



Manufacture of Microspheres as Carrier Particles for Active Biomolecules

There are many types of methods and technologies available to manufacture microspheres. Simplistically, the processes fall into two broad categories: chemical or physical.

Chemical Methods

The chemical methods can be categorized as coascervation and polymerization. The latter method is the most widely adopted process to produce the types of polymer microspheres currently used, for example, as solid phase supports in immunological tests and assays. The manufacture of such microspheres involves a chemical reaction (polymerization).

A number of processes are available: condensation-, interfacial-, suspension- and emulsion-polymerization. Suspension and emulsion polymerization are the preferred methods for the commercial production of polymer microsphere carrier particles and reference/standard particles for calibration of scientific instruments. In general, emulsion polymerization produces a smaller particle size and a narrower molecular weight distribution. Both methods are aqueous two-phase batch processes. The use of a double emulsion, e.g. water-in-oil-in-water (W/O/W), is a variation of the emulsion polymerization method.

A major advantage is the ability to produce an almost monodisperse particle size, i.e. an exceptionally low polydispersity or very narrow particle size distribution (PSD). The final particle size can be controlled by changing the chemical composition of the reactants (monomer, initiator and surfactant), the reaction temperature and the degree of mechanical agitation used. Particle size can be controlled from about 10nm up to about 1000nm. It is possible to increase the particle size up to about 50 microns but the cost per gm of material increases considerably.

Depending on the polymer it is also possible to produce a dry powder (e.g. by means of evaporative spraying) but, again, this adds considerably to the cost.

Because polymerization is a chemical reaction process there are a number of disadvantages. The first is contamination from reaction by-products and excess unreacted material. Excess monomer is, at least, partially removed by steam stripping but residual monomer can pose a long-term problem. Excess initiator is removed by washing and excess solvent (when a liquid other than water is used to dissolve monomer) by vacuum extraction. This adds considerably to the cost.

A further disadvantage is that the process involves a fixed chemical reaction for a given polymer. It is not possible to alter the matrix (i.e. polymer) composition without changing the complete recipe/formula. In addition, the range of polymers that can be used in biological applications is limited because of toxicologic considerations. Sometimes a cross-linking agent is added during the polymerization to harden the polymer surface. These agents also must be screened for unwanted reactions in addition to their toxicological potential.

Although the process used to manufacture polymers for industrial uses (e.g. floor coverings, paints) can be scaled up it can be a major problem for those polymers used in biological applications because of the need to extensively purify the monomer and then clean the polymer and remove unwanted chemicals.

Because of the need to steam strip etc the solids concentration of the final aqueous suspension is usually no more than about 20%. Accordingly, emulsion polymerization is often limited to small-scale (laboratory) preparation for academic R&D studies. A typical retail cost of polymer microspheres used in assay testing is \$120/5g for a 2 w/w% dispersion.

There are several means of attaching biological ligands to these polymer microspheres:

- Adsorption to the plain polymeric surface (PS, PMMA, PAN)
- Covalent bonding to functionalized surface groups/moieties (COOH, SO₃H, NH₃, OH, EO)
- Attachment by use of a coupling agent, e.g. a generic protein such as streptavidin, or a silane)

Physical Methods

The physical process conventionally entails co-extrusion or spraying of a polymer solution. However, it often necessitates the use of plasticizers (i.e. special chemicals added to aid in processing). For biological applications such residual materials need to be removed - again by solvent washing or steam stripping - thus adding to the cost.

The main advantages are that the method is much simpler, considerably less expensive and is much more easily adapted (and less costly) to provide a dry powder. A major disadvantage, especially concerning microsphere carrier particles is that the polymer

particle size is very large - typically 10 microns to 100 microns and the PSD is very broad.

The Particle Sciences Approach

An alternative approach is a variation of the physical method. It is based on a melt-chill process. The process variables of temperature and shear (mechanical agitation) can be varied at will to produce a given size and PSD. The method typically produces a much smaller size, (in the range 50nm to 1000nm), compared to the usual physical methods. Like suspension and emulsion polymerization it is an aqueous two-phase process but it results in an aqueous suspension with a much larger solids content- approximately 50%. It is possible, depending on the matrix, to produce a dry powder but this adds to cost. The approach offers many advantages:

Many matrix materials are available from polymers to waxes and silicones. This allows for a much wider range of choice when considering the toxicological profile (choose NF or pharmaceutical grade materials). The system is both monomer and solvent free. No components other than those of the matrix material(s) are present). It is easy to vary either or both of the physical/chemical characteristics of the matrix (e.g. hardness, hydrophobic/hydrophilic balance and surface charge functionality (anionic, nonionic, cationic) since there is no chemical reaction involved.

It is a relatively very cheap method and is easily scaled to industrial production levels with little added cost. There is no need to use plasticizers. And, importantly, the process is environmentally sound and results also in biodegradable microspheres.



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