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REVIEW ARTICLE

SOLID DISPERSION TECHNOLOGY, A CONTEMPORARY OVERVIEW ON A WELL ESTABLISHED TECHNIQUE

Mahmoud A. Younis
Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt.

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***Address for Correspondence:**
Mahmoud A. Younis, Department of Industrial Pharmacy, Faculty of Pharmacy, Assiut University, Assiut 71526, Egypt, E-mail: *mahmoud_ab32@yahoo.com*

Abstract

Solubility is a significant physicochemical parameter that affects the absorption, bioavailability and therapeutic effectiveness of any drug. Formulation development would fail if drug has a poor aqueous solubility. The low aqueous solubility of drug substances will lead to inadequate absorption and consequently, low bioavailability. Improvement of the aqueous solubility and dissolution rate of hydrophobic drugs remains one of the most difficult challenges in drug development process. Among various techniques used to improve poor aqueous solubility of drugs, solid dispersion technology has been extensively used in the literature and has become one of the well-established pharmaceutical procedures during formulation process. Although the technique seems to be "a part of the past", literature tells us that it is still used and developed to suit current needs of pharmaceutical industry. This review article highlights recent advances in solid dispersion technology and its applications in contemporary pharmaceutical research.

Keywords: Dissolution rate, hydrophilic carriers, poorly-soluble drugs, solid dispersion, solubility.

INTRODUCTION

Solubility is a significant physicochemical parameter that affects all characteristics of a drug substance[1]. According to literature, about 70% of newly-discovered drug substances have aqueous solubility problems[2]. This represents a great challenge to pharmaceutical industry as it leads to poor absorption, poor bioavailability and probably, failure of treatment[1]. Over decades, scientists have developed several approaches to overcome solubility problems including the use of surfactants[3], cosolvents[3], inclusion complexes[4], self-emulsifying systems[5], prodrugs[6] and micro-environmental buffering systems[7]. Solid dispersion technology has become one of the well-established techniques for solubilization of poorly-soluble drugs[8]. It has been extensively used in pharmaceutical literature for solubilization of massive number of hydrophobic drugs. Although the technique seems to be "a part of the past", literature tells us that it is still be used and developed to suit current needs of pharmaceutical industry. This review article highlights recent advances in solid dispersion technology and its applications in contemporary pharmaceutical research.

History and definitions of solid dispersion technology

In 1961, Sekiguchi and Obi[9] first used solid dispersions technology to increase the dissolution and oral absorption of poorly water-soluble drugs. They assumed the formation of an eutectic mixture of a poorly water-soluble drug with a physiologically inert, hydrophilic carrier. In 1966, Mayersohn and Gibaldi[10] described solid dispersion as a "solid-state dispersions" or "a solid solution". In 1971, Chiou and Riegelman[11] defined solid dispersion as "the dispersion of one or more active ingredients in an inert carrier matrix at solid-state prepared by the melting, solvent or melting-solvent method". In 1985, Corrigan[12] defined the term as "a product formed by converting a fluid drug-carrier combination to the solid state". Recently, Dhirendra *et al.*,[13] defined solid dispersion as "a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles".

Classification of solid dispersion systems

In 2007, Chokshi *et al.*,[14] classified solid dispersion systems according to the crystalline status of drug within the system. If the drug is converted to amorphous form and forms one phase system with polymer, it can be classified as a "solid solution",

whereas if the drug exists as microcrystalline dispersion, i.e., forms two-phase system, it is generally referred to as a "solid dispersion". In 2015, Meng *et al.*,[15] extended the classification according to the crystalline status of both drug and carrier. They classified the systems as the following:

i. **Class C-C:** Crystalline active pharmaceutical ingredient (API) dispersed in crystalline carrier.
ii. **Class C-A:** crystalline API dispersed in amorphous carrier.
iii. **Class A-C:** Amorphous API dispersed in crystalline carrier.
iv. **Class A-A:** Amorphous API dispersed in amorphous carrier.
v. **Class M-C:** API molecularly dispersed in crystalline carrier.
vi. **Class M-A:** API molecularly dispersed in amorphous carrier.

Table 1: Examples of drugs formulated as solid dispersions.

Drug name	Use	References
Ampelopsin	Anti-inflammatory, antimicrobial, relieving cough, antioxidant, antihypertensive, hepatoprotective and anticarcinogenic.	4
Albendazole	Anthelmintic	24
Carbamazepine	Anti-epileptic	30
Chlordiazepoxide	Sedative and hypnotic	29
Domperidone	Anti-emetic	37, 38
Indomethacin	Anti-inflammatory	19
Meloxicam	Anti-inflammatory, analgesic	27
Paracetamol	Analgesic, antipyretic	25
Sulfathiazole	Antibacterial	9
Tadalafil	Treatment of erectile dysfunction	39
Valsartan	Antihypertensive	40

Examples of drugs formulated as solid dispersions

A massive number of drugs have been formulated as solid dispersions in the pharmaceutical literature (Table 1).

Advantages of solid dispersion technology

The major advantage of solid dispersions is that they improve the solubility of poorly water soluble drugs in pharmaceutical dosage forms which results in rapid dissolution rates and improved bioavailability of drugs. Moreover, the approach also offers others advantages including[16]:

i. Rapid dispersion into water which is beneficial in the formulation of fast-dissolving tablets that can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.
ii. High degree of particle size reduction which is advantageous over traditional grinding in that it is suitable for waxy substances produces no dust and there is no danger for explosion.
iii. Ability to produce a controlled pattern of drug release using the suitable retarding excipients like cellulose derivatives.
iv. Ability to formulate liquid drugs into solid dosage forms through their mixing with molten carriers followed by rapid cooling and pulverization. This method was successful with several liquid drugs including methyl salicylate and clofibrate.
v. Solid dispersions can result in precipitation of drugs in amorphous state with higher solubility and dissolution rate than the more stable crystalline state.

Disadvantages of solid dispersion technology

1. Most of the polymers used in solid dispersions can absorb moisture, which may results in phase separation, crystal growth or conversion from the amorphous state to the crystalline state or from a metastable crystalline form to a more stable structure during storage. This may results in decreased solubility and dissolution rate[17].
2. Poor scale-up for the purposes of manufacturing[17].
3. Stability problems: Younis[18] reported the dissolution rate lowering of solid dispersions on aging owing to recrystallization of the amorphous drug in system and/or polymorphic transitions that are frequently associated with the aged solid dispersions.

Common materials used in preparation of solid dispersions

There are several materials that can be used as hydrophilic carriers in preparation of solid dispersions. Some examples are briefly discussed below.

Polyethylene glycols (PEGs)

Polyethylene glycols (PEGs) are polymers of ethylene oxide, with a molecular weight falling in the range 200-300,000. For the manufacture of solid dispersions, PEGs with a molecular weight 1500-20,000 are usually employed. PEGs have many advantages including high aqueous solubility, low cost, low toxicity and low melting points (below 65 °C) making them suitable carriers for preparation of solid dispersions by melting method[19].

Polyvinylpyrrolidone (PVP)

Polymerization of vinylpyrrolidone leads to polymers of molecular weight ranging from 2500 to 300,000. They are inert, safe, highly water-soluble and soluble in a wide variety of solvents including alcohol. The main disadvantages of PVPs are hygroscopicity and high melting points (above 265°C) making them more suitable for preparation of solid dispersions by solvent-based methods instead of heating-based methods[20].

Urea

It is the end product of protein metabolism and can also be synthesized by chemical reactions. It is highly water-soluble, soluble in many common organic

solvents and has a moderate melting point (132-135°C) making it suitable for preparation of solid dispersions by different methods[21].

Sugars

Although sugars have high aqueous solubility, they have many drawbacks regarding their use as carriers in solid dispersions. Most of them have high melting points making them problematic in the preparation of solid dispersions by heating methods. They are also poorly-soluble in most organic solvents creating problem in preparation of solid dispersions by solvent methods. Despite these draw backs, mannitol and sorbitol were reported to be used as carriers for many drugs[22].

Poloxamers

Poloxamers are poly (oxyethylene)-poly (oxypropylene) copolymers, with trade names as Supronic, Pluronic or Tetronic. They have been introduced in 1950 and were since then very famously used in diverse pharmaceutical applications. They are composed of two hydrophilic chains of polyethylene oxide (PEO) sandwiching one hydrophobic polypropylene oxide chain (PPO). They are classified according to the proportions of hydrophilic and hydrophobic chains including poloxamer 124, 188, 237, 338 and 407 as the most common types. They are used as gelling agents, surfactants, stabilizers and hydrophilic carriers. They are soluble in different solvents and have low melting points (52-57°C) making those suitable carriers for preparation of solid dispersions by different methods[23].

Methods of preparation of solid dispersions

There are several methods used to prepare solid dispersions which have been developed from simple manual procedures to advanced techniques requiring special equipment to fulfill the needs of modern pharmaceutical industry. Some of these various techniques are briefly discussed below.

1. Co-melting method

This method involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly till melting. The molten mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. The modification in the method can be done by pouring the homogenous 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, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures. Advantage of co-melting method is that it is economic and solvent less process, however this method is not suitable for the drug or carrier which is unstable at fusion temperature or evaporates at higher temperature. Some of the means to overcome these problems could be by heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier[24].

2. Fusion method

It is a modification of co-melting method. The carrier is placed in a porcelain dish and heated till melting over steam bath. The accurately weighed amount of drug is dispersed into molten carrier gradually using a glass rod. After complete dispersion of drug within carrier, the dish is removed from steam bath and left aside to cool at room temperature till solidification of its contents. Then, the solid dispersion formed is pulverized and sieved. This method is useful in reducing thermal decomposition of drugs[25].

3. Solvent evaporation method

Both drug and carrier are dissolved in a common volatile solvent which is then, removed under vacuum. The formed solid dispersion is pulverized and sieved[26].

4. Kneading technique

In this method, carrier is permeated with water and transformed to paste. Drug is then added and kneaded for particular time. The kneaded mixture is then dried and passed through sieve if necessary. This method is suitable for thermolabile drugs but, it is not suitable for drugs sensitive to moisture[27].

5. Co-precipitation method

Required amount of drug is added to the solution of carrier. The system is kept under magnetic agitation and protected from the light. The formed precipitate is separated by vacuum filtration and dried at room temperature[28].

6. Co-grinding method

Physical mixture of drug and carrier is mixed for some time employing a blender at a particular speed. The mixture is then charged into the chamber of a vibration ball mill. The powder mixture is pulverized. Then, the product is collected and kept at room temperature in a screw capped glass vial until use[29].

7. Gel entrapment technique

Hydroxyl propyl methyl cellulose (used as a carrier) is dissolved in organic solvent to form a clear and transparent gel. Then, the drug is dissolved in gel by sonication for few minutes. Organic solvent is evaporated under vacuum. Solid dispersions are reduced in size by mortar and pestle and sieved[30].

8. Spray drying method

Drug is dissolved in suitable solvent and the required amount of carrier is dissolved in water. Solutions are then mixed by sonication or other suitable method to produce a clear solution, which is then spray dried using a spray dryer to produce solid dispersion in form of fine, free-flowing particles[31].

9. Electrospinning method

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter- scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attached to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor cone). Beyond the critical

value, a charged polymer jet is ejected from the apex of the cone and carried to the collection screen via the electrostatic force[32]. This technique has potential for the preparation of nanofibres and controlling the release of biomedicines. As it is simple and cheap, this technique can be utilized for the preparation of solid dispersions in future[33].

10. Freeze-drying method

This process consists of dissolving the drug and carrier in a common solvent, which is immersed in liquid nitrogen until it is fully frozen. Then, the frozen solution is further lyophilized. Although it is concluded in literature that this is a promising and suitable technique to incorporate drug substances in stabilizing matrices, the technique is poorly exploited for the preparation of solid dispersions due to economical reasons. Advantages of freeze drying include that the drug is subjected to minimal thermal stress during the formation of the solid dispersion and the risk of phase separation is minimized[34-36].

11. Supercritical fluid (SCF) method

Supercritical fluid methods are mostly applied with carbon dioxide (CO_2), which is used as either a solvent for drug and matrix or as an anti-solvent. This technique consists of dissolving the drug and the carrier in a common solvent that is introduced into a particle formation vessel through a nozzle, simultaneously with supercritical CO_2 (the gas is heated beyond its critical temperature and pressure). When the solution is sprayed, the solvent is rapidly extracted by the SCF, resulting in the precipitation of solid dispersion particles on the walls and bottom of the vessel. Advantages of this technique include reduction of particle size and residual solvent content as well as the high yield[37-39].

12. Direct capsule filling

The technique includes direct filling of hard gelatin capsules with the liquid melt of drug and carrier. This molten dispersion forms a solid plug inside the capsule upon cooling to room temperature. Advantages include avoidance of grinding-induced changes in the crystallinity of drug, reduction of cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity.

Characterization of solid dispersion systems

There are several techniques used for characterization of solid dispersion systems including[40]:

i. Microscopic methods: Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM).
ii. Thermal methods: Differential Scanning Calorimetry (DSC) and Dissolution Calorimetry (DC).
iii. Powder X-ray diffractometry (P-XRD).
iv. Infrared Spectroscopy (IR).
v. Powder flowability: angle of repose, compressibility.
vi. Solubility studies.
vii. *In-vitro* dissolution rate studies.
viii. *In-vivo* studies: bioavailability, pharmacokinetics.
ix. Stability Studies (effect of humidity, recrystallization of amorphous drug).

CONCLUSIONS

Solid dispersion technology has been considered one of the well-established techniques in formulation of poorly-soluble drugs. Like every technique, it has several advantages and disadvantages that were discussed briefly in this article. There are several materials that can be used as carriers in formulation of solid dispersion ranging from natural sugars to synthetic polymers. There are several methods used in preparation of solid dispersions which vary from simple hand-made methods to advanced techniques requiring special equipment. Eventually, it can be concluded that solid dispersion technology still can be used and further developed to suit the needs of modern pharmaceutical industry.

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AUTHOR'S CONTRIBUTION

Younis MA: Writing original draft, review, methodology, data curation, literature survey, editing.

DATA AVAILABILITY

The data and material are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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