OVERVIEW

• Introduction
• Classification of disperse formulations
• Properties of disperse systems
• Stability characteristics
• Formulation principles

REFERENCES

• Florence and Attwood - Physicochemical Principles of Pharmacy
• Martin - Physical Pharmacy
• Aulton – Pharmaceutics: The Science of Dosage form design
• Shaw - Introduction to Colloid and Surface Chemistry
• Lieberman - Pharmaceutical Dosage Forms

DISPERSE SYSTEMS

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CLASSIFICATION of DISPERSIONS

Size of individual units in dispersed phase

1. Molecular
2. Colloidal
3. Coarse

CHARACTERISTICS of Disperse Systems

• Dispersed phase and dispersion medium
• high interfacial area
• high surface to volume ratio

1. Particle Size
2. Surface properties
3. Particle Shape and Flexibility

1. Particle Size
• significant effects on stability
  • appropriate for the formulation
    - suspensions < 10 µm
    - ointments < 30-60 µm

2. Surface properties
• Large S.A. Systems
  • the potential for particle-particle interactions
  • particle - solvent interaction
3. Particle Shape and Flexibility

- The uniformity of S/L systems is often influenced by
- Particle shape (morphology)
- Flexibility (solvation)

- The more "extended" the particle ⇒ the greater is the specific S.A. ⇒ greater opportunity for attractive forces to develop between the particles

The "hedgehog concept" and particle surface area

- dependent upon the solvent
- unfriendly environment ⇒ "rolls-up", reduction in SA
- friendly environment ⇒ "unrolls", expose maximum SA

CLASSIFICATION OF COLLOIDAL SYSTEMS

1. Lyophilic colloids
2. Lyophobic colloids
3. Association colloids

1. Lyophilic Colloids

- lyophilic (solvent loving)
- readily dispersed in the solvent
- considerable interaction between the particle and solvent
- surface-solvent interaction (Hedgehog concept)
- solvent sheath formation

2. Lyophobic Colloids

- lyophobic – "solvent hating"
- little or no interaction between the solvent and particles
- no solvent sheath formation
- not able to simply disperse the internal phase

3. Association Colloids

- Amphiphilic molecules
- occur with molecules characterized by two distinct regions
- e.g. surfactants above CMC or micelles are association colloids
- Sizes of micelles - 50-100 Å (10 nm)
PREPARATION OF DISPERSE FORMULATIONS

1. Condensation or dispersion

2. CONDENSATION Technique

- Condensation via - solvent change or temp or pH change method - precipitation \( \rightarrow \) nucleation & growth
- Involves a precipitation reaction e.g. substitution of a poor solvent or pH or temp change
- Initial nucleation
- Subsequent crystal growth

Control over nucleation and growth will depend on -
- solubility
- quantity of material available
- viscosity of medium
- impurities

2. DISPERSION TECHNIQUES

- Mortar and pestle
- Dispersion of bulk material by simple grinding
- "Colloid mills" – reduce substances to fine particles

- Re-uniting of the smaller particles

Can produce better dispersion through –
- Incorporation of an inert diluent (↓ contact)
- Wetting surface of particles – wet milling with surfactant in a slurry

PROPERTIES OF DISPERSE SYSTEMS

- KINETIC
- OPTICAL
- ELECTRICAL

Kinetic properties

- All particles in S/L systems have the capacity for movement.

Motion can be induced by
- thermal
- gravitational
- external influences (e.g. centrifugal)

Thermally induced motion

- thermally induced motion or random brownian motion
- collision of dispersed particles and molecules of dispersion medium
- velocity of movement is inversely proportional to
  - viscosity
  - size
- \(< 0.5 \mu m \Rightarrow \) brownian motion
Gravitational induced movement

- Sedimentation of particles > 0.5 µm
- The velocity of sedimentation \( v \) is governed by Stokes’ law:
  \[
  v = \frac{2}{9} \frac{r^2 (\rho - \rho_{med}) g}{\eta}
  \]
- Stokes’ law describes movement for particles that are only subjected to gravity
- colloidal systems (nm – µm) would require forces stronger than gravity
- smaller particles will not settle out \( \Rightarrow \) aspects of formulation design

Sedimentation can be reduced by
- ↓ particle size \( r \)
- ↓ density difference \((\rho - \rho_{med})\) between two phases
- ↑ viscosity \( \eta \) of the continuous phase

Optical properties

- When a beam of light is directed at a colloidal sol
  - absorbed
  - transmitted
  - Scattered
- Light scattering
  - electric field associated with light induces oscillation in the electron cloud of colloid material \( \Rightarrow \) fractional decrease in intensity of light \( \Rightarrow \) sol appears turbid
- Turbidity \( T \) is a measure of the extent of light scattering
- \( T \) can be used to estimate the molecular weight of the particle and particle shape

\[
\frac{I_o}{I_o} = \exp \left[-Tl\right]
\]
\[
H \frac{C}{T} = 2B + \frac{1}{M_w}
\]
\[
y = mx + c
\]
\[
I_o = \text{incident light}
I_t = \text{transmitted light}
T = \text{turbidity}
l = \text{cell length}
C = \text{solute concentration}
M_w = \text{molecular weight}
H \text{ and } B = \text{constants}

Electrical properties

- major determinate of the stability of disperse systems
- particles acquire electrical charge when brought in contact with a polar medium
- surface charge can be acquired by a particle through
  1. ion adsorption
  2. surface ionization

- Intensity of the scatter light varies in different directions depending on the particle surface \( \Rightarrow \) particle shape
- Intensity of scattered light depends upon different refractive indices of the particle and solution medium.
- It is difficult to see particles that have the same or similar refractive index as the solvent
  - e.g. glass particles in IV solution
(1) Ion adsorption
- Surfaces can adsorb + or - ions and acquire net surface charge.
- Surfaces in contact with aqueous media are most often -ve charged.
- Highly hydrated surfaces adsorb ions less readily than hydrophobic surfaces.

(2) Surface ionisation
- Most common means for gaining a surface charge is through simple ionization.
- E.g., an acidic drug (low pKa) ionises in relatively basic pH and carries a negative charge.
- E.g., proteins ionised based on the solution pH.

Electrical Double Layer (EDL)
- The theory of electrical double layers (EDL) deals with
  - The unequal distribution of ions around a charged particle and
  - The magnitude of the electric potentials which occur in the locality of a charged surface.
- Beyond EDL, in the bulk medium the distribution of ions (+ and -) is uniform and electric neutrality is obtained.

Electrical Double Layer
- E.g. Surface has +ve ion adsorption.
  - Inner region
    - Adsorbed ions (+ ions)
    - Adjacent layer of tightly bound counter ions (- ions)
    - Bound solvent molecules
  - Outer region
    - A diffuse layer of both + and - ions distributed according to electrostatic and thermal motion till electrical neutrality.

Zeta potential
- Electrokinetic potential occurs at shear plane.
- Zeta potential determines the degree of repulsion between adjacent similarly charged particles.
- Measure of zeta potential with a "zeta meter."
- As zeta potential ↓, particles come together ⇒ particle aggregation.
- Generally, if the zeta potential is ≤ 40 mV then aggregation or coalescence of dispersions may occur.

Added electrolyte effect on "thickness" of the EDL
- Formulation goal is to have a "reasonable" EDL thickness [1/k] to repel particles apart.
  1. Concentration of added electrolyte
    - Add too much electrolyte ⇒ ↑ counter ions ⇒ compression of EDL thickness ⇒ easier to aggregate.
  2. Valence of added electrolyte
    - ↑ valency of counter ions ⇒ compression of EDL ⇒ easier to aggregate.