Solid Solutions and Dispersions

Introduction

Solid solutions and dispersions are used in most routes of drug administration including oral, mucosal (vaginal, rectal, buccal, ocular), subcutaneous, subdermal, and transdermal. Two significant challenges in drug delivery are (1) enhancing the bioavailability of poorly water-soluble APIs and (2) controlling the release of APIs from drug-eluting devices.

Methods of Preparation

Solid solutions and dispersions are generally made by the “melt method” or the “solution method”. The excipients are usually polymers, but small molecules such as urea, sucrose, dextrose and galactose have been used, as have waxes. In the solution method, API and excipients are co-dissolved in a solvent, which is then removed to form the dosage form. This method is used to form slabs of material which can be ground to powders, and is also the basis of spray drying and emulsification/solvent removal. Spray drying involves forcing an aerosol or organic solution of API and excipients through a nozzle to form an aerosol in an evaporation chamber. The solvent evaporates leaving solid API/excipient particles. The API in the particles can be crystalline, amorphous or can show characteristics of both. Emulsification/solvent-removal involves preparing a solution of API and excipients in a water immiscible solvent which is emulsified into an aqueous surfactant solution. The solvent is removed from the emulsion droplets to form particles. Water insoluble polymers are most commonly used in this process, such as PLA, PLGA, ethyl cellulose, or cellulose acetate pthalate.

In the melt method, API is added to molten excipients and the mixture is then cooled. This method is the basis of spray chilling (spray congealing), melt/emulsification/chill-hardening, hot-melt extrusion and injection molding. Spray chilling is analogous to spray drying, but the API/excipient mixture is molten rather than in solution, and the final particles are formed by solidification of the cooling aerosol droplets rather than by solvent evaporation. Waxy excipients such as Compritol®, Dynasan® and lecithin are especially useful in this method. Melt/emulsification/chill hardening is analogous to emulsification/solvent-removal, except the final particles are formed by cooling of the emulsified melt. Hot-melt extrusion is becoming widely practiced in the pharmaceutical industry. Thermoplastic polymers such as polyethylene glycol, polyvinylpyrrolidione, various lactic acid-glycolic acid copolymers, various acrylates, and poly(vinylcaprolactam-co-vinyl acetate-g-polyethylene glycol) are co-melted with the API in a hot-melt extruder and the extrudate is further processed into the final dosage form. Injection molding is used in the manufacture of some drug-eluting devices, and has also been used more recently to prepare solid oral dosage forms. The API is mixed with thermoplastic excipients, and injected molten into a mold where the final dosage form is made on cooling.

Solid Solution and Dispersion Types

The drug may be molecularly dissolved in the solid excipients matrix (solid solution), or dispersed as crystalline or amorphous particles (solid dispersion). If dissolved, the API could in principle be miscible with the excipients over the whole composition range, however in practice the API and excipients are miscible over a limited range, as illustrated by the phase diagram in Figure 1. The eutectic composition has the lowest melting point, called the eutectic temperature, and the eutectic point is at the intersection of eutectic composition and eutectic temperature in the phase diagram.

In crystalline solid solutions the API can occupy crystal lattice sites or the interstitial spaces. If the formulation is amorphous, such as when the API is dispersed in an amorphous polymer, the API is distributed at random between the excipient molecules, and can be present as crystalline or amorphous particles, or in molecular solution.

Drug Release Mechanisms and Bioavailability

The mechanisms of API release from solid solutions and dispersions include: (1) dissolution of the entire dosage form if the excipients are soluble, (2) dissolution of API from within channels in insoluble excipients leaving the excipients more-or-less intact, and (3) molecular diffusion of the API through the bulk of the dosage form, also leaving the dosage form physically intact.

The bioavailability of an API depends on how it is incorporated into the product, the type of solid dosage form (solution or dispersion), and the mechanism of release. For example, since absorption of API requires the API to be in solution in the body, the oral bioavailability of a poorly water soluble API can be improved by increasing its rate of dissolution according to the Noyes-Whitney equation:

\[ \frac{dW}{dt} = DA(C_s - C) \]

Since dissolution rate is proportional to API surface area (A), the larger the total surface area of a given dose of API, a solid solution made from poorly water soluble API and water soluble excipients that dissolves to form colloidal particles of API will therefore have a higher rate of dissolution, and in principal bioavailability, than a formulation that dissolves to form larger particles of API.

Bioavailability is also related to API solubility, and smaller particles not only dissolve faster than larger particles, they are also more soluble than their larger counterparts, as shown by the Ostwald-Freundlich equation:

\[ \frac{RT \rho \ln S_1}{M} = 2\sigma \left( \frac{1}{r_1} - \frac{1}{r_2} \right) \]

©2012 Particle Sciences, Inc. All rights reserved.
Water soluble polymers and surfactants used to form the solid solution or dispersion increase the water solubility of the API, improving its bioavailability further.

For drug-eluting polymeric implants, whether the drug is in solid solution or solid dispersion affects release kinetics. For an intravaginal ring (IVR) device containing 5% API, with an API solubility of 1% in the matrix polymer (a solid dispersion), the in vitro release curve under sink conditions predicted using the equations of Helbling\(^6\) is shown in Figure 2(a). For a device of the same size, with the same 5% loading but made as a solid solution from excipients in which the API solubility is 10% (assuming the same API diffusion coefficient in the device), the drug release predicted using the model of Siepman and Siepmann\(^7\) is shown in Figure 2(b). Although both devices have a similarly shaped kinetic curve, drug release from the solution device is higher, especially on day 1, all other things being equal.

**Characterization**

The most commonly used tools for characterizing solid dispersions are visual, hot stage optical microscopy (OM), differential scanning calorimetry (DSC), and by x-ray diffraction (XRD). The aim of characterization is to determine if the API is in solution or dispersion and if in dispersion, then determine whether the API is in crystalline or amorphous form, whether in one or more polymorphic forms, and the API domain size as this can affect dissolution or release kinetics and hence bioavailability, and also affect long term product stability.

If the solid is transparent then the API is usually in solution; however, supersaturated forms produced by rapid cooling of viscous precursors that limit the API molecular diffusion and hence crystallization, can also appear transparent even though the API is above the solubility concentration. Opaque solids are usually API dispersions, and are always so when the solid excipients are otherwise transparent. DSC is used to determine the melting point of the API in the solid, and the melting point of the excipient matrix. It can also be used to determine the solubility of API in the excipients, as the magnitude of the area under the API melting peak is proportional to the amount of API in crystalline form in the formulation. Extrapolation of the area to loading curve to zero area can yield the solubility of API in the formulation. Care must be taken in interpreting the results of this measurement however, since the measurement is made at the melting temperature of the API where the solubilizing power of the excipients may be substantial. If the excipients melt and dissolve the API at a temperature below the API melting temperature, no API melt peak will be detected even for high API loadings. This was observed for dapivirine dispersed in ethylene vinyl acetate copolymer up to 40% API, which is well above the equilibrium API solubility of ~0.25% determined from diffusion experiments\(^7\). For crystalline excipient matrices and amorphous matrices that melt above the API melting point, this method should be suitable to determine API solubility and will also indicate the presence of polymorphs that have different melting points.

X-ray diffraction yields characteristic peaks for any crystalline components of the formulation. Thus it can be determined if the API is crystalline or amorphous in the formulation, and can clearly indicate any crystalline polymorphs present. The peak width can also be used to determine the crystal size of the API in the formulation using the Scherrer equation\(^8\):

\[
B(2\theta) = \frac{K\lambda}{L \cos \theta}
\]

**Stability**

True solid solutions are thermodynamically stable. Other solid solutions and dispersions can suffer from various instabilities. For example, API initially dissolved in supersaturated solid solutions can precipitate over time. There is no thermodynamic driving force for resolubilization of API that diffuses to the surface of a supersaturated solid solution and crystallizes there. As discussed previously, small particles are more soluble than large particles, so the size distribution of API particles in solid dispersions can evolve over time as large particles grow at the expense of the smaller ones (Ostwald ripening).

APIS dispersed in amorphous particles are also thermodynamically unstable, and can crystallize over time.

**References**

2. Soluplus™, BASF Corp.
7. Particle Sciences internal communication.

---

**Figure 2**

**API RELEASE FROM DEVICE CONTAINING 5% API**

(A) SOLID DISPERSION (B) SOLID SOLUTION

---

Particle Sciences is a leading integrated provider of formulation and analytic services and both standard and nanotechnology approaches to drug development and delivery.
For over 15 years Particle Sciences has been developing innovative drug delivery solutions for our clients. We are a full service CRO providing complete formulation, GMP/GLP analytic, bioanalytic and clinical trial material manufacturing. We specialize in nanoparticulate, semisolids and combination products.

**Unique Capabilities**

Fine-particle and nanoscale systems have been a focus of Particle Sciences since its inception in 1991. We work with all dosage forms and offer unique expertise in topical and mucosal therapeutics.

**Technology**

Our staff has extensive experience in drug delivery formats including micro- and nano-particulates, emulsions, suspensions, encapsulated API’s and polymeric controlled release dosage forms. Particle Sciences has all the necessary instrumentation and in-house expertise to produce and characterize these systems. Additionally we have a dedicated combination-product team with full compounding and injection molding capabilities.

**Exceptional Staff**

Our talented staff come from a variety of backgrounds and includes physicians, engineers, and doctorate-level surface, analytic, material science and polymer scientists. Combined, the senior management team at Particle Sciences has well over 150 years experience in innovative drug development.

**Facilities**

Particle Sciences is equipped with state-of-the art formulation equipment, analytic and bioanalytic instrumentation. Housed in 15,000 sqft, Particle Sciences provides complete services from API characterization through to clinical trial material manufacture of both sterile and non-sterile drug products.

**Integrated Process**

By structuring a program of pre-formulation, formulation, analytic, bioanalytic and manufacturing services, Particle Sciences provides clients with a powerful, integrated solution to most efficiently take a drug from discovery to the clinic. Each project has a dedicated team and leader to manage the project from start to finish.

**Problem-solving**

With years of experience to draw from, Particle Sciences can confidently handle difficult APIs, complicated intellectual property terrains and challenging delivery goals to arrive at the simplest, most efficient solution to our client's needs.

**Efficient**

Clients with demanding performance requirements and timelines will benefit from the speed, efficiency and quality that Particle Sciences delivers.

**Collaborative**

Particle Sciences maintains an "open door policy" with its clients and provides ready access to lab facilities and staff. Clients can consider Particle Sciences an expert extension of their in-house development team.

**Client-focused**

Each project receives individualized attention. Particle Sciences prefers to take a consultative approach to ensure positive project outcomes and the highest levels of client satisfaction. Projects are overseen and coordinated by a dedicated project manager in conjunction with a cross-functional team.