Nanotechnology: New Name, Old Science

Introduction
Colloidal phenomena are encountered in everyday materials (polymers, plastics, and rubber, agrochemicals, pharmaceuticals, and cosmetic chemicals, paper, foodstuffs, fabrics, textiles, and detergents) and technologies (nucleation and precipitation, liquid crystals, chromatography and ion-exchange, flotation, and heterogeneous catalysis).

Historically, humans have observed and made use of colloidal phenomena for thousands of years. Stone Age paintings in the Lascaux caves of France were produced with stabilized colloidal pigments; the Bible and other early religious writings refer to strange clouds and fogs; ancient Babylonian tablets describe the preparation of inks and pigments; ancient Egyptian hieroglyphs show scenes of silting of the Nile delta, and Hebrew slaves made bricks of clay.

Nanotechnology
In 2007, the FDA issued its Nanotechnology Task Force Report1 in which nanotechnology is defined as the ability to measure, see, manipulate, and manufacture things usually between one and 100 nanometers. Nano-size particles are but a new term for colloids.

There is a continuing and increasing interest in “nanotechnology” applications for the pharmaceutical industries, due to improved drug delivery and targeting. One estimate suggests that about 80% of the 2015 market in those industries will relate to nanotechnology.

What’s a Colloid?
The concept and the name of “colloid” are credited to Thomas Graham (1861). Using (a) restricted diffusivity (colloids are held back by a semi-permeable membrane) and (b) optical turbidity (colloids scatter light) he demonstrated (with gelatin solutions and gold sols respectively) that two distinct classes of material can be so qualified. The former is now referred to as “lyophilic” (liking and spontaneously dispersible in their liquid; they are thermodynamically stable) and the latter as “lyophobic” colloids (disliking their environment and potentially unstable).

Colloid science covers systems occupying an intermediate position (with respect to particle size) between true solutions of low MW substances and suspensions. As a rough guide, a colloid is any particle whose size includes a linear dimension (Figure 1) in the range from ~ 1 - 10 nm to ~ 500 - 1000 nm, (or alternately, between 101 and 103 atoms per particle).

Colloidal systems are termed dispersions or sols for solid-liquid systems. For particulate systems in which the size exceeds 1 μ it is usual to refer to them as suspensions, though the two terms are often used interchangeably.

The Importance of the Colloidal State
The characteristic feature of colloid science lies in the importance of:
1. Particle size
2. Particle shape (and flexibility)
3. Surface chemical (and electrical) properties

The particles in a colloidal dispersion are sufficiently large for a well-defined surface of separation, an interface, to exist between the particles and the medium. The presence of an interface also leads to effects such as capillarity (the “tears” in strong wine, the dew drops on spider webs, water-proofing and the breakup of liquid jets) and adsorption (carbon filters for clarification of water, beer, wine, bone-char to de-color sugar solutions, gas masks and the flocculation of muds at river deltas).

Particle Size
The particle size distribution (PSD) directly affects the bioavailability of active pharmaceutical ingredients (APIs) and the safety of intravenous lipid emulsions. As with suspensions, colloidal dispersions also contain a range of sizes and, hence, PSD.

Two procedures are used for the preparation of colloidal dispersions1,5. In the dispersive (or “top-down”) method one phase is dispersed in another by comminution and attrition using mills of various types; although the average particle size can be made small, the PSD is usually broad. In the condensation (or “bottom-up”) method, conditions are created starting from molecular solutions in which individual molecules combine to form aggregates. Here the resulting PSD is much narrower; these dispersions are, however, subject to Ostwald ripening.

As the particle size is reduced, the surface area increases (as 1/d3), accompanied by a large surface area-to-volume ratio per given mass for the particles. This is illustrated (Figure 2) by taking a “particle” of side 1 cm and breaking it down into smaller cubes having a side of only 104 cm (or, 10 nm. The total surface area for the same amount of material then increases from 6 cm2 (about the size of a sugar lump) to 6x106 cm2 (or, 600 m2 – enough to cover the area of two tennis courts). The particle shape is immaterial - the surface area per mass of any colloid is orders of magnitude larger than it is for particles of even only a few μ in size. This huge increase in surface area effects not just adsorption of chemicals and other moieties onto the particle surface but also the interaction between particles and system properties, such as suspension rheology, coating and adhesion. It also allows for
much faster dissolution of API’s leading to increased bioavailability in the case of sparingly water soluble but membrane permeable molecules. Low bioavailability can lead to inefficient treatment, higher cost and risk of toxic side effects; hence the drive to develop reformulations based on nanotechnology. There is also a growing body of evidence that, specifically with nanoparticulate materials, it is the surface area and not particle size that is the defining metric that controls toxicity/activity and catalysis (1). Additionally, as material is broken down, the hitherto internal surface becomes exposed and, with it, a change in the number or type of surface chemical sites and groups. Referring again to our particle (cube) of 1 cm, only two or three molecules in 10 million are “surface” molecules. However, when divided into 10 nm size particles, more molecules/atoms that comprise the molecular structure become “surface moieties” and the ratio rises to nearly 1:4; and at 1 nm particle size fully 80% of the atoms are on the surface. As a further example, a typical micellar solution containing 0.1 M amphiphile has ~4x10^12 of micellar-water interfacial area per liter of solution! Thus, at the interfaces between the disperse phase and the dispersion medium, (surface charge) effects that are normally negligible for massive solids become dominant in the description of colloidal behavior; they play an increasing part in determining the physico-chemical properties (such as surface chemistry/activity and catalysis) of the system as a whole. 

Particle Shape

Particle asymmetry is a factor of considerable importance in determining the overall physico-mechanical properties of colloidal systems. Shape is a function of the history of the formation of the particles, i.e., crystallization. Although the exact shape may be much more complex, colloidal size particles can be roughly classified as: corpuscular (spherical and ellipsoidal), laminar (disc- or plate-like) or linear (rod- or needle-like). “Globular” proteins (albumin, globulin, casein, hemoglobin) adopt a compact “random coil” configuration that approximates sphericity (2). Many APIs exist as rod- or needle-like particles. High MW macromolecular materials (proteins, polysaccharides and synthetic polymers) usually exist in the form of long thread-like or branched-chain molecules; these materials often exhibit a considerable mechanical strength and durability not possible with corpuscular or laminar particles (3). Their shape is influenced by solution conditions (temperature, pH, salt/electrolyte concentration) and ranges in configuration from hugely elongated uni-dimensional strings to tightly compacted random coils (4); their functional properties (i.e., to act as either a stabilizer or a de-stabilizer of a particulate dispersion or suspension) have been used since the days of antiquity (i.e., gum Arabic as a pigment dispersant).

Surface Charge

All dispersed particles spontaneously acquire a surface electrical charge when brought into contact with a polar medium (i.e., water); the various charging mechanisms are (5):
1. Affinity differences of two phases for electrons
2. Ionization of surface groups
3. Differential ion adsorption from an electrolyte solution
4. Differential ion dissolution from a crystal lattice
5. Surface anisotropy
6. Isomorphous substitution

For all liquid-liquid interfaces and most normal colloidal dispersions Mechanism 1 is of little significance; an exception is metal sols (i.e., gold nanoparticles). Mechanism 2 is commonly observed with carboxylic acid- and amine-containing surfaces (i.e., proteins and ionic polymers) and all oxide surfaces. Lyophobic colloidal dispersions (i.e., polymer latices and API’s) fall in the Mechanism 3 category. Ionic solids (i.e., silver halides, calcium carbonate) acquire a surface charge via Mechanism 4 by virtue of unequal dissolution of the opposing charged ions of which they are composed. Mechanism 5 arises because most crystal lattices are anisotropic; it is the cause of amphoteric hydroxyl groups in oxides, including silicas (6). Mechanism 6, isomorphous substitution, a more extreme case of Mechanism 5, occurs in aluminosilicate clay materials (i.e., montmorillonite and vermiculite) (7) where a large negative charge is initially developed on the clay crystallite because of the difference in valence between the Al^3+ and the Si^4+ ions.

Conclusion

Over 500 manufacture-identified, “nanotechnology-based” products have already been catalogued (8). In consumer healthcare, sunscreen products use “microfine” zinc oxide and titanium dioxide to attenuate the UVA and UVB radiation that causes sunburn and skin cancer yet are non-whitening on the skin (9); toothpastes contain nanoparticulate hydroxyapatite for filling minute cracks in tooth enamel and many anti-aging products use nanocapsule technology to deliver actives such as vitamins into the skin (10). Nanosilver particles can be found in FDA-approved wound dressings. Bioactive ceramic material (based on mixtures of nanosize zirconia and hydroxyapatite) are in the development stage for orthopedic weight-bearing implants; one major advantage of nanoparticles is a vast improvement in sintering behavior. Thus, the new field of “nanomedicine” promises to impact all stages of healthcare (11). Drug delivery is one of four main areas in nanomedicine (the others are molecular diagnostics, tissue engineering and cell/gene therapy). The challenge for traditional pharmaceutical companies is to deliver the right therapeutic to the right target with no, or minimal, side effects and ideally at reduced cost. Nanotechnology may provide improved, differentiated products for all common routes of administration - oral, injection, transdermal, transmucosal, ocular, pulmonary and implant. The global market for nanotechnology-enabled products in 2007 totaled $147 billion but is projected to grow to $3.1 trillion by 2015 (12).

References

1. www.fda.gov/nanotechnology.