Encapsulation

Introduction

Active pharmaceutical ingredients (APIs) are often administered as aqueous solutions or suspensions, and pharmacokinetics are primarily determined by drug concentration or particle size, respectively. Sometimes additional functionality is required of a formulation, such as taste-masking, physicochemical protection of fragile APIs, and extended API release. API-loaded micro and nanoparticles may achieve these goals. Excipients used to prepare such particles include polymers (usually polyesters such as poly (L-lactic-co-glycolic acid, polycaprolactone, etc.), lipids (phospholipids, triglycerides and natural waxes) or insoluble metal salts and oxides (such as silica, calcium phosphate and calcium carbonate). This technical brief will focus on ways to prepare and characterize drug-loaded microcapsules in the micron to millimeter size range with two types of morphology; matrix-type in which the API is distributed homogeneously throughout the microcapsule, and core-shell in which the particle has a layered structure with API contained in the core (see Figure 1). Various processes, and the properties of the capsules they yield, are in Table 1.

Matrix Microcapsules

Solvent Cast/Grind

A simple way to prepare API-loaded matrix microcapsules is to dissolve the API and the particle-forming excipient in a solvent, remove the solvent to produce a slab of drug-loaded excipient, then grind the slab to produce a powder of drug-loaded particles. The volatile organic solvents must be removed from the final product to acceptably safe levels. In the case of lipidic excipients, casting the slab from a mixture of API and molten excipient avoids the use of solvents. If the API is soluble in the excipient, then homogeneous particles result from grinding the slab, otherwise inhomogeneous distribution can result. This may be minimized by first micronizing the API to a size much smaller than the final desired microcapsule.

Spray Processes

An alternative method to make particles from a solution of API and excipient is spray drying; the API/excipient/solvent solution is atomized through a heated nozzle into a chamber where the solvent evaporates from the droplets to yield solid particles (see Figure 2). The solvent is recovered for disposal or recycling, and the particles are collected in a cyclone. Particles are usually approximately spherical, and in the size range of 1 – 50 μm. For matrix excipients that melt at relatively low temperatures (such as waxes and lipids), solvent-free spray-chilling can be used – here the API and excipients are co-melted, and sprayed in molten form through the nozzle and the particles harden on cooling. Spraying under laminar flow conditions from a vibrating nozzle yields particles with a very narrow size distribution.

Emulsion-based Processes

For water-insoluble APIs, the API/excipient/solvent solution can be emulsified into an aqueous surfactant solution using industry-standard emulsification equipment such as overhead paddle mixers, rotor-stator homogenizers and inline static mixers. Precise control of droplet size can be achieved with emulsification techniques such as tangential-flow membrane (TFM) emulsification2, microfluidics and vibrating nozzles. Emulsions are made by TFM by forcing the organic phase through the pores of a membrane separating it from a tangentially flowing aqueous emulsifier phase. Flow-rates and pore size, shape, angle, and surface-chemistry control the droplet size and distribution. Vibrating nozzles and microfluidic devices

<p>| ENCAPSULATION METHODS AND THE TYPICAL PROPERTIES OF CAPSULES PRODUCED |</p>
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can also form particles with a very narrow size distribution. In all emulsion-based processes, the organic solvent must be relatively insoluble in water, and preferably have a low boiling point for easy removal. Methylene chloride is often the solvent of choice, though ethyl acetate is also used since it can be readily removed by distillation due to its higher water solubility (~8%), and has lower toxicity than chlorinated solvents. If low melting-point particle-forming excipients are used, the molten excipient/API phase can be emulsified and the solid-lipid microcapsules form on cooling without the use of organic solvents.

In a related process, alginate-based microcapsules can be made without the use of any organic solvents. An aqueous solution of sodium alginate containing API is dripped into a solution of Ca+2 ions. The divalent metal ions cause the dissolved alginate polymer to gel and form particles. This process has even been used to encapsulate live cells and bacteria.

**Hot-Melt Extrusion (HME)**

API and thermoplastic excipients can be intimately mixed without solvent under high shear and elevated temperature using co-rotating intermeshing screws of a hot-melt extruder. The extruded ribbon can be micropelletized, ground, or spheronized to produce final API-loaded particles. API/microcrystalline cellulose microparticles are made this way for filling into gelatin capsules.

Since matrix particles contain API homogeneously distributed throughout the particle, material at the surface can be released too quickly, be degraded or impart an unpleasant taste, and release is not constant over time. Core-shell particles offer more control.

**Core-shell Microcapsules**

Core-shell microcapsules are useful when no active material is desired at the particles surface. This may be for taste-masking, chemical protection of the active or control over release kinetics. By coating API particles with an excipient that is insoluble in stomach, but soluble at the elevated pH of the lower intestine, the API can be released where desired. Enteric coating, excipients such as acrylic Eudragit™ polymers and cellulose acetate phthalate are used for this purpose. The shells can be deposited on solid or liquid cores.

**Spray Coating and Pan Coating**

The simplest core-shell microcapsule is a particle of an active substance coated with an excipient. The API particles can be coated by spraying a solution or suspension of the excipient into a fluidized bed of the core particles. Tablets can be encapsulated in enteric polymers by spraying them with enteric coating solution or dispersion in a V-blender, or by pan-coating where the tablets are agitated in a hot "pan" containing molten coating excipients.

**Polymer Phase-separating from Solution**

API particles can be coated by precipitating a dissolved polymer onto the surface of co-dispersed API particles by reduction of temperature, or addition of a polymer non-solvent. Polysobutylene has been used as a co-phase inducer and final particle stabilizer.

Microcapsules containing liquid cores are generally produced from oil-in-water emulsions. Processes to encapsulate droplets are now discussed.

**Coacervation**

Oil-in-water emulsion droplets are coated in polyelectrolytes (such as gelatin and gum-Arabic) by coacervation. At specific pH and concentrations, the polymers form a complex that coats the emulsion droplets that can be chemically hardened to form a shell.

**Interfacial Polymerization**

Monomers dissolved in the oil droplets can react with others dissolved in the aqueous phase to build a wall at the interface. Walls made of polyurethane, polyester and polyanime are most common. Droplets may also be encapsulated by polymerization of urea and formaldehyde dissolved in the aqueous phase.

**Phase Separation in Emulsions**

Removal of a low-boiling organic solvent from emulsified droplets containing the solvent, shell forming polymer, active ingredient, and high-boiling non-solvent, can yields microcapsules when the low boiling solvent is removed if the emulsifier is chosen properly.

**Concentric Nozzles**

The same vibrating nozzle discussed earlier can be configured to yield monodisperse core-shell particles. The nozzle is concentrically aligned within a second nozzle, and core material is ejected from the inner nozzle while shell material is ejected from the outer nozzle (Figure 3). Drying the resulting liquid core-shell droplets yields core-shell microcapsules.

**References**