

COMMONWEALTH OF AUSTRALIA

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DISPERSE SYSTEMS

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 Pharmaceutical Formulations

Dispersed	Continuous	Example
S	L	suspensions
L	L	emulsion/cream
L	G	liquid aerosol
S	G	solid aerosol

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 \Rightarrow the greater is the specific S.A. \Rightarrow greater opportunity for attractive forces to develop between the particles

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The "hedgehog concept" and particle surface area

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

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CLASSIFICATION OF COLLOIDAL SYSTEMS

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

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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

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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

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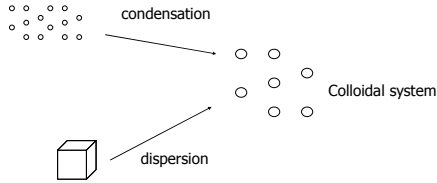
3. Association Colloids

- 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)

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PREPARATION OF DISPERSE FORMULATIONS

1. Condensation or
2. Dispersion



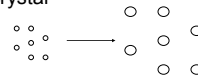
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1. CONDENSATION Technique

- 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 -

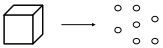
- solubility
- quantity of material available
- viscosity of medium
- impurities



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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 (\downarrow contact)
 - wetting surface of particles
 - wet milling with surfactant in a slurry



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PROPERTIES OF DISPERSE SYSTEMS

- KINETIC
- OPTICAL
- ELECTRICAL

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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)

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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
- $< 0.5 \mu\text{m} \Rightarrow$ brownian motion

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Gravitational induced movement

- Sedimentation of particles $> 0.5 \mu\text{m}$
- The velocity of sedimentation (v) is governed by **Stokes' law**:

$$v = \frac{2 r^2 (\rho - \rho^{\text{med}}) g}{9 \eta}$$

Sedimentation can be reduced by

- \downarrow particle size (r)
- \downarrow density difference ($\rho - \rho^{\text{med}}$) between two phases
- \uparrow viscosity (η) of the continuous phase

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- Stokes' law describes movement for particles that are only subjected to gravity
- colloidal systems ($\text{nm} - \mu\text{m}$) would require forces stronger than gravity
- smaller particles will not settle out \Rightarrow aspects of formulation design

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Optical properties

- When a beam of light is directed at a colloidal sol -
 - absorbed
 - transmitted
 - Scattered

Light scattering

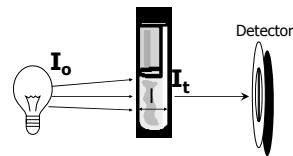
- electric field associated with light induces oscillation in the electron cloud of colloid material \Rightarrow fractional decrease in intensity of light \Rightarrow sol appears turbid
- Turbidity (T) is a measure of the extent of light scattering
- T can be used to estimate the molecular weight of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

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Turbidity (T)

- $I_t/I_o = \exp[-T \cdot l]$
- $H C / T = 2 B C + 1/Mw$
- $y = mx + c$

I_o = incident light
 I_t = transmitted light
 T = turbidity
 l = cell length
 C = solute concentration
 Mw = molecular weight
 H and B = constants



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- 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

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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

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(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

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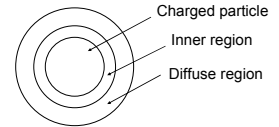
Electrical Double Layer (EDL)

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.

The two regions of the EDL are -

1. inner region
2. diffuse region



Beyond EDL, in the bulk medium the distribution of ions (+ and -) is uniform and electric neutrality is obtained.

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Electrical Double Layer

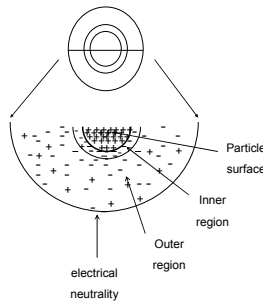
e.g. surface has +ve ion adsorption.

Inner region

- adsorbed ions (+ ions)
- adjacent layer of tightly bound counter ions (- ions)
- bound solvent molecules

Outer region

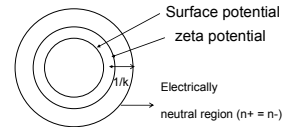
- A diffuse layer of both + and - ions distributed according to electrostatic and thermal motion till electrical neutrality



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EDL example

- Surface ions = -ve ions
- Inner region $n_+ \gg n_-$
- Diffuse region $n_+ > n_-$ continues to the distance where there is $n_+ = n_-$
- Surface potential = ψ_0 = potential at the surface of the particle
- Shear plane potential = ζ = potential at the boundary of the inner region or shear plane
- thickness of the electrical double layer = $1/k$ = The distance from the stern plane (i.e. mid inner region) to electrically neutral region
- repulsive forces arise from the interaction of EDL surrounding particles with same surface charge and magnitude of zeta potential



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zeta ζ potential

- Electrokinetic potential occurs at shear plane

ζ potential determines the degree of repulsion between adjacent similarly charged particles

- measure of ζ potential with a "zeta meter"
- As ζ potential \downarrow , particles come together \Rightarrow particle aggregation
- Generally, if the zeta potential is ≤ 40 mV then aggregation or coalescence of dispersions may occur

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Added electrolytes 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 \Rightarrow \uparrow counter ions \Rightarrow compression of EDL thickness \Rightarrow easier to aggregate

2. Valence of added electrolyte

- \uparrow valency of counter ions \Rightarrow compression of EDL \Rightarrow easier to aggregate

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