

3.1 Microcapsules and microspheres: definitions

Microencapsulation packages solid, liquid or even gaseous material inside a polymeric coating, producing microparticles roughly in the range of 1 to 1000 micrometres. Two structures result:

- **Microcapsules** are reservoir systems: a distinct core of drug is surrounded by a continuous wall or shell of polymer. The wall controls release, protects the core and masks taste and odour.
- **Microspheres** are matrix systems: the drug is dissolved or dispersed throughout a solid polymer matrix, often in a spherical particle, and release occurs by diffusion through the matrix and by its erosion.

The two are used for sustained and controlled release, for protecting labile drugs from moisture, oxygen and gastric fluid, for masking the taste of bitter drugs, for converting liquids into free flowing solids, and for targeted and site specific delivery, since microparticles of a chosen size can be lodged in a chosen capillary bed or taken up by a chosen tissue. Biodegradable microspheres based on PLGA are a standard long acting injectable platform; the first such product, Lupron Depot (leuprolide acetate microspheres, 1989), releases the peptide for a month after one intramuscular injection, and Risperdal Consta (risperidone microspheres) applies the same idea in psychiatry.

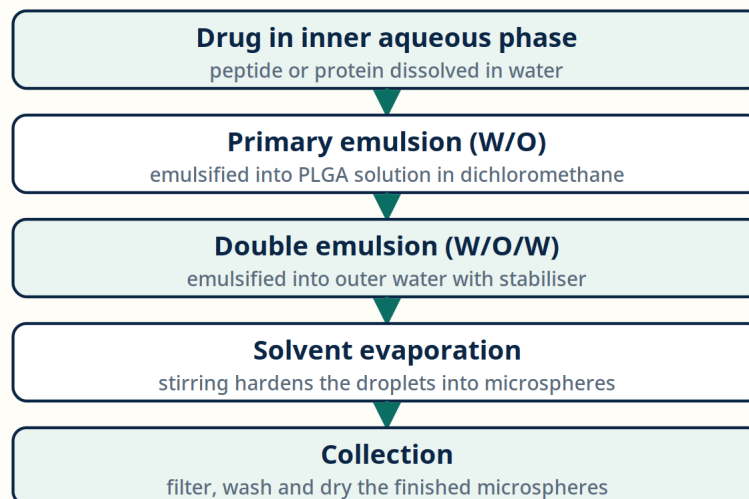
3.2 Types of microcapsules and microspheres

- **By structure:** mononuclear (single core) and polynuclear (many cores in one shell) capsules, matrix type microspheres, and coated or double walled systems.
- **By polymer origin:** natural polymers (gelatin, gum acacia, albumin, chitosan, sodium alginate, starch) and synthetic polymers (PLGA, PLA, polycaprolactone, polymethyl methacrylate, ethyl cellulose, cellulose acetate phthalate, Eudragit grades).
- **By degradability:** biodegradable systems (PLGA, PLA, albumin, gelatin, chitosan), which release drug as the matrix erodes and need no removal, and non biodegradable systems (ethyl cellulose, PMMA), used where the device stays outside the body or is excreted intact, such as oral products.
- **Magnetic microspheres**, containing magnetite, belong to physical targeting (Unit 2) and are localised by an external magnet in research and clinical studies.

The choice of polymer decides the release mechanism (diffusion, erosion, or both), the route the product can be given by, and the preparation method that can be used.

3.3 Preparation of microcapsules and microspheres

Microspheres by Double Emulsion Solvent Evaporation



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Figure: The water in oil in water double emulsion solvent evaporation method, the standard preparation for peptide loaded PLGA microspheres.

- **Phase separation (coacervation)**: the coating polymer is made to separate from solution as a polymer rich phase (coacervate) that deposits around the dispersed core. In simple coacervation a single polymer (for example gelatin) is desolvated by adding a competing substance or changing temperature; in complex coacervation two oppositely charged polymers (classically gelatin and gum acacia) are mixed and the pH is adjusted so that they separate together around the core. The soft coating is then hardened, for example with glutaraldehyde.
- **Interfacial polymerisation**: two reactive monomers, one in each of two immiscible phases, meet and polymerise at the interface around the droplets, forming a thin strong shell; used for both microcapsules and nanocapsules.
- **Emulsion and solvent evaporation**: the workhorse method for microspheres. The drug and polymer are dissolved or dispersed in a volatile organic solvent and emulsified into an aqueous phase (oil in water single emulsion for lipophilic drugs). For water soluble drugs and peptides a water in oil in water double emulsion is used, with the drug solution as the inner water phase. The solvent then evaporates under stirring, the droplets harden into microspheres, and the product is filtered, washed and dried.

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Double emulsion solvent evaporation (for peptides and proteins)
Drug dissolved in inner aqueous phase
|
v
Emulsify into polymer solution in dichloromethane (W/O)
|
v
Emulsify into outer water with stabiliser (W/O/W)
|
v
Stir: solvent evaporates, droplets harden
|
v
Filter, wash, dry: PLGA microspheres
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- **Emulsion crosslinking**: droplets of a natural polymer solution containing the drug (for example albumin or chitosan) are hardened by chemical crosslinking (glutaraldehyde) or by heat, giving matrix microspheres.

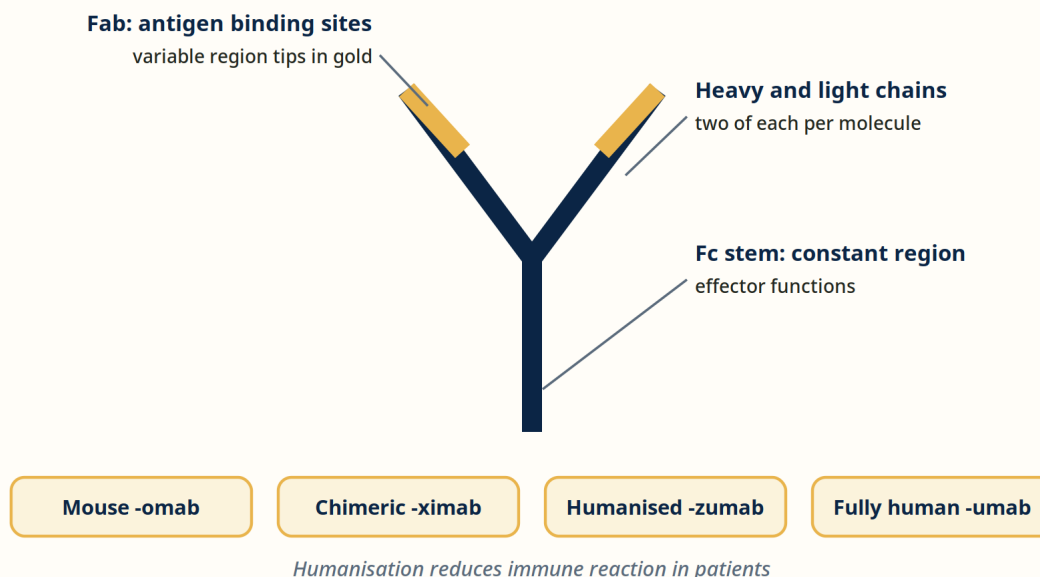
- **Ionotropic gelation:** sodium alginate solution containing the drug is dropped into calcium chloride solution; calcium ions gel the alginate instantly and form beads, a gentle solvent free method suited to labile drugs and cells.
- **Spray drying and spray congealing:** a drug polymer solution or suspension is atomised into hot air (spray drying) and the solvent flashes off to give microparticles in one step; in spray congealing the drug is dispersed in a molten wax or polymer that is atomised into cold air and solidifies.
- **Coating methods (pan coating and air suspension):** used for larger cores, where a coating is applied in a rotating pan or in a fluidised bed (Wurster) coater; these are coating rather than particle forming processes but are part of classical microencapsulation practice.

3.4 Evaluation of microcapsules and microspheres

- **Particle size and distribution:** sieving, microscopy, laser diffraction and Coulter counting; size decides injectability, deposition site and release rate.
- **Shape and surface morphology:** scanning electron microscopy shows sphericity, surface smoothness, pores and cracks, all of which affect release.
- **Drug content and encapsulation efficiency:** drug is extracted from a weighed sample and assayed; high efficiency matters most for expensive peptide drugs.
- **Yield and flow properties:** percentage yield of the process; angle of repose, bulk density and flow for products to be filled into capsules or sachets.
- **Swelling and density:** swelling behaviour of hydrophilic matrices in release medium; density for floating or sinking behaviour where relevant.
- **In vitro drug release:** release in a suitable apparatus or dialysis system over the full intended duration (weeks for PLGA depots), fitted to kinetic models; an initial burst release is looked for and controlled, because a burst of a potent drug can be toxic.
- **Stability and (for injectables) sterility, endotoxin and syringeability** through the intended needle.

3.5 Monoclonal antibodies: preparation and application

Structure of a Monoclonal Antibody



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Figure: Structure of a monoclonal antibody and the naming suffixes that show how human the molecule is.

A monoclonal antibody is a homogeneous population of identical antibodies, all produced by one clone of cells and all directed against one epitope of one antigen. Antibodies are Y shaped immunoglobulin molecules: two heavy and two light chains, with antigen binding sites in the variable regions at the tips of the arms (Fab) and effector functions in the stem (Fc).

Preparation. The classical method is the hybridoma technique of Kohler and Milstein (1975). An animal (usually a mouse) is immunised with the antigen; its spleen B lymphocytes, which make the wanted antibody but cannot be cultured indefinitely, are fused with immortal myeloma cells that do not make antibody. The fused hybridoma cells are selected in HAT medium (in which unfused cells die), screened for the wanted antibody, and cloned so that one clone producing one antibody is expanded. The clone is then cultured at scale, and the antibody is purified from the culture medium (protein A affinity chromatography is the standard capture step), characterised and formulated. Because mouse antibodies provoke a human anti mouse antibody response in patients, therapeutic antibodies are progressively humanised: chimeric antibodies carry mouse variable regions on human constant regions, humanised antibodies carry only the mouse antigen binding loops (CDRs) in a human framework, and fully human antibodies are produced by phage display or transgenic animals. The suffix of the generic name shows the origin: -omab (mouse), -ximab (chimeric), -zumab (humanised), -umab (fully human). Trastuzumab (HER2 positive breast cancer) and rituximab (CD20, B cell lymphomas) are standard examples.

Applications in drug delivery. Monoclonal antibodies are the most specific targeting ligands available:

- **Immunoliposomes and immunonanoparticles:** the antibody is attached to the carrier surface so that the whole carrier binds antigen bearing cells (active targeting, Unit 2).
- **Antibody drug conjugates (ADC):** the cytotoxic drug is chemically linked to the antibody, which carries it to the antigen positive cell, where the conjugate is internalised and the drug is released. Ado-trastuzumab emtansine (Kadcyla) and brentuximab vedotin (Adcetris) are approved examples.
- **Direct therapy:** the antibody itself is the drug (blocking a receptor, or marking a cell for immune destruction), which is therapy rather than delivery but uses the same products.

- **Diagnostics and targeting support:** labelled antibodies localise tumours for imaging and guide the choice of targeted therapy.

The limits are cost, the need for the target antigen to be accessible and fairly specific, possible immune reactions, and poor penetration of large antibody molecules into solid tissue.

3.6 Niosomes

Niosomes are vesicular carriers built like liposomes but from nonionic surfactants instead of phospholipids. Hydration of a film of a nonionic surfactant (commonly Span 20, 40 or 60, or Tween grades) with cholesterol and a small amount of a charge inducer such as dicetyl phosphate gives closed bilayer vesicles with an aqueous core. Cholesterol stiffens the bilayer and reduces leakage, as it does in liposomes. Preparation follows the liposome methods of Unit 2: thin film hydration is standard, with ether injection, sonication and other variants also used. Niosomes were developed to overcome the weaknesses of liposomes: the surfactants are cheaper and chemically more stable than phospholipids (no oxidative degradation of unsaturated chains), the vesicles are more stable on storage, and the surfactants themselves can improve skin penetration. They are used experimentally and in marketed cosmetic and some pharmaceutical preparations for antifungal, anti inflammatory, anticancer and vaccine delivery, and systemically they behave like other vesicles (RES uptake unless surface modified).

3.7 Aquasomes

Aquasomes are three layered nanoparticulate carriers, typically 60 to 300 nm. The three layers are: a solid ceramic core (calcium phosphate is the most used; diamond and tin oxide cores are also described), a coating of a polyhydroxy oligomer (a carbohydrate such as cellobiose, sucrose, trehalose or lactose) adsorbed on the core, and the drug, which is adsorbed on the coated core surface without covalent bonding. Preparation is equally stepwise: the core is prepared and cleaned, the carbohydrate is adsorbed onto it, and the drug solution is added and the drug adsorbs, followed by freeze drying. Because the drug sits on the surface held by weak forces rather than being encapsulated or chemically bound, it keeps its native conformation and activity, and the carbohydrate layer acts as a protective, water like environment; the design is meant to mimic the way molecules sit in the aqueous environment of the body. Aquasomes (developed by Kossovsky and co-workers) are applied to the delivery of proteins and peptides such as insulin, enzymes, antigens for vaccines, and haemoglobin as an oxygen carrier in experimental work.

3.8 Phytosomes

Many plant constituents with good pharmacological activity (flavonoids such as silymarin, curcumin, ginkgo flavonoids, catechins) are poorly absorbed because they are either too water soluble to cross lipid membranes or too poorly soluble to dissolve. A phytosome is a molecular complex of such a phytoconstituent with a phospholipid, usually phosphatidylcholine, in a defined ratio (commonly 1:1 or 1:2). Preparation is a reaction, not just a mixing: the constituent and phosphatidylcholine are reacted in an aprotic organic solvent (such as dioxane, acetone or ethanol in some processes), and the solvent is removed to give the complex, in which the polar head of the phospholipid forms hydrogen bonds with the polar groups of the constituent. The resulting complex is lipid compatible as a whole, so it crosses membranes and is absorbed far better than the free constituent, while the constituent keeps its activity. Characterisation uses spectroscopy (NMR, IR) to confirm complex formation, solubility and partition studies, and dissolution and pharmacokinetic comparison with the free extract. Marketed examples include silymarin phytosome (Siliphos) and Ginkgo biloba phytosome (Ginkgoselect), developed by Indena, for liver protection and vascular indications.

3.9 Electrosomes

Electrosomes are soft bilayer vesicular carriers in the phospholipid family, described in the prescribed texts as electrically responsive delivery systems: the vesicles are designed to carry drug across biological barriers, particularly the skin, when an electric field is applied, for example by iontophoresis or electroporation assisted delivery. The applied field promotes the movement of the charged vesicles and the transient permeabilisation of the barrier, so that molecules which otherwise cross poorly (including some large and hydrophilic molecules) can be delivered. They remain an experimental system, taught here as the PCI syllabus names them: a vesicular carrier related to liposomes whose application depends on electrical stimulation of the site of administration.

Carrier	Building material	Drug location	Key advantage
Liposome	Phospholipid bilayer	Aqueous core and bilayer	Versatility, clinical record
Niosome	Nonionic surfactant + cholesterol	Aqueous core and bilayer	Stability and low cost
Aquasome	Ceramic core + carbohydrate coat	Adsorbed on the surface	Native conformation of proteins preserved
Phytosome	Phytoconstituent phospholipid complex	Part of the complex itself	Much improved absorption of plant actives

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