

Amorphous Solid Dispersions

Amorphous solid dispersions combine the increased solubility of an amorphous material and the improved physical stability of more stable solid forms. Amorphous solid dispersions can be used in early animal studies and in marketed products.

Amorphous materials can include amorphous drug substance [1], amorphous solid dispersions [2], and co-amorphous [3]. Amorphous drug substances exhibit high apparent solubility but potentially low physical and chemical stability. In order to improve the solid-state physical/chemical stability and maintain the high apparent solubility in solution, amorphous solid dispersions have been produced with polymers. The goal of the polymer is to form a miscible solid [4] (one phase containing the amorphous API and polymer in contrast to a physical mixture of an amorphous API and polymer) which decreases or prevents crystallization in the solid state and in solution. Surfactants may also be added to form ternary or quaternary systems. The term amorphous solid dispersion has also been used for other solubilization mechanisms, such as complexation (cyclodextrins) [5] and micelle formation (phospholipids) [6]. While these systems are called dispersions, it is important to note the different mechanism so appropriate studies can be performed to obtain a better understanding of the overall system. For all

the system [7] and note that water and solvent content will affect the glass transition (T_g) and stability, therefore initial solvent content and hygroscopicity will be important when developing these materials [1,2].

Amorphous solid dispersions have been shown to alter the properties of an API, including solubility, dissolution, and bioavailability [8]. A variety of polymers or additives are available and a screen is needed to find possible miscible dispersions that will have the properties needed for development. It is helpful to start with common polymers or pharmaceutical excipients used for drug products, since their toxicity is known. Once a number of amorphous solid dispersions are found, additional properties can be examined and these data will be used for form selection. When the ideal candidate has been found, it will be scaled-up using spray-drying, melt extrusion, or other methods. The amorphous solid dispersion will then be used in simple formulations for early development (such as suspensions, drug in capsule, or preliminary formulations) or formulated into a drug product (such as tablets or capsules) for later development and marketed products [9]. Additional work on maintaining the amorphous nature of the dispersion and determining the chemical stability under a variety of conditions will be needed.

A number of marketed products contain amorphous solid dispersions as listed in Table 1. Various methods have been used to produce the dispersions (spray drying, melt extrusion, fluid bed granulation). The dispersions have been used in drug products such as tablets and capsules.

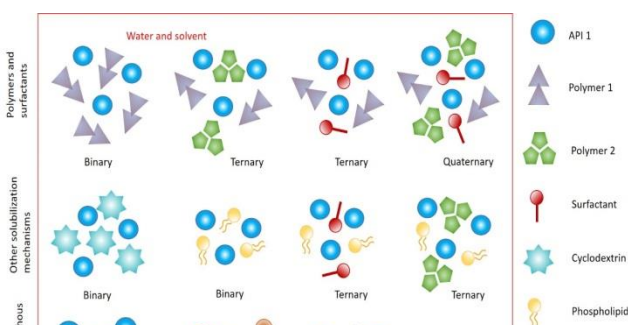


Figure 1. Schematic of amorphous systems using various components to improve solubility and stability.

amorphous systems, it is important to fully characterize



Table 1. Marketed products containing amorphous solid dispersions [9]

Product	API	Carrier	Processing technology	Company
Norvir®	Ritonavir	PVP-VA	Melt Extrusion	Abbott
Kaletra®	Ritonavir/Lopinavir	PVP-VA	Melt Extrusion	Abbott
Isoptin SR-E 240®	Verapamil	HPC/HPMC	Melt Extrusion	Abbott
Onmel®	Itraconazole	PVP-VA	Melt Extrusion	GSK/Stiefel
Gris-PEG®	Griseofulvin	PEG	Melt Blending	Pedinol Pharm
Cesamet®	Nabilone	PVP	Wet granulation	Lilly
Prograf®	Tacrolimus	HPMC	Solvent Process	Fujisawa
Certican®	Everolimus	HPMC	Solvent Process	Novartis
Sporanox®	Itraconazole	HPMC	Bead Coating	Janssen
Zelboraf®	Vemurafenib	HPMCAS	Coprecipitation	Roche
Intelence®	Etravirine	HPMC	SD	Janssen
Incevik/Incivo®	Telaprevir	HPMCAS	SD	Vertex/Janssen

API: Active pharmaceutical ingredient; HPMC: Hydroxypropyl methylcellulose; HPMCAS: Hydroxypropyl methylcellulose acetate succinate; PVP: Poly(vinyl pyrrolidone); PVP-VA: Poly(vinyl pyrrolidone)-co-(vinyl acetate); SD: Spray drying.

Summary

- Amorphous solid dispersions are a miscible mixture of API and a polymer. Ternary systems with surfactants or other components (such as small molecules, cyclodextrins, phospholipids) have also been reported.
- Amorphous solid dispersions provide improved solubility and physical/chemical stability.
- They can be used in simple formulations for early animal studies or in marketed products.

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The formulators toolbox: designing and developing disordered systems, Jayne Hastedt.
The Use of Amorphous Solid Dispersions to Enhance Dissolution, and Oral Bioavailability of Poorly Water-Soluble Pharmaceutical Compounds, George Zografi.