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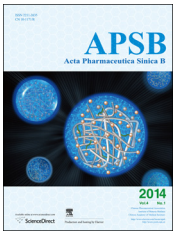

REVIEW

# Fundamental aspects of solid dispersion technology for poorly soluble drugs

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**Abstract** The solid dispersion has become an established solubilization technology for poorly water soluble drugs. Since a solid dispersion is basically a drug–polymer two-component system, the drug–polymer interaction is the determining factor in its design and performance. In this review, we summarize our current understanding of solid dispersions both in the solid state and in dissolution, emphasizing the fundamental aspects of this important technology.



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## 1. Introduction

It is estimated that most compounds undergoing development at the present time are subjected to dissolution problems[1]. To meet this pharmaceutical challenge, various solubilization technologies have been developed including solid dispersions, nanocrystals, cyclodextrin complexes and lipid formulations. With accelerated increase in the number of FDA-approved products in recent years (Table 1), solid dispersion is now firmly established as a platform technology for the formulation of poorly-soluble drugs. Specifically, solid dispersion technology has been successfully applied to develop formulations with a high drug loading (*e.g.* 375 mg per tablet in Incivek) and/or containing drugs with a high tendency to crystallize (as indicated by the high melting point of 291 °C of ivacaftor in Kalydeco) (Table 1).

At least three methods of preparing solid dispersions have been successfully used in commercial production[2] (Table 1). These are melt extrusion, applicable to drugs with not-very-high melting points[3], spray drying, useful for drugs soluble in at least one volatile solvent[4], and co-precipitation, useful for drugs with high melting point and low solubility in common organic solvents[5]. The encouraging progresses should more-or-less ease previous concerns on solid dispersion regarding its drug loading, manufacturing, and stability issues[6].

Historically, the term "solid dispersion" was defined as a dispersion of drug in a solid matrix where the matrix was either a small molecule or polymer. The dispersed state has included many forms such as eutectic mixtures, crystalline/glass solutions, and amorphous/crystalline suspensions[7,8]. Taking account of its currently most-used form (Table 1), a solid dispersion can now be more narrowly defined as dispersion of drug in an amorphous polymer matrix where the drug is preferably in the molecularly dispersed state (*i.e.* as a glass solution to use the old term, Fig. 1A). The following discussion is limited to systems that fit this more limited definition.

Although other additives (particularly surfactants) are often included and products may be made using polymer mixtures, solid dispersions are mainly drug–polymer two-component systems. As discussed below, the drug–polymer interaction is fundamental to understanding the most important issues that arise in the design of a solid dispersion *viz.* the drug loading, stability of the system and its dissolution performance. The objective of this short review is to summarize our current understanding of solid dispersions in terms of this important factor. Other aspects related to solid dispersions can be found in a number of excellent reviews already in the literature[6,9–13].

## 2. Drug–polymer interactions in the solid state

### 2.1. Phase diagram and phase separation

A solid dispersion is a deceptively simple two component system where the drug and the polymer act as solute and solvent, respectively. Despite this apparent simplicity, these two-component systems can form multiple structures depending on their composition and sample processing history[14] (Fig. 1). When the drug loading is lower than the equilibrium solubility of drug in polymer, the drug is molecularly dispersed within the polymer matrix (Fig. 1A) and should form a thermodynamically stable, homogeneous solution. This is the most desirable structure of solid dispersion. However, for most drug–polymer pairs, this situation only appertains at very low drug loading and/or high temperature (see below). As temperature is decreased, the mixture becomes a supersaturated solution and the drug tends to precipitate out. This can result in a dispersion of crystalline drug particles in a polymer matrix, in which the drug concentration corresponds to its equilibrium solubility at that temperature (Fig. 1B). Alternatively, as drug crystallization is a slow process with a higher energy barrier compared to amorphous phase separation, an intermediate meta-stable structure may form in which amorphous drug aggregates are dispersed in a polymer matrix containing drug at its amorphous solubility at that temperature (Fig. 1C).

As with all multi-component systems, a phase diagram is very useful to understand its structure under different conditions and to design a processing protocol to obtain a desired structure. By analogy with many small molecule–polymer systems described in the literature[15,16], a simplified drug–polymer phase diagram is shown in Fig. 2A. The curve of drug solubility in the polymer (solid curve) is particularly important not only to select the lower

**Table 1** Examples of FDA-approved medicines that use solid dispersion technologies.

| Product name | API | Polymer[a] | Maximum API dose per tablet or capsule (mg)[b] | API $T_m$ (°C)[c] | Solid dispersion preparation method[e] | Year of approval[b] |
|---|---|---|---|---|---|---|
| Cesamet | Nabilone | PVP | 1 | 160 | — | 1985 |
| Sporanox | Itraconazole | HPMC | 100 | 166 | Spray drying on sugar beads | 1992 |
| Prograf | Tacrolimos | HPMC | 5 | 128 | Spray drying | 1994 |
| Kaletra | Lopinavir/ritonavir | PVP/VA | 200/50 | 125/122 | Melt extrusion | 2005 |
| Intelence | Etravirine | HPMC | 200 | 265[d] | Spray drying | 2008 |
| Zotress | Everolimus | HPMC | 0.75 | 115 | Spray drying | 2010 |
| Novir | Ritonavir | PVP/VA | 100 | 122 | Melt extrusion | 2010 |
| Onmel | Itraconazole | HPMC | 200 | 166 | Melt extrusion | 2010 |
| Incivek | Telaprevir | HPMCAS | 375 | 246 | Spray drying | 2011 |
| Zelboraf | Vemurafenib | HPMCAS | 240 | 272 | Co-precipitation | 2011 |
| Kalydeco | Ivacaftor | HPMCAS | 150 | 291 | Spray drying | 2012 |

[a]Best guess based on the inactive ingredient list, patents and other literature information.
[b]Information based on the drug product labels from the FDA website.
[c]From Merck index or otherwise specified.
[d]Decomposition temperature.
[e]From Brough and Williams[2].