STABILITY OF DISPERSE SYSTEMS

Complex area of pharmaceutics as there are a number of factors to consider

1. electrical → stabilization
2. physical → solvation, sedimentation, aggregation
3. chemical → hydrolysis, oxidation

- Stabilization of disperse systems will be governed by the effective balance between *aggregation* (attractive forces) and *repulsion* (repulsive forces).

Aggregation/Attractive forces

- mainly due to van der waals forces acting at short range
- ↑ V.D.W. forces as
  - ↓ inter-particular distance
  - ↓ particle size
  - ↑ S.A

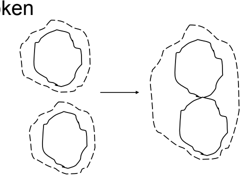
Repulsion

- Three major contributors to repulsion between particles

1. particle-solvent interaction
2. electrical repulsion
3. steric repulsion

PARTICLE SOLVENT INTERACTION

- Important for lyophilic particles
- For 2 particles to come together, solvent sheath must be broken



increasing the affinity of the solvent sheath for individual particle will increase the stability

Modify particle - solvent sheath affinity by -

(i) Change solvent to alter affinity
(ii) Add electrolyte or other solutes
- ability of electrolyte to "grab" hold of solvent

- E.g. gelatin has good affinity for H_20
- gelatin can be precipitated (de-solvated) by the addition of electrolytes (e.g. NaCl) at higher concentrations

SALTING OUT

- occurs where added electrolyte ions <u>dehydrate</u> hydrophilic colloid
- It is also called the de-solvation process
- competing for the water of hydration ⇒ leading to precipitation and aggregation

- the salting out tendency of an electrolyte depends upon the affinity of the electrolyte to become hydrated
- There are various electrolyte series :
  - $Na^+ > K^+ > NH_4^+$
  - $Citrate^{3-} > S0_4^{=} > Cl^- > N0_3^-$
- e.g. $(NH_4)_2\ S0_4$ often used to precipitate proteins from solution as it is highly water soluble and highly hydrated

ELECTRICAL REPULSION

- Where particles have a same surface charge, overlapping of the diffuse regions of the EDL ⇒ repulsion
- The "best and easy" estimate of the surface charge is through the <u>zeta potential</u>
- if change the effective surface charge e.g. by formulation variables this will alter the tendency for aggregation

Example alteration of zeta potential

- By adjusting ionic strength of solution to reach isotonicity
  - In this situation, ↑ concentration of salt (NaCl) could lead to a ↓ in the zeta potential which could lead to aggregation
  - Addition of colouring agents (polyvalent substances)
- some electrolytes are required to form good EDL but too much will decrease the zeta potential which could lead to aggregation

"Schulze-Hardy Rule"

↑ valency of counter ion ⇨ ↓ conc required to cause aggregation

Counter Ion	Conc. to cause aggreg.
NaCl	51
$CaCl_2$	0.65
$AlCl_3$	0.093

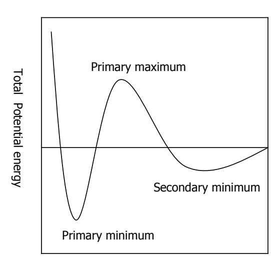
DLVO THEORY

- The DLVO theory of colloid stability helps explain the basis for aggregation due to attraction/repulsion forces
- $V_T = V_A + V_R$

total energy of interaction = attractive forces + repulsive forces

DLVO - Derjaguin, Landau, Verwey and Overbeek

Interaction between two particles vs surface separation distance (H)



- Primary minimum
  - When H is very small $V_A > V_R$ particles strongly associate (irreversible)
- Primary maximum
  - $V_R >> V_A$, energy barrier prevents particles into contact
- Secondary minimum
  - As ↑ H ⇨ more V_R ↓ ⇨ flocculation
  - Loose aggregates (flocs) easy to redisperse
  - important for suspension stability

- *Primary maximum:* like an energy barrier in a chemical reaction. If sufficiently high, prevents particles coming into contact with each other
- If get past primary maximum, move into the *primary minimum* where the particles are then strongly associated with each other because of the small inter-particle distances
- The *secondary minimum*, represents an area of stabilization of loose aggregates which are <u>easy to redisperse</u> and is responsible for *flocculation*.

Effect of electrolyte concentration on energy-distance relationships

- *low conc:* large diffuse region of EDL, high primary maximum but no secondary minimum
- *high conc:* complete compression of diffuse region, no primary maximum producing unstable system
- *intermediate conc:* compression of diffuse region, smaller primary maximum with a secondary minimum.

Effect of surface potential on energy-distance relationships

- *high value:* large diffuse region of EDL, high primary maximum but no secondary minimum.
- *low value:* no primary maximum as surface potential too low, produces unstable system
- *intermediate value:* small diffuse region, smaller primary maximum with a stable secondary minimum

3. STERIC REPULSION

- The stability of many colloidal dispersions can not be explained ONLY by consideration of EDL repulsion and particle/solvent affinity factors.
- The term *steric repulsion* is used rather loosely to explain these *"other effects“*
- generally refers to addition of surfactants or polymers to colloidal dispersions

e.g. addition of SAA

- lyophobic portion of SAA: interact with colloidal particle
- lyophilic portion of SAA: interact with solvent
- Before the particles actually come in contact and approach the primary minimum on the DLVO graph, the polymeric chains will interact
- Tendency for particle-particle interaction to occur ⇨ free energy of interaction ($\triangle G$)

Free energy of interaction

- $\triangle G = \triangle H - T\triangle S$
- $\triangle G < 0$ ⇨ spontaneous interaction
  aggregation occurs
- $\triangle G > 0$ ⇨ no spontaneous interaction
- There are two forms of stabilization:
  - entropic
  - enthalpic

(i) Entropic Stabilization

- Require G > 0
- $\Delta G = \Delta H - T\Delta S$
- $+ve = \Delta H - T\Delta S$
- If ΔS is – ve

  $= \Delta H - T(-ve)$

  $= + ve$

  As ↑ temp, this will increase the extent of entropic stabilization
- If product is entropically stabilized, do not store product in fridge as it could aggregate

Entropically stabilised product –

For ΔS to be < 0, it requires (S2 - S1) < 0

- For (S2 - S1) < 0 ⇒ more ordered after particles interaction
- as particles approach, the polymer chains/SAA interact in a manner where the conformation of the SAA is more ordered (or rigid)
- i.e. chains are not free to "flop around"
- unfavourable state and therefore particles separate

(ii) Enthalpic Stabilization

- For no interaction ⇒ $\Delta G > 0$
- $\Delta G = \Delta H - T\Delta S$
- require $+(\Delta H) > (T\Delta S)$

Upon interaction of two particles with polymers, net removal of $H_2 0$ from hydrated chains

- This is an endothermic reaction (i.e. $\Delta H > 0$)
- The loss of hydration/solvation leads to $\Delta H > 0$
- this occurs commonly in aqueous systems

- However, the loss of water of hydration will increase the flexibility of polymer chain ⇒ $\Delta S > 0$
- $\Delta G = +ve – T (+ve)$
- For $\Delta G > 0$, $\Delta H > T \Delta S$
- T must be lower to make ΔS less +ve
- i.e. for enthalpic stabilization, store product at lower temperatures (in fridge)

Sensitisation and Protection

- a more stable solid in liquid dispersion can be formulated by adsorbing a lyophilic polymer to the surface of the lyophobic colloid
- Protective lyophilic colloid layer adsorbed onto lyophobic colloid particle and solvent sheath around it will protect the particles from close contact and aggregation
- However, at low conc, lyophilic polymer ions could also act as the counter ions and compress EDL – this is called the “sensitisation”

Stability of lyophobic colloid