FORMULATION PRINCIPLES

- Disperse formulations are complex systems
- Basic criteria for good pharmaceutical suspensions

1. not settle too rapidly (uniformity of dose)
2. easy to redisperse (does not cake)
3. appropriate rheological properties (can pour and measure accurate dose)

Three major product types

a) Oral
- 10-20% w/v solids
- antacids contain up to 50% w/v

b)Topical
- dermatological
- up to 30% w/v solids

c) Parenterals
- IM or SC (not for I.V. use)
- e.g. procaine penicillin (0.5-30%)
- require control over particle size otherwise potential tissue necrosis

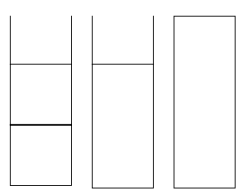
- Best formulations require
  - application of colloidal stability theory
  - controlled flocculation approach

Flocculation

- Particles in dispersion are loosely associated where they can be easily redispersed
- Best system for long storage time
- The characteristics of flocculation include -
  - weak bonding
  - 3D character
  - do not form a cake
  - easy re-dispersion
  - high F ratios

Sedimentation quantitation

Sedimentation volume (F)
F = Vu/Vo
Vu = ultimate sediment volume
Vo = initial suspension volume



F = 0.5 F = 1.0 F = 1.5

<u>deflocculated system</u>
- particles settle, close packing of sediment likely to form hard cake

F = 0.5

<u>flocculated system</u>
- no clear supernatant,, random arrangement of particles in flocs, no caking

F= 1

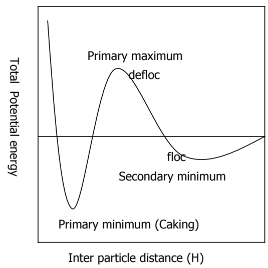
- not settle even after add more solvent

F = 1.5

*Pharmaceutically acceptable systems

Floc vs defloc systems

- Deflocculated systems often form hard cakes upon sedimentation
- the forces in the "compressed cake" are such that the energy barrier of the primary maximum is passed and they go straight on to the primary minimum
- Relative value of the primary maximum vs. the secondary minimum is important for flocculation
- If primary maximum is too high, no chance to form a flocculated system in secondary minimum



FLOCCULATION can be induced by

Electrolyte addition

Surfactants or polymer addition

- Flocculated systems do not cake upon particles settling but easy to redisperse

Electrolyte addition

1. Add electrolytes to adjust zeta potential and EDL thickness and therefore inter-particle distance (H)
   - 2^{nd} minimum distance = Floc formation
2. Electrolytes to cause formation of bridge between adjacent particles to form loose clusters
   - E.g. divalent cation such as calcium in calamine lotion forms bridges with the negatively charges bentonite clay particles

Surfactant or Polymer addition

1. Act as bridges between particles
2. Protection vs. sensitisation effect depends on the concentration
3. entropic vs. enthalpic stabilisation

- Flocculated systems are good, addition of a suspending agent is even better
- Suspending agents will retard sedimentation of a floc
  - e.g. carboxymethylcellulose, tragacanth, carbopol

- Ideally, the vehicle used should be pseudoplastic in character
  - at high shear stress (i.e. upon shaking)
    - Low viscosity
    - Pourability
    - Dose uniformity
  - at low shear stress (upon standing)
    - High viscosity
    - minimise particles from settling and caking

Other stability aspects

AGEING of Suspensions

- Suspensions - crystal growth
- Solutions - potential for crystallization and precipitation

Crystallization

1. Supersaturation
2. Formation of crystal nuclei
3. Crystal growth around the nuclei

- The relative rates of these processes will determine the final particle size.

Supersaturation

Supersaturation by

- Cooling
- Solvent evaporation
- addition of extra solid material

- However, supersaturation itself is insufficient to cause crystals to form

Formation of crystal nuclei

The crystal embryos must form by
- collision of solute molecules
- addition of seed crystals (dust or particles)

- As soon as stable crystal nuclei are formed, they will form into visible crystals
- Crystallization can be considered the reverse of dissolution

Crystal Growth

- opposite to dissolution

There are two major steps in crystal growth

1. Transport of solute molecules to surface
2. Arrangement of molecules in ordered fashion

- Polymorphism: different crystal structures of the same compound
- Different solid state characteristics e.g. m.pt, solubility, stability, bioavailability

OSTWALD RIPENING

- crystals can grow and also can re-dissolve, but at different rates
- In any dispersion there is an equilibrium between rates of dissolution and precipitation.
- Smaller particles tend to redissolve and then precipitate out on larger particles
- The smaller particles tend to have a higher solubility and dissolve while the larger particles will grow at their expense
- The balance between these processes is the important formulation aspect

- Often add stabilizing agent (e.g. polymers) to decrease the potential *Ostwald* effect in dispersion systems.
- In stability testing, always consider temperature cycling as this can often lead to *Ostwald ripening* due to the changing temperature and solubility environment.
- Warm $\rightarrow$ cold $\rightarrow$ warm cycles