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Review article

Current trends and future perspectives of solid dispersions containing poorly water-soluble drugs

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ABSTRACT

Over 40% of active pharmaceutical ingredients (API) under development pipelines are poorly water-soluble drugs which limit formulation approaches, clinical application and marketability because of their low dissolution and bioavailability. Solid dispersion has been considered one of the major advancements in overcoming these issues with several successfully marketed products. A number of key references that describe state-of-the-art technologies have been collected in this review, which addresses various pharmaceutical strategies and future visions for the solubilization of poorly water-soluble drugs according to the four generations of solid dispersions. This article reviews critical aspects and recent advances in formulation, preparation and characterization of solid dispersions as well as in-depth pharmaceutical solutions to overcome some problems and issues that limit the development and marketability of solid dispersion products.

1. Introduction

The poor aqueous solubility and dissolution rate of API is one of the biggest challenges in pharmaceutical development and is becoming more common among new drug candidates over the past two decades due to the use of high throughput and combinatorial screening tools during the drug discovery and selection phase [1–3]. According to the Biopharmaceutics Classification System (BCS), a drug compound is poorly soluble if the highest dose strength is not soluble in 250 ml aqueous media over the pH ranges at 37 °C [4]. These compounds mostly belong to Class II (IIa or IIb), which are poorly soluble and highly permeable according to the pH of the gastrointestinal fluid and tend to present dissolution-limited absorption [5]. Despite their high permeability, these drugs often have low oral bioavailability because of their slow and limited release of drug in gastrointestinal fluid [6]. Therefore, one of the major challenges of the pharmaceutical industry is to apply strategies that improve the dissolution and/or apparent solubility of poorly soluble drugs to develop such problematic compounds into orally bioavailable and therapeutic effective drugs [3,5].

Various approaches to overcome the poor aqueous solubility of drug candidates have been investigated in drug research and development such as salt formation [7], prodrug formation [8], particle size reduction [9], complexation [10], micelles [11], microemulsions [12], nanoemulsions [13], nanosuspensions [14], solid–lipid nanoparticle [15] and solid dispersion which is considered one of the most successful strategies to improve the dissolution profile of poorly soluble drugs. The term solid dispersions has been defined as a dispersion of one or more API in an inert carrier or matrix at the solid state prepared by solvent, melting or solvent–melting method [16]. The API in solid dispersions can be dispersed in separate molecules, amorphous particles, or crystalline particles while the carrier can be in crystalline or amorphous state. Numerous studies on solid dispersions have been published and have showed many advantageous properties of solid dispersions in improving the solubility and dissolution rate of poorly water-soluble drugs. These advantages include reducing particle size, possibly to molecular level, enhancing wettability and porosity, as well as changing drug crystalline state, preferably into amorphous state [6].

Despite such high active research interests, the number of marketed products arising from solid dispersion approaches is disappointingly low. This low number is mainly due to scale-up problems and physicochemical instability in the manufacturing process or during storage leading to phase separation and crystallization [17–20]. Only a few commercial products have been marketed during the past half-century (Table 1). Therefore, in-depth knowledge that has been acquired on various aspects of solid dispersions such as carrier properties, preparation methods, physicochemical characterization techniques as well as the

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Table 1
Marketed products using solid dispersions [5,72,118].

Product	Model drug	Carrier type	Dosage form
Certican®	Everolimus	HPMC	Tablet
Cesamet®	Nabilone	PVP	Tablet
Gris-PEG®	Griseofulvin	PEG	Tablet
Isoptin® SR-E	Verapamil	HPC/HPMC	Tablet
Nivadil®	Nivaldipine	HPMC	Tablet
Rezulin®	Troglitazone	HPMC	Tablet
Kaletra®	Lopinavir, Ritonavir	PVPVA	Tablet
Intelence®	Etravirine	HPMC	Tablet
Zelboraf®	Vemurafenib	HPMCAS	Tablet
Incivek®	Telaprevir	HPMCAS-M	Tablet
Crestor®	Rosuvastatin	HPMC	Tablet
Afeditab® CR	Nifedipin	Poloxamer/PVP	Tablet
Fenoglide®	Fenofibrate	PEG	Tablet
Prograf®	Tacrolimus	HPMC	Capsule
Sporanox®	Itraconazole	HPMC	Capsule

pharmaceutical mechanism of matrix formation and drug release are very important to ensure the preparation of a productive and marketable solid dispersion. The aim of this review is to provide new knowledge from recent advances on solid dispersion areas to overcome some problems and issues that limit the marketability of solid dispersion products. As a continued work of previous reviews in this field, this article newly suggests the four classifications of solid dispersions according to the development by generation-to-generation that has been investigated so far. Finally, the future perspectives and strategies of solid dispersions are also discussed.

2. The classification of solid dispersions

Depending on the physical state of the carrier which is crystalline or amorphous, the solid dispersions are divided into crystalline solid dispersions and amorphous solid dispersions respectively. The solid dispersions can also be classified into four generations based on their composition (Fig. 1).

2.1. First generation

The first generation solid dispersions are crystalline solid dispersions. Sekiguchi and Obi [21] prepared the first solid dispersions for pharmaceutical application in which urea was used as a carrier to form eutectic mixture with sulphathiazole. In crystalline solid dispersions, a crystalline drug is dispersed within a crystalline carrier forming a eutectic or monotectic mixture [16,21]. In the eutectic mixture, the melting point of the mixture is lower than the melting point of the drug and carrier whereas in the monotectic mixture, the melting point of the carrier and drug are constant. The eutectic mixture is always more preferable because both the drug and carrier will crystallize simultaneously in cooling process, resulting in a well-dispersed state of the drug in carrier, thus enhancing the dissolution rate. Moreover, the process temperature for melting eutectic mixture is lower than that of monotectic mixture. However, if the mixture of the drug and carrier is not exactly at the eutectic composition, the solid dispersion will contain a mixture of the microfine dispersion and another component as a separate phase because one component will progressively crystalline until the eutectic composition is reached. In fact the number of studied solid dispersions having the exact eutectic composition is very limited [22]. The API in crystalline solid dispersions may also exist in amorphous particles or separate molecules (crystalline solid solutions). In crystalline solid solutions, the drug molecules can replace carrier molecule in the crystal lattice (substitutional crystalline solid solutions) or occupy the interstitial spaces between the solvent molecules in the crystal lattice (interstitial crystalline solid solutions) [23].

Crystalline carriers in the first generation solid dispersions comprise of urea [21] and sugars such as sorbitol and mannitol [24]. These carriers, especially sugars, have high melting point which is not favorable for preparing solid dispersions by melting method. Urea exhibits high solubility in water and many common organic solvents while sugars have poor solubility in most of organic solvents; therefore, sugars were less commonly used than other carriers. The particle size reduction, wettability improvement and polymorphic change are the main reasons for enhancing drug solubility and dissolution rate. Zajc et al. [25] prepared the solid dispersions of nifedipine and mannitol with different ratios by melting method. The results showed markedly enhanced dissolution rate of nifedipine in comparison with physical mixture although the crystalline state of nifedipine did not change. The SEM results elucidated the mechanism of dissolution rate enhancement which is improving the wettability of nifedipine crystals. Okonogi et al. [26] also tried to improve the dissolution rate of ofloxacin by solid dispersion systems with urea and mannitol. The dissolution rate of ofloxacin was significantly increased in urea

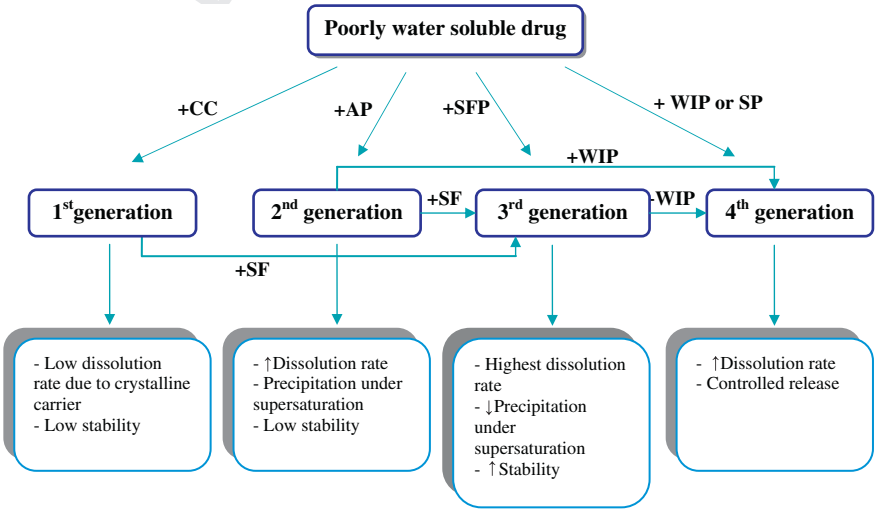

Fig. 1. Composition and properties of four generations of solid dispersions. CC: crystalline carrier, AP: amorphous polymer, SFP: surfactant polymer, WIP: water insoluble polymer, SP: swellable polymer, SF: surfactant, (↑): increase, (↓): decrease.

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