 nm in diameter in the presence of electric field. Formation of solid dispersion fibres occurs when the liquid, or molten polymer with the drug substance, is pressed through a one millimeter nozzle and injected toward a focusing screen. The charged fibers dry or solidify on /their way to collector. They may be directed or accelerated by electric forces. However, accelerating them to high velocities is not favourable due to their tendency to roll and fold. The final fibre size is affected, in addition to the mentioned injection speed, by Coulomb repulsion forces which result in decrease in fibre diameter. This process can be countered by increasing viscosity of the polymer [30]. Electrospinning enables receiving of nanofibers that vary in terms of composition, length and physicochemical properties [31].

The release mechanism of drug substance in form of nanofibers from solid dispersions can be regulated by the appropriate quantitative ratio of substance to polymer, diameter of received fibers, and further technological process, e.g. incorporating of fibers into hard gelatin capsule. Verreck et al. presented solid dispersion in the form of nanofibers containing sparingly soluble in water itraconazole and readily soluble polymer – hydroxypropyl methylcellulose (HPMC) [31].

Supercritical Fluid Technology – SCF

In SCF method role of a carrier and a solvent for the drug plays most often carbon dioxide. Use of carbon dioxide is determined by the physical parameters, i.e. low critical temperature (Tc = 31.1°C) and low critical pressure (Pc = 73.8 bar). This gas may be present in supercritical state, where temperature and pressure are greater than the pressure and temperature of its critical point [1, 32]. At this point, difference in density between liquid and gas phase of a given substance disappears, and therefore there is no boundary between liquid and gas in the supercritical state. By definition, such a substance cannot be condensed by increasing the pressure, as it is possible for gas below its critical temperature (vapour).

In the SCF method carbon dioxide, in which both carrier and drug are dissolved, is injected as aerosol through a nozzle into container in which fluid is rapidly expanded. This results in its cooling [8]. Carbon dioxide density is reduced and the liquid is supersaturated, causing recrystallization and precipitation of drug particles much reduced in size. By manipulating pressure of carbon dioxide in supercritical state, the desired characteristics of gas may be obtained, i.e. high diffusion coefficient, low viscosity and low liquid surface tension [32]. This method of solid dispersion preparation does not require employment of organic solvents (RESS – rapid expansion of supercritical solution), however, its use is limited due to poor solubility of majority of drug substances in carbon dioxide [8].

Other modifications of this technique, so called supercritical precipitation methods, employ organic solvents to dissolve the drug substance and the carrier, and in contrast to the method described above do not require such a high solubility of components in carbon dioxide. Examples of precipitation methods include: Gas-Anti-Solvent (GAS) technology or precipitation from gas saturated solution (PGSS). Application of GAS technic is possible only if the drug or drug-polymer combination dissolves in the selected organic solvent. Medium is combined with substrates, and then injected as aerosol to SCF. The drug is required not to dissolve in SCF, while the organic solvent used to be miscible with SCF. SCF is dispersed within the sprayed aerosol droplets, which causes solvent to expand. When the volume of solution increases, ability to dissolve the drug decreases. This process results in precipitation of the carrier and the drug [32]. The use of PEG as a carrier in this method, enables to obtain solid dispersion with crystalline matrix (amorphous precipitates in crystalline carrier or solid solutions). Precipitation from a gas saturated solution covers dispersion of solution containing the drug and the carrier, in form of aerosol, through a nozzle into a container which contains fluid or anti-solvent in supercritical state. The supercritical solvent quickly penetrates to droplets, which are supersaturated with the drug and carrier molecules, causes them to crystallize, and eventually form precipitates. A general term for this technique is PCA, Precipitation with Compressed Antisolvent. A critical step in these processes is dissolving of drug and carrier in one solvent. Use of water for this purpose is limited, because of its low ability to dissolve in the compressed CO_2. Typically, to dissolve the drug and the carrier organic solvents are used, i.e. dichloromethane or methanol. Low solubility of both drugs and surfactants in supercritical CO_2 and high pressure values limit popularization of this method in the pharmaceutical industry [8].

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