Amorphous solid dispersion: a promising technique for improving oral bioavailability of poorly water-soluble drugs

Prashant Ghule[1,2], Ritu Gilhotra[1], Aukunuru Jithan[3], Shripad Bairagi[1,4], Abhijeet Aher[4]

[1] Department of Pharmaceutics, School of Pharmacy, Suresh Gyan Vihar University, Jaipur, Rajasthan, India

[2] Mula Rural Institute of Pharmacy, Sonai, A/p- Sonai, Newasa, Ahmednagar, Maharashtra, India 414105

[3] Mankind R&D, Gurgaon, Haryana, India

[4] Mula Education Society's College of Pharmacy, Sonai affiliated to Savitribai Phule Pune University, Pune, A/p- Sonai, Newasa, Ahmednagar, Maharashtra, India

Correspondence to: Prashant Jalindar Ghule, e-mail: prashantpharma07@gmail.com

Keywords: amorphous solid dispersion, oral bioavailability, poorly water soluble

Abstract

Out of many, one of the most promising strategies to improve the oral bioavailability of poorly water-soluble drugs is to develop amorphous solid dispersions. Reduction in drug particle size improves drug wettability and oral bioavailability significantly. Poorly soluble drugs are benefited by formulation approaches that overcome the issue of poor solubility and dissolution rate limited bioavailability. As Gibbs free energy is higher, the solubility of amorphous compounds is much greater than the more stable crystalline form. Moreover, amorphous forms are kinetically trapped high energy disordered materials that lack the periodicity of crystals but behave mechanically as solids. Lipophilic drugs, especially those belonging to the biopharmaceutics classification system (BCS) class II and IV, dissolve at a slower rate, leading to incomplete release of drug from the dosage form, poor oral bioavailability, increased food effect, and high inter-patient variability. Hence, to improve the solubility and dissolution of poorly water-soluble drugs, several formulation approaches can be considered, among which formulating the active pharmaceutical ingredient (API) in an amorphous form is recently gaining prominence. Formulating amorphous solid dispersions of poorly water-soluble drugs with water-soluble carriers has reduced the incidence of these problems and enhanced the rate of dissolution. This review mainly focuses on advantages, classification of solid dispersion, methods of preparation, and characterisation of the amorphous solid dispersion.

This article was peer reviewed. © **Medpharm** **S Afr Pharm J 2018;85(1):50-56**

1. Introduction

The utilisation of solid dispersions in order to increase the dissolution and oral bioavailability of poorly water-soluble drugs was first proposed by Sekiguchi and Obi[1] in 1961 and Mayersohn and Gibaldi (1966) were the first to use it.[2] Chiou and Riegelman in 1971 defined solid dispersion as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting (fusion), solvent or melting-solvent method".[3] On the basis of in vitro solubility and in vivo permeability data, the BCS divides drugs into four classes.[4] Class II drugs show poor solubility and high permeability. Class II drugs therefore have a limited ability to dissolve which is a most important limitation to their overall rate and extent of absorption and their ability to permeate through the membrane. Among the various strategies for improving the aqueous solubility or dissolution of drugs, the preparation of a solid dispersion system has often proven to be very successful.[5,6]

1.1 Salient features and advantages of amorphous solid dispersion (ASD)

- ASD is applicable to acidic, basic, neutral, and Zwitterionic drugs.[7]
- ASD minimises active drug requirements necessary to evaluate efficacy and safety.[8]
- ASD increases the dissolution rate and absorption of drug, which may produce quick onset of action.[9]
- ASD provides alternative pathways in order to improve oral bioavailability.
- ASD provides increased oral bioavailability, more rapid onset, and decrease in dose. It supports toxicology studies and provides a platform for clinical studies.[10,11]
- ASD may be used to obtain a homogeneous distribution of a small amount of drug in solid state.

2. Classification of solid dispersion based on molecular structure

Table I. Classification of solid dispersions

Serial number	Type of solid dispersion	State of API	Number of phases
1	Solid solution	Crystalline	1
2	Eutectic mixture	Crystalline	2
3	Glass solution	Amorphous	1
4	Glass suspension	Amorphous	2

2.1 Eutectic mixtures

A simple eutectic mixture consists of two compounds which are completely miscible in the liquid state (melt) but show limited miscibility in the solid state. At a specific composition (E in Figure1), the two components crystallise simultaneously when the temperature is reduced (Figure1). If the mixtures with different compositions to the eutectic composition of A and B are cooled, one component will start to crystallise before the other, which initially leads to a mixture of pure solid compound and liquid. Therefore, a true eutectic only exists for a defined composition of A and B. The microstructure of a eutectic mixture is different from the microstructure of each of either components, and this characteristic may be used in order to differentiate the eutectic mixture from other forms of crystalline mixtures. Eutectics of poorly soluble compounds and water-soluble inert carriers have shown enhancement in the dissolution rate of the poorly soluble compound. When the eutectic mixture is exposed to water or gastrointestinal (GI) fluids, the carrier dissolves rapidly and releases fine crystals of the drug. Through the large surface area and the improved wettability from the carrier, the dissolution rate of the drug will be enhanced.

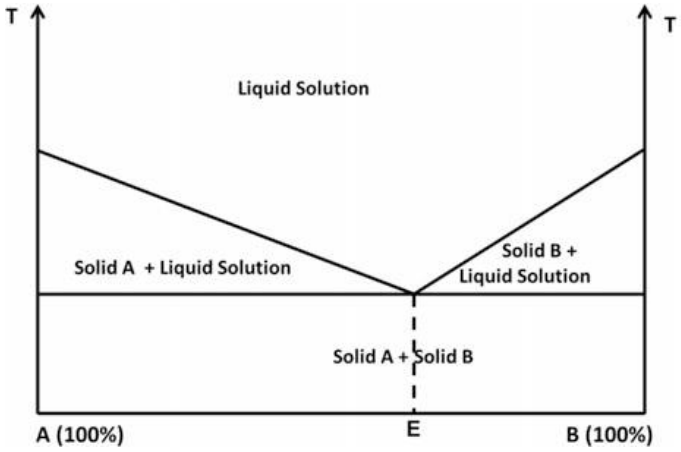

Figure 1. Phase diagram of a simple eutectic system

2.2 Solid solutions

Solid solutions are formed when a solute is nonstoichiometrically incorporated in the crystal lattice of the solvent (Moore and Wildfong 2009). Solid solutions may be classified according to the solubility of the solute in the crystal lattice (continuous vs. discontinuous) or according to the way in which the solute molecules are distributed. In general, the terminology "solid solution" refers to the system that contains a crystalline carrier.

2.2.1 Continuous solid solutions. In continuous solid solutions, all the components are miscible in all proportions. This occurs when the strength of the bonds between the two different molecules is higher than the bonds of the molecules of the same species. Organic molecules do not tend to form this kind of solid solution and therefore, they are not that important in the pharmaceutical industry.

2.2.2 Discontinuous solid solutions. The term "discontinuous" refers to the fact that solid solubility will only exist in specific compositions of the mixture, and not over the entire compositional range. Figure 2 represents a phase diagram of a discontinuous solid solution. Each component has the capability of completely dissolving the other component within a specific compositional region (regions α and β in Figure 2) whereby the solubilisation capacity of the components is temperature-dependent. It is maximum at the eutectic temperature and decreases with the decrease in temperature (Leuner and Dressman 2000). In reality, limited solid solubility most likely exists for all, or at least very many, binary systems. Goldberg et al (1965) therefore proposed to use the term "solid solution" only when the mutual solubility of the two components is more than 5%.

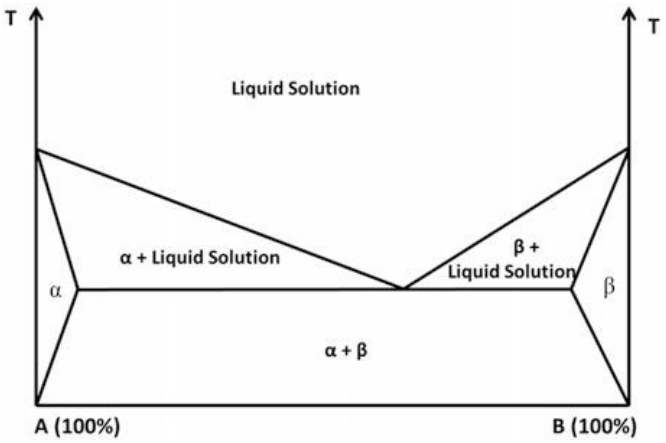

Figure 2. Phase diagram of a discontinuous solid solution

2.2.3 Substitutional solid solutions

In typical solid solutions with a crystalline carrier, a solute molecule can substitute for a carrier molecule in the crystal lattice (illustrated in Figure 3a). Substitution is possible only when the size of the solute molecule is approximately equal to the size of the carrier molecule. Substitutional solid solutions can be continuous or discontinuous.

2.2.4 Interstitial solid solutions

When the solute molecules are smaller than the solvent molecules, it is possible for solute molecules to occupy

the interstitial spaces in the crystalline lattice (illustrated in Figure 3b). In diameter the solute molecules should not exceed 0.59 times the diameter of the solvent molecule. Interstitial solid solutions can only form the solid solutions of discontinuous type (Khachaturyan 1978).

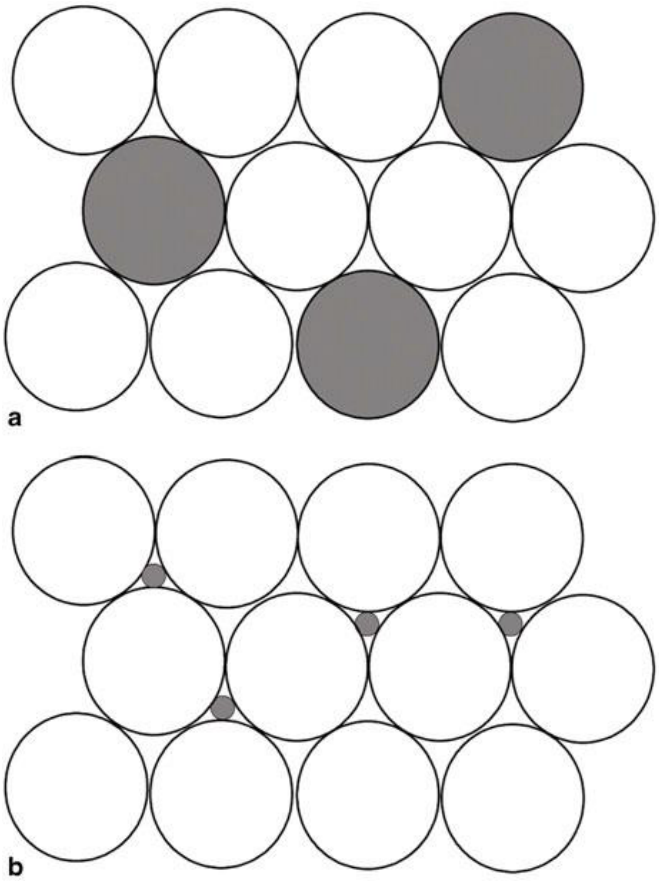

Figure 3. a. Substitutional crystalline solid solution
b. Interstitial crystalline solid solution

2.3 Glass solutions

In glass solutions, the carrier is amorphous in which the solute molecules are dispersed molecularly. A glass solution therefore forms homogeneous one-phase systems. However, because of the higher viscosity of glass solutions as compared to liquid solutions, the distribution of solute molecules may be irregular in the carrier and a homogeneous distribution within the glass solution can be ensured by mixing. In the past, sugars and urea were used as amorphous carriers, but now, in recent times organic polymers such as polyvinylpyrrolidone (PVP) and cellulose derivatives are commonly used. These polymers often exhibit amorphous regions (or are fully amorphous) and can be tailor-made for specific purposes. The glass solution is thermodynamically stable if the solubility of the drug in the carrier is not exceeded. However, the concentration of solute is often supersaturated to achieve a higher drug load which thus causes recrystallisation and precipitation. Recrystallisation may be reduced by kinetic stabilisation. Phase separation, being the first step to recrystallisation, requires a certain degree of molecular mobility within the system, and storing glass solutions at temperatures well below the glass transition temperature (Tg) will decrease the mobility and may lead to an increase in stability of the supersaturated glass solutions.

2.4 Glass suspensions

As stated above, it is usually observed that the miscibility of the amorphous drug in an amorphous carrier is limited, and as the drug content increases, phase separation occurs. If the drug forms a separate amorphous phase (or a drug-rich amorphous phase), the glass solution is converted to a glass suspension. As the drug in this state still remains in the amorphous form, it shows an increase in dissolution behaviour as compared to the crystalline form; however, these amorphous precipitates have a high affinity for recrystallisation of the amorphous drug (usually the Tg of the drug or drug-rich phase is lower than the Tg of the polymer or polymer-rich phase).

3. Methods of preparation of amorphous solid dispersion

3.1 Fusion method

The fusion method is also referred to as the melt method, when the starting materials are crystalline. The melting method was first introduced by Sekiguchi and Obi to prepare simple eutectic mixtures. Leuner and Dressman (2000) used to describe the melting method as the hot melt method. This method includes melting of the drug within the carrier followed by cooling and pulverisation of the obtained product. The fusion method has some limitations such as the use of high temperature leading to degradation of the drug during melting, and incomplete miscibility between drug and carrier.[12] In this method the physical mixture of a drug and a water-soluble carrier is prepared and heated directly until it is melted. The molten mass is then solidified rapidly in an ice-bath with continuous vigorous stirring. The resulting solid mass is crushed, pulverised and sieved. Appropriately this method has undergone many modifications in pouring the homogeneous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. In addition, super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature.[13] Under such conditions, the solute molecule is trapped in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when it is used for simple eutectic mixtures.

3.2 Solvent evaporation method

Solvent evaporation method is a simple way of producing amorphous solid dispersions where the drug and carrier are solubilised in a volatile solvent.[14] In the solvent evaporation method the solution of both matrix material and drug is prepared first. In a second step the solvent is removed resulting in the formation of a solid dispersion.[14] Mixing at the molecular level is preferred, because this results in optimal dissolution properties. In using the solvent evaporation method, the pharmaceutical

engineer faces two challenges.[15] The first challenge is the mixing of both drug and matrix in one solution, which is difficult when there is a significant difference in their polarity. To minimise the drug particle size in the solid dispersion, the drug and matrix have to be dispersed in the solvent as finely as possible, preferably with drug and matrix material in the dissolved state in one solution. The second challenge in this method is to avoid phase separation, e.g. crystallisation of either drug or matrix, during removal of the solvent(s).

3.3 Hot melt extrusion

Hot melt extrusion is used for manufacturing amorphous solid dispersions, in which the drug substance is melted or dissolved within a dispersion carrier and is mixed to produce and stabilise the amorphous form of the drug substances. Excipients, such as surfactants, are often added to further aid in the process, or to improve the dissolution performance of the formulation upon administration. The melt is extruded through a shape-forming orifice, and on rapid cooling, remains a solid, single-phase, glassy amorphous matrix that is stable throughout the shelf life. Post-extrusion processing equipment can be adapted in order to manage the extruded shapemaking so that it can be modified to downstream processing into a dosage form. In general, these materials are milled to reduce the particle size which is to be incorporated into a traditional oral solid dosage form such as a tablet or capsule, while maintaining the desired release profile for the drug.

3.4 Lyophilisation (freeze drying)

Freeze drying of pharmaceutical products is particularly used for the formulation and long-term storage of proteins,[16,17] and can also be used to prepare amorphous solid dispersion.[18,19] The process consists of three segments, viz, freezing, primary drying and secondary drying.[20] During freezing, most of the water is removed forming a freeze concentrate of the drug and carrier. When the pressure inside the chamber is reduced, ice begins to sublime as primary drying occurs. In secondary drying, elevated temperatures and low pressures are used to remove water from the freeze concentrate. Primary drying is the longest of the three stages and should be optimised in order to reduce time, money and resource requirements.

3.5 Spray drying

As in the case of hot melt extrusion, spray drying is also another processing technique adopted from the food industry. Spray drying can be divided into three separate segments, namely, atomisation, drying and collection of the powder. All three segments have an impact on both the physical properties of the powder and process yield and efficiency.[21] During atomisation, a fine mist with a large surface area is sprayed into a heated chamber. Heat is transferred and immediate evaporation of the liquid phase occurs due to the formation of fine droplets. On the basis of the properties of the sprayed liquid, desired powder properties and limitations of the spray drying equipment, a rotary, hydraulic, pneumatic or ultrasonic atomiser can be selected to atomise the liquid. After the liquid is atomised, the droplets enter in the drying chamber where hot air is used to evaporate the solvent. The temperature of the incoming air can be modified in order to achieve an optimum thermal efficiency. The humidity of the incoming air should be monitored as it influences the product drying, process efficacy and the physical properties of the dried powder.[22,23] After drying, the air stream carries particles out of the drying chamber and into a separation device. Cyclones use centrifugal force to separate the powder from the air stream while bag filters may also be used to collect the product.

3.6 Supercritical fluid method

Supercritical fluid (SCF) possesses the characteristics of both liquid and gas. Under supercritical conditions, the material has liquid-like solvent properties and gas-like viscosity, diffusivity, and thermal conductivity. Although the solvent properties are beneficial for drug/polymer solubilisation, the gas-like properties significantly enhance the mass transport characteristics of the fluids. In this method supercritical carbon dioxide (CO_2) is mostly used either as a solvent for drug and polymer or as an antisolvent.[24] The drug and polymer are dissolved in supercritical CO_2 and sprayed through a nozzle into a low-pressure region which causes adiabatic expansion of the CO_2 and rapid cooling. Thus, drug particles of reduced size can be produced using this technique. This method is known as rapid expansion of supercritical solution (RESS). Current SCF methods have demonstrated the potential of developing the nano particulate suspensions of particles of size 5–2000 nm in diameter.[25] This technique is referred to as being environmentally friendly because it is not dependent on the use of organic solvents and the small amount of the residual CO_2 which is trapped inside the polymer poses no danger to the patients. Furthermore, the ability of CO_2 to plasticise and swell polymers can also be utilised. However, low solubility of most of the pharmaceuticals in CO_2 limits the practical application of this approach.[26] Several methods of SCF processing have been developed in order to address individual aspects of these limitations and to improve the solubility. These methods include precipitation with a compressed antisolvent,[27] solution-enhanced dispersion by SCF,[28] supercritical antisolvent processes,[29] gas antisolvent recrystallisation,[30] and aerosol supercritical extraction system.[31]

3.7 Gel entrapment technique

Carriers which have a tendency to swell are dissolved in a suitable organic solvent in order to form a clear and transparent gel. The drug is then dissolved in gel by sonication for a few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by glass mortar and sieved.[32]

3.8 Direct capsule filling

Direct filling of hard gelatin capsules with the molten liquid of solid dispersions avoids grinding-induced changes in the crystallinity of the drug.[33] This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross

contamination and operator exposure in a dust-free environment, better fill-weight and content uniformity can be obtained than with the powder-fill technique.[34]

3.9 Dropping solution method

The dropping method facilitates the crystallisation of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a molten drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round-shaped particles. The size and shape of the particles is influenced by factors such as the viscosity of the melt and the size of the pipette. As viscosity is highly temperature-dependent, it is crucial to adjust the temperature, so that when the melt of the drug carrier mixture is dropped onto the plate it solidifies to a spherical shape. The dropping process may be facilitated by using the carriers that solidify at room temperature. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate.[35] It does not use organic solvents and therefore has none of the problems associated with solvent evaporation. The method also avoids the pulverisation, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermo-stable drugs can be used and the physical instability of solid dispersions is a further challenge.[36]

4. Effect of degree of crystallinity on the performance of amorphous solid dispersions

Amorphous solids are generally more soluble and faster dissolving than their crystalline counterparts, which makes them potentially useful for delivering poorly soluble drugs whose bioavailability is limited by their low solubility.[37] As crystallisation negates solubility advantage, so amorphous drugs must resist their thermodynamic tendency to crystallise.[38]

Sun et al reviewed several modes of crystallisation of amorphous solids[39] (summarised in Table II).

Table II. Modes of crystallisation

Modes of crystallisation	Occurrence
Fast mode of crystal growth	Organic liquids cooled to become glasses
GC mode (glass-to-crystal)	In bulk of powders
Fast growth at free surface	At the free surface of solids

The growth of crystals in amorphous pharmaceutical solids can be minimised by polymeric inhibition. Although amorphous pharmaceutical formulations may contain polymers as the major component, recent studies have examined the use of low-concentration polymers as crystallisation inhibitors. Such studies are a necessary first step for understanding more complex formulations, and could discover effective polymer additives that significantly improve the properties of amorphous drugs.[40-42]

Recent work has found that low-concentration polymer additives can be remarkably effective in slowing bulk crystal growth in organic glasses, but their effect on surface crystal growth is much weaker. It was also discovered recently that ultra-thin polymer coatings can inhibit surface crystallisation, as well as improve the flow and wetting of a hydrophobic drug. These results suggest the possibility of using low concentration polymer additives to stabilise amorphous drugs; for example, a bulk additive to inhibit bulk crystallisation and an ultra-thin surface coating to halt surface crystallisation.[40]

5. Mechanism of bioavailability enhancement

The enhancement in dissolution rate because of amorphous solid dispersion formation, compared to that of pure drug, varies from as high as 400 fold to less than two fold.[43] The increase in dissolution rate can be attributed to myriad factors and it is very difficult to show experimentally that any one particular factor is more important than the other. Solid dispersions increase the dissolution rate of poorly aqueous soluble drugs by one of the following mechanisms[44]:

- Reduction in particle size
- Improvement in wettability and dispersibility
- Changing crystalline form of drug to amorphous form
- Reduction in aggregation and agglomeration of drug particles

6. Polymers used as carrier for solid dispersions

The selection of the polymer carrier influences the dissolution characteristics of the dispersed drug, as the dissolution rate of one component from the surface is affected by the other component in a multiple component mixture. Therefore, selecting a water-soluble carrier will result in a faster release of the drug from the matrix. A poorly soluble or insoluble carrier will lead to slower

Table III. Polymers used as carrier for solid dispersion

Serial number	Category	Example
1	Sugars	Dextrose, sucrose, galactose, sorbitol, maltose, xylitol, mannitol, lactose
2	Acids	Citric acid, succinic acid
3	Polymeric materials	Polyvinyl pyrrolidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), methyl cellulose (MC), hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan
4	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate (HPMCP), eudragit L100, eudragit E100, eudragit RL, eudragit RS
5	Surfactants	Polyoxyethylene stearate, poloxamer 188, deoxycholic acid, tweens, spans
6	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

release of a drug from the matrix. If the active drug present is a minor component in the dispersion, faster release of a drug can be achieved from the matrix.[45,46] Various carriers used for the preparation of solid dispersions are tabulated in Table III.

7. Characterisation of solid dispersions

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Many attempts have been made in order to investigate the molecular arrangement in solid dispersions. However, much effort has been put to differentiate amorphous and crystalline material. For this purpose many techniques are available which can detect the amount of crystalline material in the solid dispersion. The amount of amorphous material cannot be measured directly but can be derived from the amount of crystalline material present in the sample. It should be noted that through the assessment of crystallinity as the method to determine the amount of amorphous drug, it becomes difficult to reveal whether the drug is present as amorphous drug particles or as molecularly dispersed molecules.[47] Table IV summarises various methods used to characterise solid dispersions along with their significance.

8. Marketed preparations[48]

(See Table V)

9. Recent advances and future trends

Amorphous solid dispersion has great potential of increasing both the bioavailability of drug and developing controlled-release preparations. Thus, to overcome bioavailability issues of poorly water-soluble drugs, amorphous solid dispersion technology has grown rapidly. The dosage form can be developed and prepared using very small amounts of drug substances in the early phase of the drug development process. The system might have an advantage over such other commonly employed techniques used for bioavailability enhancement.

10. Conclusion

Solid state modification by developing amorphous solid dispersion is a subject of intensive research owing to its considerable potential for enhancing dissolution and bioavailability. Despite substantial advancement that has been made in this area, physical instability (in the form of phase separation, moisture sorption or

Table IV. Common characterisation techniques for amorphous solid dispersions

Characterisation technique	Information generated	Property determined
Differential Scanning Calorimetry	Tg, heat capacity, excess properties	Phase miscibility
Thermogravimetric Analysis	Weight loss against temperature	Water content
Powder X-ray diffraction (PXRD)	Diffraction pattern	Phase miscibility, crystallinity
Fourier-Transform Infrared Spectroscopy	IR spectrum	Intermolecular interactions (e.g. hydrogen bond)
Solid-state NMR	Spin-lattice relaxation time	Phase miscibility, intermolecular interaction, molecular mobility
SEM/AFM particle size	Morphology particle size	Particle size
Dynamic Vapor Sorption	Water sorption isotherm	Hygroscopicity
Laser diffraction	Particle size distribution	Particle size
Dissolution	Drug release profile	Solubility, supersaturation level
BET analysis	BET adsorption profile	Specific surface area
High pressure liquid chromatography	Sample concentration	Drug loading, encapsulation efficiency
Inverse Gas Chromatography	Retention volume and dispersive surface free energy	Kinetic of surface relaxation (tendency of surface crystallisation)

Table V. List of marketed preparation of solid dispersion

Product/substance	Dispersion polymer or carrier	Technology used	Company
Gris-PEG® (Griseofulvin)	Polyethylene glycol	Melt process; exact process unknown	Novartis
Sproramax capsules (Itraconazole)	Hydroxypropyl methylcellulose (HPMC)	Spray layering	Janssen pharmaceutica
Cesamet® (Nabilone)	Povidone	Process unknown	Lilly
Kaletra (lopinavir and ritonavir)	Polyvinyl pyrrolidone (PVP)/polyvinyl acetate	Melt extrusion	Abbott Laboratories
Torcetrapiba	HPMC acetate succinate	Spray drying	Pfizer
Ibuprofen	Various	Melt extrusion	Soliqs
Isoptin SRE-240 (Verapamil)	Various	Melt extrusion	Soliqs
Rezulinb (Troglitazone)	PVP	Melt extrusion	Pfizer
LCP-Tacro (Tracrolimus)	HPMC	Melt granulation	Life Cycle Pharma
Intelence (Etravirine)	HPMC	Spray drying	Tibotec
Certican (Everolimus)	HPMC	Melt or spray drying	Novartis
Afeditab (Nifedipine)	Poloxamer or PVP	Melt/absorb on carrier	Élan Corp

recrystallisation), which is often unpredictable, remains the major problem in the development and eventual commercialisation of solid dispersion formulations. Judicious selection of polymer carriers with adequate antiplasticising effect, high Tg and good miscibility with the drug is crucial for preventing or minimising the unwanted phase separation or rapid recrystallisation both in the solid state and in aqueous solution upon dissolution. In addition, during the development phase, monitoring and elucidation of the potential solid phase changes have been made possible by the application of mutually complementary solid-state characterisation tools such as powder x-ray diffraction, differential scanning calorimetry and fourier transform infra-red spectroscopy. Thus amorphous solid dispersion is one of the most effective approaches to achieve the goal of solubility enhancement of poorly water-soluble drugs.

Declaration of interest

All authors have nothing to declare.

Acknowledgement

Authors are thankful to Suresh Gyan Vihar University, Jaipur Rajasthan and Mula Rural Institute of Pharmacy, Sonai for providing the necessary infrastructure and facilities.

References

1. Sekiguchi K, Obi N. Studies on absorption of eutectic mixture. I. A comparison of behavior of eutectic mixture of sulphathiozole and that of ordinary sulphathiozole in man. Chem Pharm Bull. 1961;9;866-872.
2. Mayersohn M, Gibaldi M. New method of solid state dispersion for increasing dissolution rates. J Pharm Sci. 1966;55:1323-1324.
3. Chiou WL, Riegelman S. Preparation and dissolution characteristics of several fast-release solid dispersions of griseofulvin. J Pharm Sci. 1969;58(12):1505-1510.
4. Amidon GL, Lennernas H, Shah VP, Crison JR. A theoretical basis for a biopharmaceutical drug classification: correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995; 12: 413-420.
5. Monkhouse DC, Lach JL. Use of adsorbents in enhancement of drug dissolution. J Pharm Sci. 1972;61:1430-35.
6. Chiou WL, Riegelman S. Pharmaceutical applications of solid dispersion systems. J Pharm Sci. 1971;60:1281-1302.
7. Kalpana Patidar, Manish Soni, Dinesh Sharma K, Surendra Jain K. Drug Invent Today. 2010;2(7):349-357.
8. Birdar VS, Patil Arpana R, Sudarshan Guditi V, Pokharkar Varsha B. Comparative studies of approaches improve solubility of roxithromycin. Int J Pharm. 2006;169(1):22-32.
9. Chaudhari PD, Sharma PK, Badagale MM, et al. Curr Trend Solid Dis Tech. 2006;4(3):2-12.
10. Dhirendra K. Solid dispersions: a review. Pak J Pharm Sci. 2009;22(2):234-246.
11. Remingtons Pharmaceutical Sciences, 1980. vols. 1 & 2.
12. Patterson James E, James Michael B, Forster Angus H, et al. The influence of thermal and mechanical preparative techniques on the amorphous state of four poorly soluble compounds. J Pharm Sci. 2005;94:1998-2012.
13. Arunachalam A, Karthikeyan M, Konam Kishore, et al. Solid dispersions: a review. Curr Pharm Res. 2010;1(1):82-90.
14. Saharan Vikas A, Kukkar Vipin, Kataria Mahesh, et al. Dissolution enhancement of drugs. Int J Health Res. 2009;2(2):107-124.
15. Kalpana Patidar, Manish Soni, Dinesh Sharma K, Surendra Jain K. Solid dispersion: approaches, technology involved, unmet need and challenges. Drug Invent Today. 2010;2(7):349-357.
16. Pikal MJ. Freeze-drying of proteins. Part I: process design. BioPharm. 1990;3(8):18-20,22-4,26-8.
17. Pikal MJ. Freeze-drying of proteins part II: formulation selection. BioPharm. 1990;3(9):26-30.
18. Van Drooge DJ, Hinrichs WLJ, Visser MR, Frijlink HW. Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques. Int J Pharm. 2006;310(12):220-9.
19. Betageri GV, Makarla KR. Enhancement of dissolution of glyburide by solid dispersion and lyophilization techniques. Int J Pharm. 1995;126(12):155-160.
20. Tang X, Pikal MJ. Design of freeze-drying processes for pharmaceuticals: practical advice. Pharm Res. 2004;21(2):191-200.
21. Cal K, Sollohub K. Spray drying technique. I: Hardware and process parameters. J Pharm Sci. 2010;99(2):575-86.
22. Goula AM, Adamopoulos KG. Spray drying of tomato pulp in dehumidified air: I. The effect on product recovery. J Food Eng. 2005;66(1):25.
23. Goula AM, Adamopoulos KG. Spray drying of tomato pulp in dehumidified air: II. The effect on powder properties. J Food Eng. 2005;66(1):35.
24. Thakkar F, Soni T, Gohel M, Gandhi T. Supercritical fluid technology: a promising approach to enhance the drug solubility. J Pharm Sci Res. 2009;1:1-14.
25. Sunkara G, Kompella U. Drug delivery application of supercritical fluid technology. Drug Deliv Tech. 2002;58:615-619.
26. Subramaniam B, Rajewski A, Snavely K. Pharmaceutical processing with supercritical carbon dioxide. J Pharm Sci. 1997;86:885-890.
27. Wu K, Li J, Wang W, Winstead D. Formation and characterization of solid dispersions of piroxicam and polyvinyl pyrrolidone using spray drying and precipitation with compressed antisolvent. J Pharm Sci. 2009;98:2422-2431.
28. Jun S, Kim M, Jo G, et al. Cefuroxime axetil solid dispersions prepared using solution enhanced dispersion by supercritical fluids. J Pharm Pharmacol. 2005;57:1529-1537.
29. Kim M, Jin S, Kim J, et al. Preparation, characterization and in vivo evaluation of amorphous atorvastatin calcium nanoparticles using supercritical antisolvent (SAS) process. Eur J Pharm Biopharm. 2008;69:454-465.
30. Corrigan O, Crean A. Comparative physicochemical properties of hydrocortisone-PVP composites prepared using supercritical carbon dioxide by the GAS anti-solvent recrystallization process, by co-precipitation and spray drying. Int J Pharm. 2002;245:75-82.
31. Lee S, Nam K, Kim M, et al. Preparation and characterization of solid dispersion of itraconazole by using aerosol solvent extraction system for improvement in drug solubility and bioavailability. Arch Pharm Res. 2005;2:866-874.
32. Bhise SB, Rajkumar M. Effect of HPMC on solubility and dissolution of carbamazepine form III in simulated gastrointestinal fluids. Asian J Pharm. 2008;2(1):38-42.
33. Karanth H, Shenoy VS, Murthy RR. Industrially feasible alternative approaches in the manufacture in the the solid dispersion: A technical report. AAPS Pharm Sci Tech. 2006;7(4):E1-E8.
34. Serajuddin ATM, Sheen PC, et al. Effect of vehicle amphiphilicity on the dissolution and bioavailability of a poorly water soluble drug from solid dispersions. J Pharm Sci. 1988;77:414-417.
35. Shaharoodi AB. Dropping method for formulating solid dispersion. Pharm Tech Eur. 2003;1:1-2.
36. Shahroodi AB, Nassab PR, et al. Preparation of a solid dispersion by a dropping method to improve the rate of dissolution of meloxicam. Drug Dev Ind Pharm. 2008;34(7):781-788.
37. Craig DQM. The mechanism of drug release from solid dispersion in water soluble polymers. Int J Pharm. 2002;231:131-144.
38. Hancock BC, Parks M. What is the true solubility advantage for amorphous pharmaceuticals? Pharm Res. 2000;17:97-104.
39. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86:1-12.
40. Sun Y, Zhu L, Wu T, et al. Stability of amorphous pharmaceutical solids: crystal growth mechanisms and effect of polymer additives. AAPS Journal. 2012;14(3):380-388.
41. Kestur US, Lee H, Santiago D, et al. Effects of the molecular weight and concentration of polymer additives and temperature on the melt crystallization kinetics of a small drug molecule. Cryst Growth Des. 2010;10:3585-95.
42. Cai T, Zhu L, Yu L. Crystallization of organic glasses: effects of polymer additives on bulk and surface crystal growth in amorphous nifedipine. Pharm Res. 2011;28:2458-66.
43. Ishida H, Wu T, Yu L. Sudden rise of crystal growth rate of nifedipine near Tg without and with polyvinylpyrrolidone. J Pharm Sci. 2007;96:1131-8.
44. Arise MJ, Gines JM, Moyano JR, Perez M. Influence of preparation method of solid dispersions their dissolution rate; Study of triamterene d-mannitol system. Int J Pharm. 1995;123:25-31.
45. Ansel CH, Allen VL, Popovich AN. Pharmaceutical dosage forms and drug delivery systems. 7th Ed, Wolters Kluwer, India, pp. 248-252 (2000).
46. Patidar K, Soni M, Sharma KD, Jain KS. Solid dispersion: approaches, technology involved, unmet need & challenges. Drug Inv Today. 2010;2(7):349-357.
47. Vasconcelos T, Sarmento B, Costa P. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discover Today, 2007;12(23-24):1068-1075.
48. Arunachalam A et al. Solid dispersion: A review. Current Pharm Res., 2010;1(1):83-90.