Pharmaceutical technology

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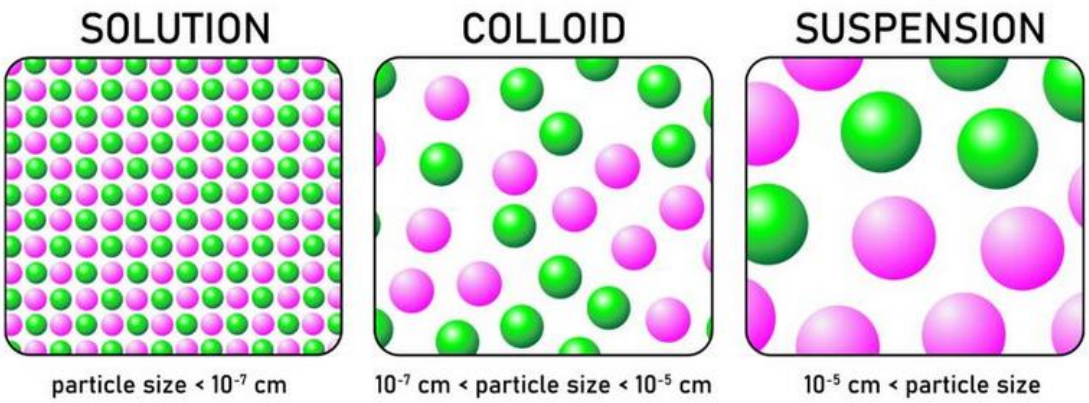
Dispersion systems

Pharmaceutical dispersions are systems where one substance is dispersed within another substance.



In pharmacy, dispersions are found in a wide **variety of dosage forms** and in nearly **all routes of drug administration**. Examples range from solutions of **very large molecules (macromolecules) such as albumin and polysaccharides, to liquid suspensions of "nano"-sized crystals (nanocrystals) and of "micro"-sized droplets (microemulsions), to coarse (larger particle) emulsions and suspensions**.

Terms used to describe dispersion components include **internal or noncontinuous phase** to describe the **dispersed phase** component (the particles) and the **external or continuous phase** to describe the **dispersion medium**.

Two main approaches to classification being:

(1) the nature of the dispersion's internal and external phases (e.g., solid, liquid, or gas) and

(2) the size range of its dispersed particles (colloidal versus coarse).

1. Dispersed systems classified by their phases

In addition to the macromolecular dispersions liquid-in-liquid emulsions, and solid-in-liquid suspensions, they include solid-in-solid suspensions (e.g., some suppositories), semisolid emulsions (e.g., creams), and gas-in-liquid foams.

Table 1: Types of colloidal dispersions

Dispersion Medium	Dispersed Phase	Colloid Type	Examples
Solid	Solid	Solid sol	Pearls, opals
Solid	Liquid	Solid emulsion	Cheese, butter
Solid	Gas	Solid foam	Pumice, marshmallow
Liquid	Solid	Sol, gel	Jelly, paint
Liquid	Liquid	Emulsion	Milk, mayonnaise
Liquid	Gas	Foam	Whipped cream, shaving cream
Gas	Solid	Solid aerosols	Smoke, dust
Gas	Liquid	Liquid aerosols	Clouds, mist, fog

* A gas in a gas always produces a solution.

2. Dispersed systems classified by their particle size

The two main categories in this context are **colloidal dispersions**, which roughly encompass the particle diameter range of **0.1 to 1000 nm (1 µm)**, and **coarse dispersions**, which have larger particles (e.g., **1 to200 µm**).

The reason that dispersions are often classified based on particle size is that dispersions of colloidal-sized particles can **exhibit somewhat different behavior than particles in coarse dispersions**. For example, coarse dispersions are more prone to **settling problems** because of their larger particle size and their relative lack of influence by **Brownian motion**.

Table 2: Classification of dispersed systems based on particle size

Class	Particle Size*	Characteristics of System	Examples
Molecular dispersion	Less than 1 nm	Invisible in electron microscope Pass through ultrafilter and semipermeable membrane Undergo rapid diffusion	Oxygen molecules, ordinary ions, glucose
Colloidal dispersion	From 1 nm to 0.5 μm	Not resolved by ordinary microscope (although may be detected under ultramicroscope) Visible in electron microscope Pass through filter paper Do not pass semipermeable membrane Diffuse very slowly	Colloidal silver sols, natural and synthetic polymers, cheese, butter, jelly, paint, milk, shaving cream, etc.
Coarse dispersion	Greater than 0.5 μm	Visible under microscope Do not pass through normal filter paper Do not dialyze through semipermeable membrane Do not diffuse	Grains of sand, most pharmaceutical emulsions and suspensions, red blood cells

* 1 nm (nanometer) = 10^{-9} m; 1 μm (micrometer) = 10^{-6} m.

Colloidal Dispersions

Colloidal dispersions are those in which very small particles approximately **1 and 1000 nm** in length are dispersed in a continuous phase of a different composition.

There are three general classifications based primarily on how and to what degree they interact with their medium:
(1) lyophilic and lyophobic and (2) association colloids.

1. Lyophilic and lyophobic colloids

Lyophilic colloids are those that have a strong affinity with their medium, whereas **lyophobic colloids** have little or no affinity with their medium. The prefix **lyo** refers to the **solvent or medium**. Since for most pharmaceutical dispersions the medium is **water**, the terms **hydrophilic** and **hydrophobic** are used.

Hydrophilic colloids:
It had polar regions (e.g., from hydroxyl groups or ionizable groups) that enable them to become hydrated in contact with aqueous environments. Common examples of these are certain **macromolecules, such as proteins (e.g., albumin and gelatin) and polysaccharides (e.g., natural gums and semisynthetic cellulose derivatives)**.

The **macromolecular dispersions** (**hydrophilic colloids**)are sometimes referred to as **colloid solutions** to distinguish them from **crystalloid solutions**, which are true solutions of smaller molecules such as **electrolytes**.

One of the most common usages of the term's **colloid and crystalloid solutions in medicine** is in the field of **plasma volume expansion**, where the choice to increase a patient's plasma volume (e.g., in circulatory shock) includes **intravenous crystalloid solutions** (e.g., sodium chloride or lactated Ringer's) and **intravenous colloid solutions** (e.g., albumin or hydroxyethyl starch).

Hydrophobic colloids:

It does not have sufficient surface hydrophilicity to enable them to interact well with water. Examples of hydrophobic colloidal dispersions include **milk, intravenous lipid emulsions, and nanocrystal suspensions**.

Intravenous lipid emulsions are used primarily to provide calories as part of an **intravenous nutrition strategy**. One of the problems of hydrophobic colloids is their tendency to aggregate in an aqueous environment. This is a significant concern for intravenous lipid emulsions, because it's important that the lipid particles do not aggregate to a size that can block small blood vessels.

Nanocrystals are becoming increasingly used as an approach to improve the solubility of poorly soluble drugs. For example, the nanocrystal suspension formulation of **megestrol acetate (a progesterone receptor agonist)** showed a dramatic improvement in absorption compared to its larger crystal predecessor, because its nanocrystals dissolved more readily.

2. Association colloids

Association colloids are those formed by the association of dissolved molecules of a substance to create particles of colloidal dimensions, most commonly termed **micelles**. They include the surfactant micelle, liposomes (bilayer spheres formed mainly from phospholipids), and microemulsions.

The surfactants of classic **surfactant micelles and the phospholipids of liposomes** are amphiphiles that spontaneously self-associate when their concentrations reach a certain level known as their **critical micelle concentrations**. They interact in such a way, so as to minimize contact between the lipophilic portion of the amphiphile and water, usually resulting in a spherical shape to the micelle. Surfactant micelles are typically 2 to 5 nm in diameter, whereas the commercially available liposomes (e.g., liposomal doxorubicin and daunorubicin) are about 50 to 100 nm.

Another type of association colloid is the **microemulsion**. Like conventional coarse emulsions, microemulsions are also dispersions of oil droplets in water (or water-in-oil). However, they differ from conventional emulsions in that the droplets are much smaller (e.g., 10 to 100 nm diameter), the dispersions are **transparent**, and they are considered **thermodynamically stable**. This achievement of these properties owes to the particular blends of oil, surfactant, and cosurfactant. The **cosurfactant**, often a four to seven carbon-chain alcohol, helps reduce surface tension and adds sufficient flexibility to the interfacial film to enable it to attain the high curvature needed to cover the tiny droplet. A commercial example of the use of a microemulsion to help solubilize a drug is the product **Neoral® (cyclosporine)**, an immunosuppressant.

Table 3: Classification and typical examples of surfactants

	Example		
Type	**Compound**	**Amphiphile**	**Gegenions**
Anionic	Sodium lauryl sulfate	$CH_3(CH_2)_{11}OSO_3^-$	Na^+
Cationic	Cetyl trimethyl-ammonium bromide	$CH_3(CH_2)_{15}N^+(CH_3)_3$	Br^-
Nonionic	Polyoxyethylene lauryl ether	$CH_3(CH_2)_{10}CH_2O(CH_2OCH_2)_{23}H$	–
Ampholytic	Dimethyldodecylammonio-propane sulfonate	$CH_3(CH_2)_{11}N^+(CH_3)_2(CH_2)_3OSO_2^-$	–

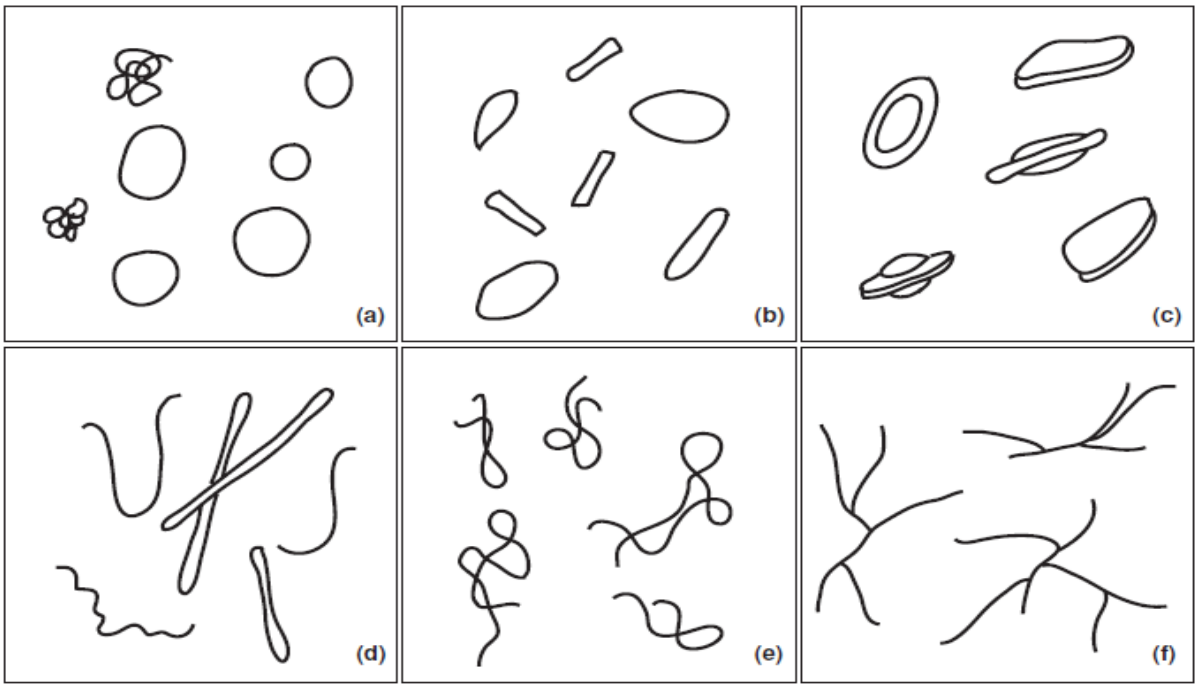


Figure 1: Some shapes that can be assumed by colloidal particles: (*a*) spheres and globules, (*b*) short rods and prolate ellipsoids, (*c*) oblate ellipsoids and flakes, (*d*) long rods and threads, (*e*) loosely coiled threads, and (*f*) branched threads.

Table 4: Comparison of properties of colloidal solution

Lyophilic	Association (Amphiphilic)	Lyophobic
Dispersed phase consists generally of large organic *molecules* lying within colloidal size range	Dispersed phase consists of aggregates (*micelles*) of small organic molecules or ions whose size *individually* is below the colloidal range	Dispersed phase ordinarily consists of inorganic particles, such as gold or silver
Molecules of dispersed phase are solvated, i.e., they are associated with the molecules comprising the dispersion medium	Hydrophilic or lipophilic portion of the molecule is solvated, depending on whether the dispersion medium is aqueous or nonaqueous	Little if any interaction (solvation) occurs between particles and dispersion medium
Molecules disperse spontaneously to form colloidal solution	Colloidal aggregates are formed spontaneously when the concentration of amphiphile exceeds the critical micelle concentration	Material does not disperse spontaneously, and special procedures therefore must be adopted to produce colloidal dispersion
Viscosity of the dispersion medium ordinarily is increased greatly by the presence of the dispersed phase; at sufficiently high concentrations, the sol may become a gel; viscosity and gel formation are related to solvation effects and to the shape of the molecules, which are usually highly asymmetric	Viscosity of the system increases as the concentration of the amphiphile increases, as micelles increase in number and become asymmetric	Viscosity of the dispersion medium is not greatly increased by the presence of lyophobic colloidal particles, which tend to be unsolvated and symmetric
Dispersions are stable generally in the presence of electrolytes; they may be salted out by high concentrations of very soluble electrolytes; effect is due primarily to desolvation of lyophilic molecules	In aqueous solutions, the critical micelle concentration is reduced by the addition of electrolytes; salting out may occur at higher salt concentrations	Lyophobic dispersions are unstable in the presence of even small concentrations of electrolytes; effect is due to neutralization of the charge on the particles; lyophilic colloids exert a protective effect

Some unique properties of colloids

1) light-scattering properties (Tyndall effect),
2) osmotic properties (of colloid solutions),
3) electrical properties, and
4) dispersed particle movement (Brownian motion).

Table 5: Colloidal based delivery systems for therapeutics

Typical Mean Particle Diameter	Delivery System Type	Representative Systems of Each Type	Characteristic Applications
0.5–20 μm	Microspheres, hydrogels	Alginate, gelatin, chitosan, polymeric microspheres, synthetic, biodegradable, polymeric hydrogels	Sustained release of therapeutics, scaffolds for cell delivery in tissue engineering
0.2–5 μm	Microparticles	Polystyrene, poly(lactide) microspheres	Targeted delivery of therapeutics
0.15–2 μm	Emulsions, microemulsions	Oil-in-water, water-in-oil, lipid emulsions, oil-in-water microemulsions	Controlled and targeted delivery of therapeutics
30–1000 nm	Liposomes	Phospholipid and polymer-based bilayer vesicles	Targeted delivery of therapeutics
3–80 nm	Micelles	Natural and synthetic surfactant micelles	Targeted delivery of therapeutics
2–100 nm	Nanoparticles	Lipid, polymer, inorganic nanoparticles	Targeted delivery of therapeutics, in vivo navigational devices
2–100 nm	Nanocrystals	Quantum dots	Imaging agents