Solid dispersions

A pharmaceutical solid dispersion is defined as a mixture of an API with one or more hydrophilic carrier excipients in the solid state, in which the API is evenly distributed throughout the carrier and the release rate is governed by the carrier solubility in addition to other physical properties.[30] The excipients are selected according to their physical properties, including wettability, solubility, dissolution rate, melting point, compatibility with the API and the method of preparation. Excipients typically selected are more water soluble than the API, improving the solubility by dissolving quicker than the API and therefore improving the rate at which it is released into solution. This allows for the preparation of either immediate or modified release dosage forms depending on the physical properties of the excipients selected.

Various methods are available to prepare solid dispersions with common techniques employing either melting or solvent evaporation of a suspension or solution of the API and excipients to produce a uniform solid mixture.

In the case of melting, the API is mixed with a molten carrier, such as a sugar or polymer, and cooled to produce the solid dispersion. Examples of melt techniques used to produce solid dispersions include hot melt extrusion,[31] melt agglomeration, and injection molding.[32] The resulting structure may have a lower lattice energy than the pure API, and so is easier to disrupt, thus enhancing the kinetic solubility of the API by increasing the dissolution rate. Further processing such as milling may then be used to produce granules or particles suitable for the preparation of dosage forms if required. Melt techniques may therefore be used as a tool to further decrease the particle size of the API and thus enhance its solubility. Examples of crystalline excipients that have been used for melt processes include urea, mannitol and other simple sugars. Polymer excipients which are utilized include polyethylene glycols (PEGs), povidone (PVP), polyvinyl alcohol (PVA) and polymethacrylates, polyvinyl caprolactams, polyvinyl acetates, and natural polymers including cellulose derivatives such as ethylcellulose (EC), hydroxypropyl cellulose (HPC) and hypromellose (HPMC). In order to further increase the solubility of the API, surfactants such as sodium lauryl sulfate, inulin, polysorbates, stearoyl polyoxylglycerides or poloxamers may also be incorporated into the formulation.[33] Modified release formulations may also be prepared by using polymers such as poly(lactic-co-glycolic acid) (PLGA).

In the case of solvent evaporation, a solution of the API and the excipients is produced with a volatile solvent which is then removed to produce the solid dispersion. This typically results in the production of an amorphous solid solution, again with a lower lattice energy than that of the pure API, thus increasing its solubility. Depending on the method, solvent evaporation may be advantageous over high temperature methods of producing solid dispersions if the API is thermally labile. Two commonly used techniques to prepare solid dispersions via solvent evaporation are spray drying and lyophilization.

During spray drying, the API and excipients are atomized and exposed to a heated drying gas to evaporate the solvent; this leaves behind solid particles consisting of an amorphous dispersion of the API and excipients. Various carrier excipients may be used for spray drying in combination with poorly soluble APIs, including cellulose derivatives such as HPMC, HPMC acetate succinate, sodium carboxymethylcellulose, and MCC; vinyl polymers such as PVP and PVA; lipids such as stearoyl polyoxylglycerides and glyceryl dibehenate; polytheylene oxides (and derivatives) such as polyethylene glycols and poloxamers; and carbohydrates such as mannitol, lactose, acacia gum and inulin.

During lyophilization, a solution or suspension of the API and excipients is frozen and then dried under vacuum. Drying consists of both primary drying (sublimation of frozen water) followed by secondary drying (the removal of nonfrozen 'bound' water).[34] The most common application of lyophilization is to provide a stable dispersion of an API and excipients suitable for reconstitution and intravenous or subcutaneous injection. However, other uses include the preparation of solid dispersions for incorporation into tablets and capsules, and the preparation of wafers for buccal delivery and orally disintegrating tablets (ODTs).[35] Excipients are used within a lyophilized formulation to improve the physical properties and stability of the formulation,[36] for instance as bulking agents,

Table IV: Excipients commonly used for freeze-drying.

Bulking agent	Buffering agent	Solubilizing agent	Tonicity agent	Antimicrobial preservatives	Collapse temperature modifier
Sugars:	Buffers:	Complexing agents:	Sodium chloride	Benzyl alcohol	Dextran
Mannitol	Citric acid	Edetic acid (EDTA)	Sucrose	Phenol	Hydroxyethyl starch
Lactose	Sodium citrate	Alfadex	Mannitol	*m*-Cresol	*Ficoll*
Sucrose	Potassium citrate	Hydroxypropyl	Dextrose	Methyl paraben	Gelatin
Trehalose	Tartaric acid	betadex		Ethyl paraben	
Sorbitol	Sodium phosphate				
Glucose	Tris base				
Raffinose	Tris HCl				
	Tris acetate				
	Zinc chloride				
	Sodium acetate				
	Potassium acetate				
	Arginine				
Amino acids:	pH Adjusters:	Surfactants:			
Arginine	Hydrochloric acid	Polysorbate 80			
Glycine	Sodium hydroxide				
Histidine	Meglumine				
Polymers:		Co-solvents:			
Dextran		Tert-butyl alcohol			
Polyethylene glycol		Iso-propyl alcohol			
		Dichloromethane			
		Ethanol			
		Acetone			
		Glycerol			