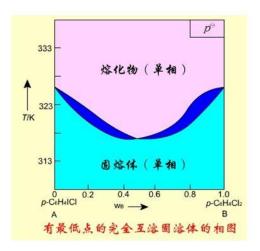
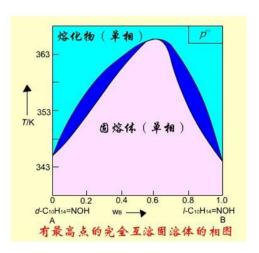
(2) Have upper or lower consolute temperature



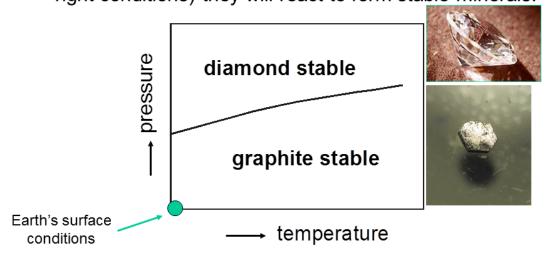


 $Na_2CO_3 - K_2CO_3$, KCl - KBr, Ag - Sb, Cu - Au

Stability and Metastability

Minerals that persist in an environment in which they are not chemically stable are said to be *metastable*.

Most of the minerals in the rocks at the Earth's surface are metastable. Given enough energy (or enough time and the right conditions) they will react to form stable minerals.



1. What is the molality of a solution containing 0.46 mole of solute in 2.0 kg water?

Given:

Moles of Solute – 0.46 mole Kilogram of Solvent – 2.0 kg

Formula: Molality = Moles of Solute

Kilogram of Solvent

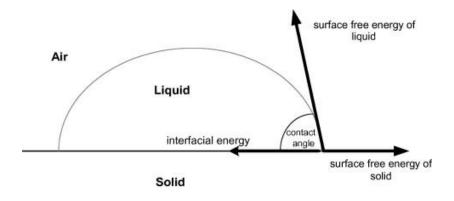
Answer: *m* = Moles of Solute

Kilogram of Solvent

= 0.46 mole

2.0kg

= 0.23 m

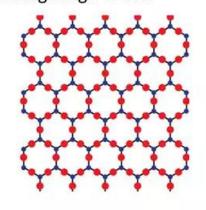




DIFFERENCES

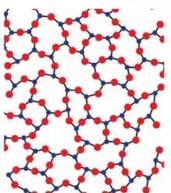
CRYSTALLINE SOLIDS

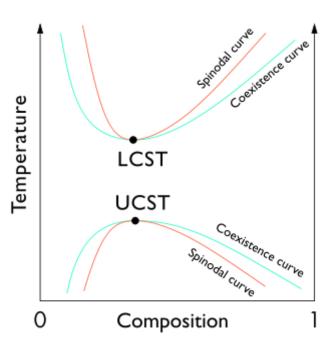
1. Constituent particles are arranged in a regular fashion containing short range as well as long range order.

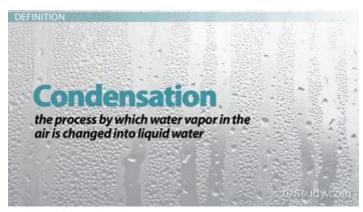


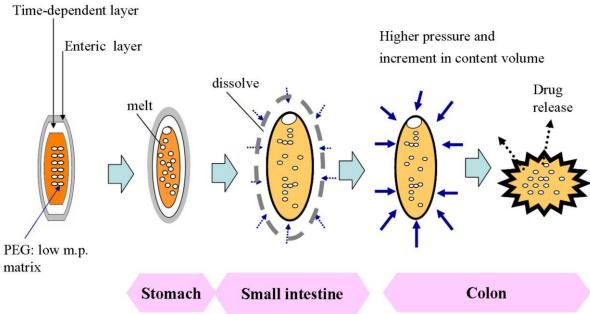
AMORPHOUS SOLIDS

 Constituent particles are not arranged in any regular fashion; they may be at the most some short range order.



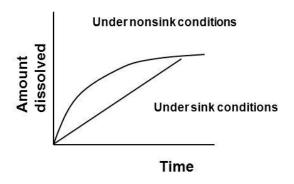






②. Dissolution of particles

Sink conditions and nonsink conditions



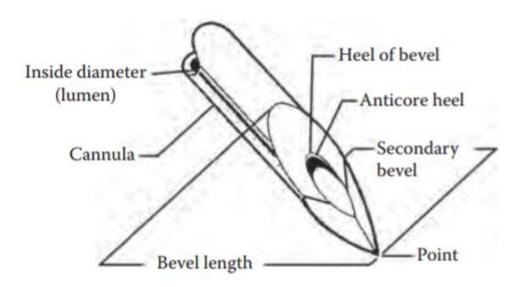
What is sink condition?

→ When the conc. of the drug in the bulk solution << the saturated solubility,</p>

we called sink condition.

SKKU Physical Pharmacy Laboratory 성균관대학교 **물리약학연구실**

Model	Equation
Zero-order model	$M_t/M_{\infty} = kt + C$
First-order model	$\ln(1-M_t/M_{\infty})=kt+C$
Higuchi model	$M_t/M_{\infty}=kt^{1/2}+C$
Ritger-Peppas model	$\ln(M_t/M_\infty) = k \ln t + C$
Hixson-Crowell model	$(1-M_t/M_{\infty})^{1/3} = kt + C$
Baker-Lonsdale model	$3/2[1-(1-M_t/M_{\infty})^{2/3}]-M_t/M_{\infty}=kt+$



Determination of Acid Value Definition:

The acid value is defined as the number of milligrams of potassium hydroxide required to neutralize the free fatty acids present in one gram of fat. It is a relative measure of rancidity as free fatty acids are normally formed during decomposition of oil glycerides. The value is also expressed as per cent of free fatty acids calculated as oleic acid.

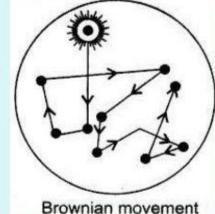
Principle:

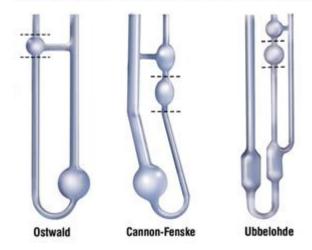
The acid value is determined by directly titrating the oil/fat in an alcoholic medium against standard potassium hydroxide/sodium hydroxide solution.

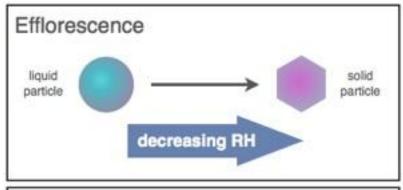
What is Brownian movement?

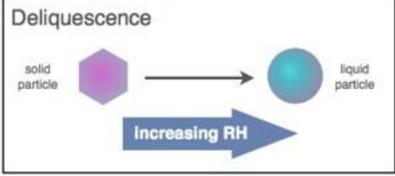
Brownian movement: the random motion of small colloidal particles suspended in a liquid or gas medium,

caused by the collision of the medium's molecules with the particles. Also called **Brown'ian** movement.









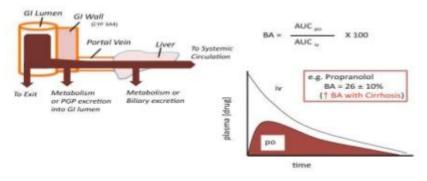
INTRODUCTION

Definition:-

The rate and extent (amount) of absorption of unchanged drug from its dosage form.

Bioavailability

 the fraction absorbed into the systemic circulation is the drug's bioavailability



INTRODUCTION

DEFINITIONS:

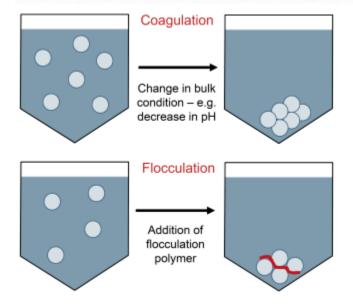
Bioavailability:

Bioavailability means the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.

• Equivalence:

It is a relative term that compares drug products with respect to a specific characteristic or function or to a defined set of standards. There are several types of equivalences:

 Chemical equivalence: It indicates that two or more drug products contain the same labeled chemical substance as an active ingredient in the same amount.



SPIRITS / ESSENCES

- Alcoholic or hydroalcoholic solutions of volatile substances.
- Usual alcohol content is 60%.
- When mixed with water, the volatile material separates and forms a milky solution.

COLLODIONS

□ Ethereal solutions



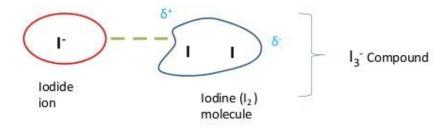
Are liquid preparations composed of PYROXILLIN (soluble gun cotton, collodion cotton) dissolved in a solvent mixture usually composed of alcohol and ether with or without added medicinal

COLLODIONS

- □ Intended for **external use only**
- Applied to the skin with a fine camel's hair brush or glass applicator
- Stored in a tight-closed container at a temperature not exceeding

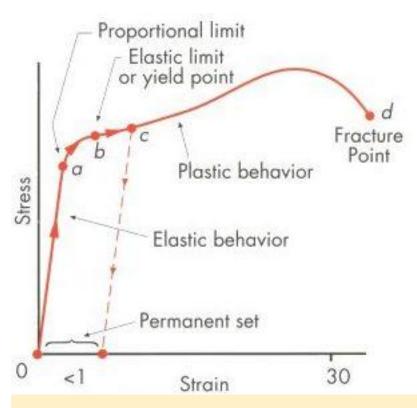
Ion-induced dipole forces

A nonpolar molecule or atom may be polarized by an electron cloud of an ion and the induced dipole may make a bond with the ion. Such a bond is called an ion-induced dipole force.



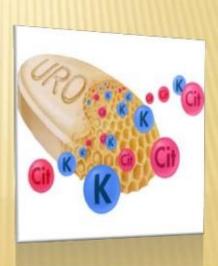
Another example- Li⁺ nG , where G is a noble gas and n= 1 or 2

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MATRIX TABLETS:

- ☐ Introduction of matrix tablet excludes complex production procedures such as coating and pelletization
- ☐ Drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations
- Advantages offered by matrix tablets:
- □ Reduction in toxicity by slowing drug absorption.
- ☐ Minimize the local and systemic side effects.
- ☐ Improved patient compliance.



Condensed Binary Systems

- >Other systems show both an upper and lower consolute temperatures.
- Such systems are known as closed miscibility loops.

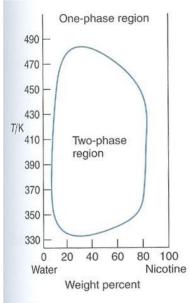


FIGURE 6.14
Solubility of water and nicotine as a function of temperature.

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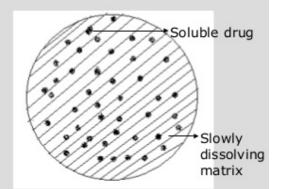


*Liquid - Surface film theory:

Thin liquid films form which bond the particles together at the particles surface. The energy of compression produces melting of solutions at the particles interface followed by subsequent solidification or crystallization thus in the formation of bonded surface.

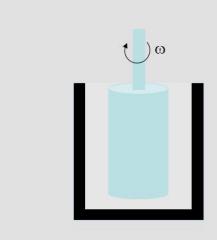


- Also called as Monolith dissolution controlled system.
- Controlled dissolution by:
 - 1. Altering porosity of tablet.
 - 2.Decreasing its wettebility.
 - 3. Dissolving at slower rate.
- First order drug release.
- Drug release determined by dissolution rate of polymer.
- Examples: Dimetane extencaps, Dimetapp extentabs.



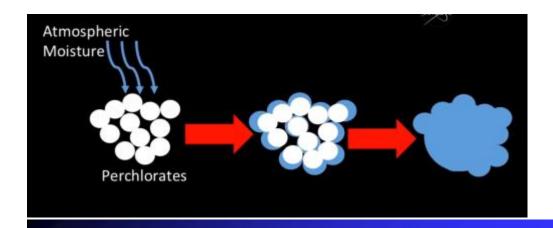
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Cup and Bob Viscometer



Stormer instrument: known weights cause bob to turn with known torque (shearing stress) and speed of rotation (rate of shear) is measured. Plot rpm versus mass added. Need to be calibrated with liquids of known viscosity for quantitative use.

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Dielectric Constant

Dielectric Constant is the ratio between the permittivity of the medium to the permittivity of free space.

$$\varepsilon_r = \frac{\varepsilon}{\varepsilon_0}$$

The characteristics of a dielectric material are determined by the dielectric constant and it has no units.

Dissolution

The dissolution rate is the time required for a drug substance to dissolve in the fluids at the absorption site. It is often the rate-limiting step in the absorption process.

 Dissolution is important for the bioavailability of solid dosage forms including oral capsules, tablets and suspensions and intramuscular suspensions.

Methods for increasing dissolution rates:

- Decrease particle size. This increases the available surface area to the dissolving fluid. [Note: In rare cases, agglomeration of the particles may occur leading to decreased dissolution rates.]
- Increase solubility in the diffusion layer. The ionized form of the drug (salt of the weak acid or salt of the weak base) will have greater solubility in the diffusion layer than the unionized weak acid or weak base. (e.g. penicillin V potassium will dissolve faster than penicillin V itself).
- Alter pH of dissolution medium (e.g. buffered aspirin).
- Increase agitation of dissolution medium (e.g. effervescent, buffered aspirin)

Non sink conditions :-

Modified noyes-whitney's equation represents the first order dissolution process, the driving force which the concentration gradient $(C_s - C_b)$, and this condition is said as non sink condition, done only for *in-vitro*

Sink conditions :-

The in-vivo dissolution is always rapid than in-vitro dissolution because the moment the drugs dissolves, it is absorbed in the systemic circulation, as a result $C_b = 0$ and the dissolution is at maximum.

3

DISSOLUTION TESTING

- ➤ Dissolution and drug release tests are in-vitro tests that measure the rate and extent of dissolution or release of the drug substance from a drug product, usually aq.medium under specified conditions.
- ➤ It is an important QC procedure for the drug product and linked to product performance in-vivo.

* NEED FOR DISSOLUTION TESTING:

- > Evaluation of bioavailability.
- ➤ Batch to batch drug release uniformity.
- Development of more efficacious and therapeutically optical dosage forms.
- ➤ Ensures quality and stability of the product.
- ➤ Product development, quality control, research and application.

Intrinsic Dissolution rate

- Rate which is independent of rate of agitation, area of solute available, etc.
- Intrinsic Dissolution Rate (IDR): rate of mass transfer per area of dissolving surface.
- It is independent of boundary layer thickness and volume of slolvent.

DISSOLUTION 20

Sink condition

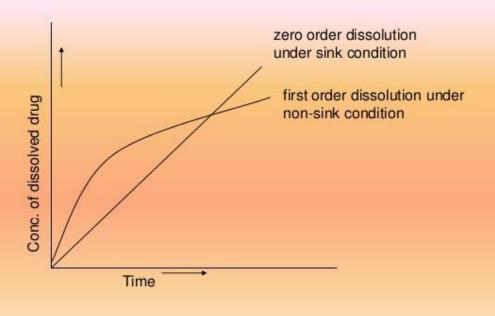
A Sink conditions describe a dissolution system that is sufficiently dilute so that the dissolution process is not impeded by approach to saturation of the compound of interest.

Sink conditions affect the production of the sample but not the condition of the solution upon sampling.

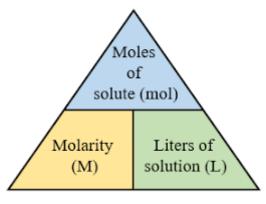
In vivo condition, there is no conc. build up in the bulk of the solution and hence no retarding effect on the dissolution rate of the drug i.e. Cs>>Cb and sink condition maintain.

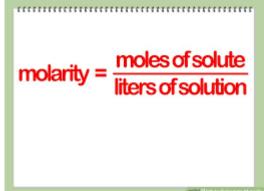
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Dissolution rate under non-sink and sink conditions.

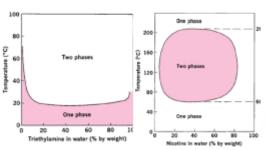


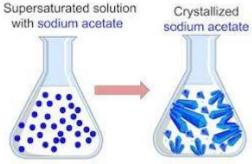
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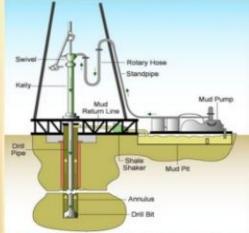
Upper and lower consulate temperatures





WHAT IS DRILLING MUD

- In the course of drilling an oil or gas well by means of rotary drilling tools, a so called (Drilling mud) is circulated downwardly through the hollow drill stem and bit to the bottom of borehole and then upwardly to the surface through the annular space between the drill stem and the interior of the borehole.
 - The most common mud used in the drilling process is Bentonite due to; its mixed friendly with water and allow mud additives to perform efficiently. Beyond that, it is cheap.





Topical dosage forms (Cont.):

11- Collodion:

Collodion is a solution of nitrocellulose in ether or acetone, sometimes with the addition of alcohols.

- -Its generic name is pyroxylin solution.
- -It is highly flammable.
- As the solvent evaporates, it dries to a celluloid-like film.
- Compound Wart Remover consists of acetic acid and salicylic acid in an acetone collodion base used in Treatment of warts by keratolysis.

Essential trace elements

Trace elements

Iron, zinc and copper

Ultra trace elements

Manganese, selenium, cobalt, chromium, fluoride, iodine, and molybdenum

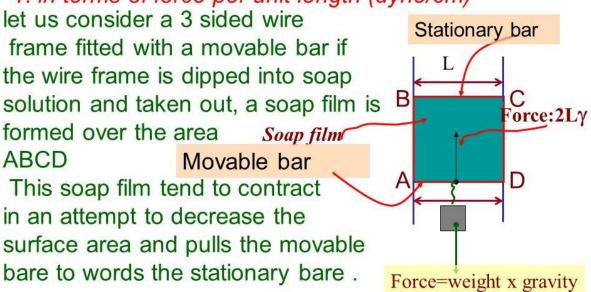
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Expression of surface tension

The S.T. can be expressed in one of the following ways

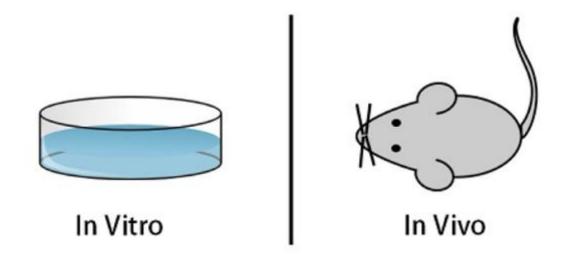
1. in terms of force per unit length (dyne/cm)

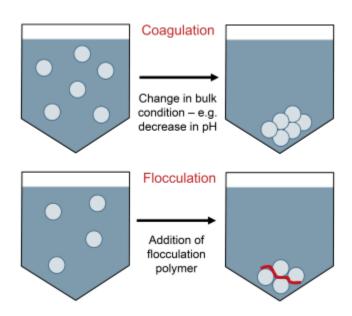


2-Saponification number

- Definition: Number of milligrams of KOH required to completely saponify one gram of fat.
- Uses: Each carboxyl group of a fatty acid reacts with one mole of KOH during saponification, so, the amount of alkali needed to saponify certain weight of fat depends upon the number of fatty acids present per weight.
- Fats containing short-chain acids will have more carboxyl groups per gram than long chain fatty acids and consume more alkali, i.e., will have higher saponification number.

THE STATE OF THE S	
Home Science	Fats



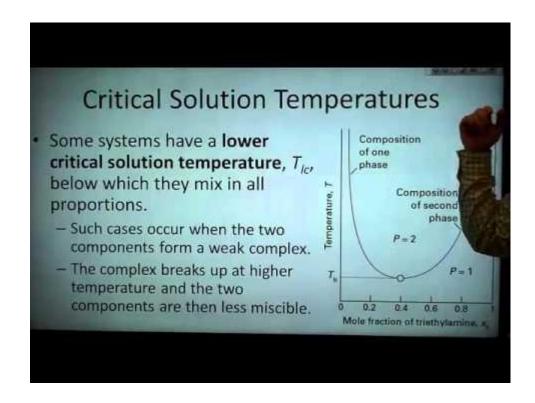


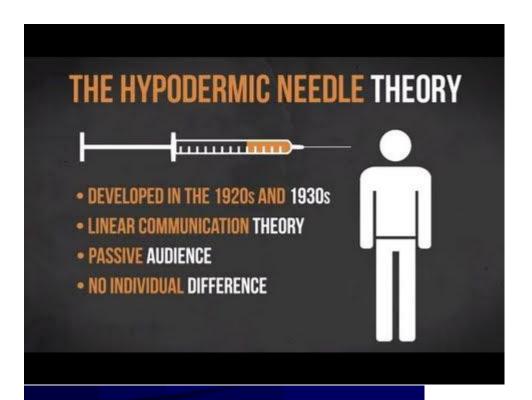
How the plastic flow is produced

Plastic flow is associated with the presence of flocculated particles in concentrated suspensions, so in this case the yield value results from the contacts between adjacent particles which must be broken down before flow can occur.

So the yield value indicate the force of flocculation in that the higher the flocculated suspension the higher the yield value.

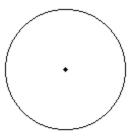
At a value of shearing stress above the yield value the plastic systems become resemble Newtonian systems in that there is a direct relation ship between the shearing rate and shearing stress.



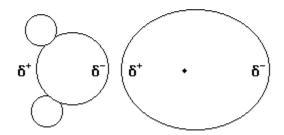


Definition of Bioequivalence

 Pharmaceutical equivalents whose rate and extent of absorption are not statistically different when administered to patients or subjects at the same molar dose under similar experimental conditions



Spherical atom with no dipole. The dot indicates the location of the nucleus.

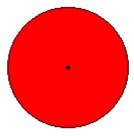


Upon approach of a molecule with a dipole, electrons in the atom respond and the atom develops a dipole.

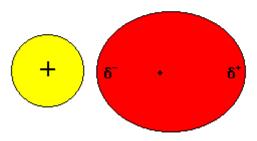
Parameters for correlations

SL. No.	IN VITRO	INVIVO
1.	Dissolution rate	Absorption rate (or
		absorption time)
2.	Percent drug dissolved	Percent of drug absorbed
3.	Percent drug dissolved	Maximum plasma concentration, C _{max}
4.	Percent drug dissolved	Serum drug concentration, C _p

5



Spherical atom with no dipole. The dot indicates the location of the nucleus.



Upon approach of a charged ion, electrons in the atom respond and the atom develops a dipole.

Ion-Induced Dipole Attractions

- Attractions between ion and dipole it induces on neighboring molecules
 - o Depends on
 - olon charge and
 - oPolarizability of its neighbor
 - Attractions can be quite strong as ion charge is constant, unlike instantaneous dipoles of Londondispersion forces

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Brownian Motion

- The constant and random motion of small solid particles in fluids (liquids and gases) is called <u>Brownian motion</u>.
- Brownian motion provided the evidence of molecular motion & proved the existence of particles that cannot be observed with a normal microscope.
- Just for info:

Brownian motion is first observed in 1827 by Robert Brown. Through the microscope, he observed the motion of pollen grains suspended in water. However, he was unable to provide an explanation for Brownian motion.

3. Higuchi Model-

Higuchi proposed this model in 1961 to describe the drug release from matrix system.

Hypotheses:

- (i) initial drug concentration in the matrix is much higher than drug solubility
- (iii) drug particles are much smaller than system thickness
- (iv) matrix swelling and dissolution are negligible
- (v) In the release environment perfect sink conditions are maintained.

The basic equation of Higuchi model is.....



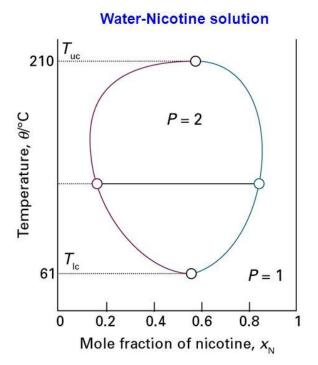
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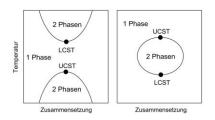
Liquid-only Phase diagrams

Lower consolute temp. (T_{Ic)}Is the temperature at which both liquids are miscible.

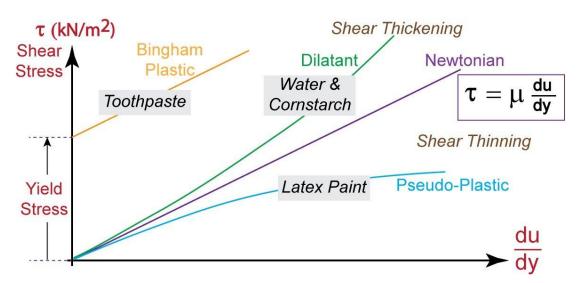
Inside the circle, two phases exist.

Each composition is given by the lever rule.



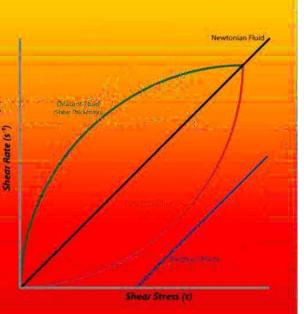


NON-NEWTONIAN FLUIDS



Non-Newtonian Fluids

- Viscosity is a function of applied stress.
- Common Time Independent Types:
- Pseudoplastic
 - (Shear Thinning)
- Dilatant
 - (Shear Thickening)
- Viscoplastic or Bingham
 - (Required Minimum Force)



Molality =
$$m = \frac{moles\ of\ solute}{kg\ of\ solvent}$$

$$m = \frac{mol}{kg}$$

Mole Fraction (X)

 $X_{\text{Solute}} = \underline{\text{Moles of solute}}$ Total moles of solution

X_{Solvent} = Moles of solvent
Total moles of solution

Where:

$$X_{\text{solute}} + X_{\text{Solvent}} = 1$$



Types of fluids

Newtonian Fluids

These fluids follow Newton's viscosity equation.

For such fluids viscosity does not change with rate of deformation.

Non- Newtonian Fluids

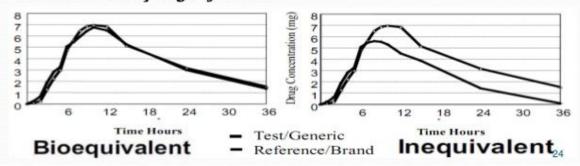
These fluids do not follow Newton's viscosity equation.

Such fluids are relatively uncommon e.g. Printer ink, blood, mud, slurries, polymer solutions.

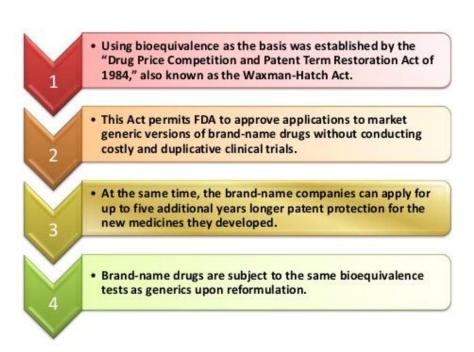
What is Bioequivalence?

A generic drug is considered to be bioequivalent to the brand name drug if:

- The rate and extent of absorption do not show a significant difference from listed drug, or
- The extent of absorption does not show a significant difference and any difference in rate is intentional or not medically significant



Bioequivalence: Background



Structured vehicle

Ø Structured vehicles called also thickening or suspending agents.

Ø They are aqueous solutions of natural and synthetic gums.

Ø It is applicable only to deflocculated_suspensions.

E.g. methyl cellulose, sodium carboxy methyl cellulose,

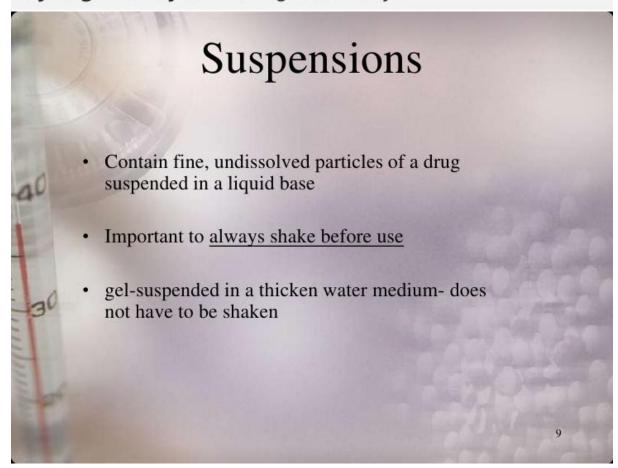
acacia, gelatin and tragacanth.

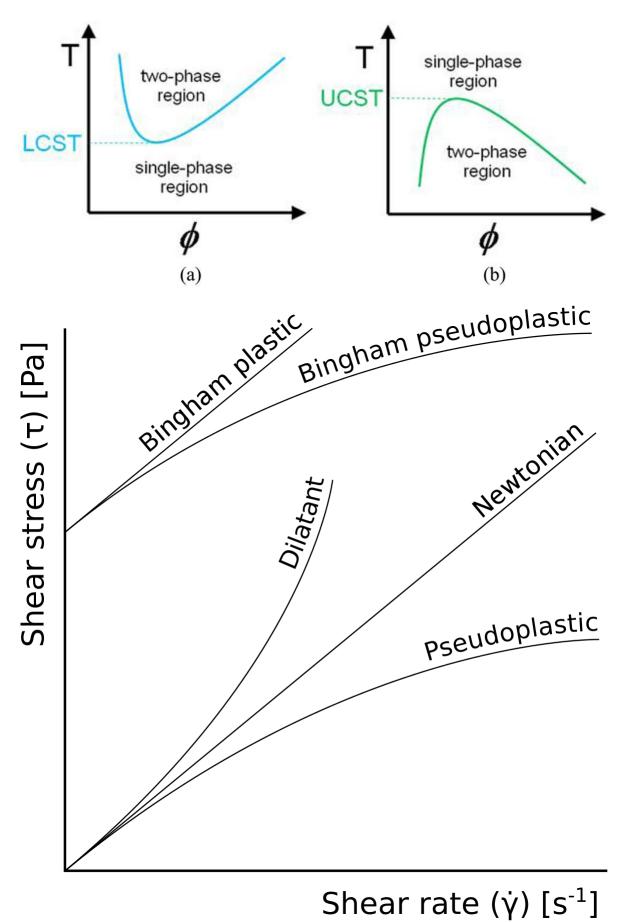
Ø These structured vehicles entrapped the particle and reduces the sedimentation of particles.

Ø Thus, the use of deflocculated particles in a structure vehicle may form solid hard cake upon long storage.

Ø Structured vehicle is not useful for **Parenteral suspension** because they may create problem in **syringeability** due to high viscosity.

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RHEOLOGY OF SUSPENTIONS

- The flow property of suspension depend upon their rheological characters
- The rheological properties of suspension decide the pourability, easy of injection, sedimentation, its redispersibility.
- The viscosity of flocculated suspension greater than deflocculated particles in same suspension.
- The flocculated suspension has yield value and behave like a plastic or pseudo plastic system.
- Example: conc.parenteral suspension contain 40- 70 % w/v of procain pencillin G

Flocculation of a suspension system:

Flocculation

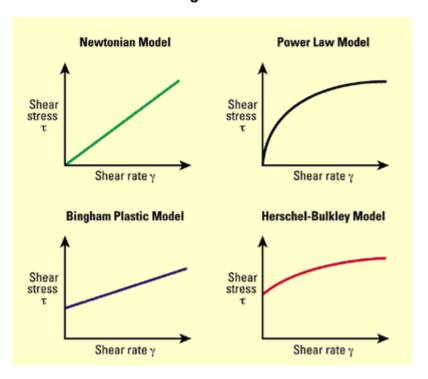
viscosity & thixotropy.

The flocs or aggregates are held weakly together and are capable of forming extended networks which give the flocculated suspension its structural properties.



Immobilization of a portion of the dispersing media in the network & between the flocs viscosity.

Rheological Models

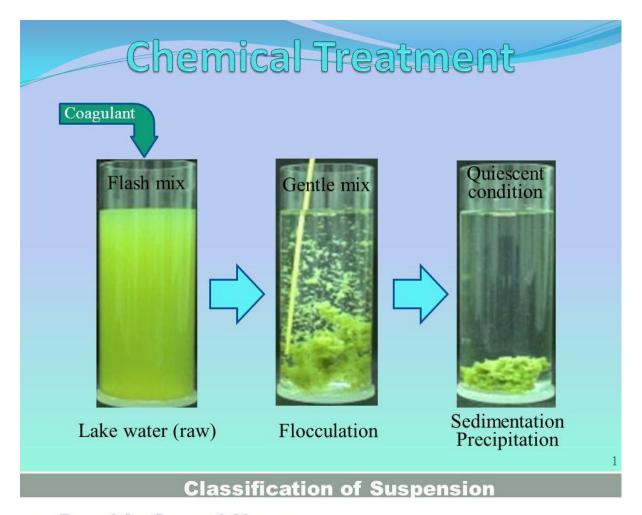


Need to study polymorphism

- Depending upon their relative stability, one of the several polymorphic form will be physically more stable than others.
- Stable polymorph represent s the lowest energy state, has highest melting point and least aqueous solubility.
- Metastable form represent the higher energy state, have lower melting point and high aqueous solubility.
- Metastable form converted to the stable form due to their higher energy state.
- Metastable form shows better bioavailability and therefore preferred in formulations.
- Only 10% of the pharmaceuticals are present in their metastable form.

Cont...

2/1/2013



- Based On General Classes
 - Oral suspension
 - Externally applied suspension
 - Parenteral suspension
- Based On Size Of Solid Particles
 - Colloidal suspension (< 1 micron)
 - Coarse suspension (>1 micron)
 - Nano suspension (10 ng)
- Based On Proportion Of Solid Particles
 - Dilute suspension (2 to10%w/v solid)
 - Concentrated suspension (50%w/v solid)
- Based On Electro-kinetic Nature Of Solid Particles
 - Flocculated suspension
 - Deflocculated suspension

Relative Magnitudes of Forces

The types of bonding forces vary in their strength as measured by average bond energy.

Ionic bonds

Strongest Weakest Ion-dipole interactions

Hydrogen bonding (12-16 kcal/mol)

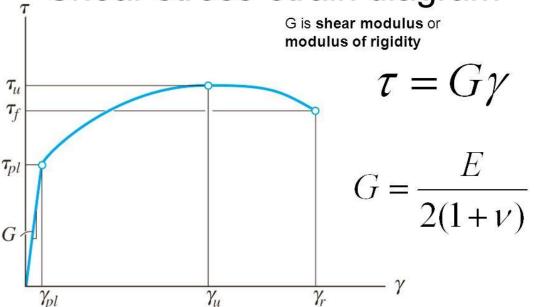
Dipole-dipole interactions (2-0.5 kcal/mol)

Ion induced dipole interactions

Induced Dipole-dipole interactions

London forces (less than 1 kcal/mol)







- Drug Product Performance Parameters:
- 1- Minimum effective concentration (MEC): The minimum concentration of drug needed at the receptors to produce the desired pharmacologic effect.
- 2- Minimum toxic concentration (MTC): The drug concentration needed to just produce a toxic effect.
- 3- Onset time: The time required for the drug to reach the MEC.
- 4- Duration of action: The difference between the onset time and the time for the drug to decline back to the MEC.

Intermolecular Forces

Ion-Induced Dipole and Dipole-Induced Dipole

Attractive forces that arise as a result of **temporary dipoles induced** in non-polar atoms or molecules



Non-polar atom or molecule





ion-induced dipole interaction





dipole-induced dipole interaction

Polarizability and Dispersion Force @ KSU - YouTube 11.2

Surface Free Energy

We now define the Surface Free Energy as:

$$\sigma^{\phi} = \left[\frac{\partial G}{\partial A} \right]_{T,P,n}^{\phi}$$

- The surface free energy represents those energetic effects that arise because of the difference in atomic environment on the surface of a phase.
- Surface free energy is closely related to surface tension.
- The total surface free energy of a phase is minimized by minimizing the phase's surface area.
 - Thus a water-drop in the absence of other forces will tend to form a sphere, the shape that minimizes surface area.

0

Concentration Units Continued

Molarity (M)

$$M = \frac{\text{moles of solute}}{\text{liters of solution}}$$



$$m = \frac{\text{moles of solute}}{\text{mass of solvent (kg)}}$$



12.3

Non-newtonian systems

1. Bingham plastic flow

- does not begin to flow until a shear stress corresponding to the yield value is exceeded.
- Flocculated colloid particles

Pseudoplastic flow

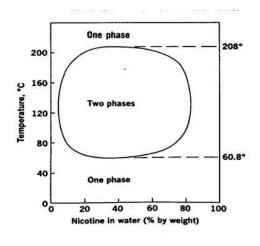
- Typically exhibited by polymers in solution (tragacanth, sodium alginate, methylcellulose, NaCMC)
- Viscosity decreases with the increase of shear rate/shear thinning
- Caused by the re-alignment of polymer and/or the release of solvents associated with the polymers.

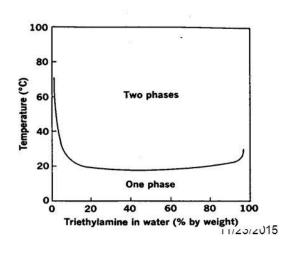
Dilatant flow

- Volume increases when sheared
- Shear-thickening
- Suspension containing a high concentration of small, deflocculated particles

Two component systems containing liquid phases

- Upper consolute temperature: All combinations above this temperature are completely miscible (one phase).
- Lower consolute temperature: below which the components are miscible in all proportions.







The work W required to create a unit area of surface is known as SURFACE FREE ENERGY/UNIT AREA (ergs/cm²)

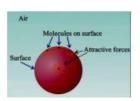
erg = dyne . cm

Its equivalent to the surface tension y Thus the greater the area A of interfacial contact between the phases, the greater the free energy.



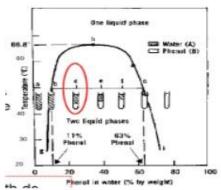


For equilibrium, the surface free energy of a system must be at a minimum. Thus Liquid droplets tend to assume a spherical shape since a sphere has the smallest surface area per unit volume.



Two component system containing liquid phase

- Tie Line: bc line: The line at which the system at equilibrium will separate into phases of constant composition, termed 'conjugate phases'
- Lever Rule: a way to calculate the proportions of each phase present on a phase diagram in a two phase field (at a given temperature and composition).



e.g. for point d (24%)

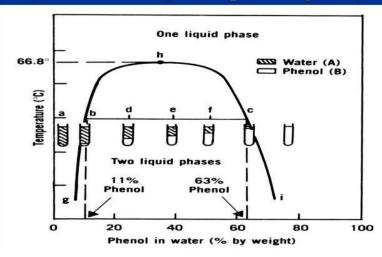


PROPERTIES OF STRUCTURED VEHICLE SUSPENSIONS

- May appear as a semi-solid when undisturbed
- Fluid when shaken
- Thixatropic (becomes fluid when stirred or shaken and returning to the semisolid state upon standing)
- No sedimentation

The Critical Solution Temperature: CST

- Is the maximum temperature at which the 2-phase region exists (or upper consolute temperature). In the case of the phenol-water system, this is 66.8°C (point h)
- All combinations of phenol and water > CST are completely miscible and yield 1-phase liquid systems.



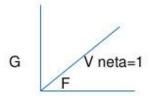
Calculating molality

25.3 g of KNO₃ was dissolved in 125 mL of water. What is the molality of the solution? (Molar mass of $KNO_3 = 101.1 \text{ g/mol}$, density of water = 1.00 g/mL) ___ m

Importance of rheology

- Formulation of medicinal and cosmetic creams. pastes and lotion.
- Formulation of emulsion, suspension, suppositories and tablet coatings.
- Fluidity of solutions for injection.
- In mixing and flow of materials, their packaging into containers, their removal prior to use, whether by pouring from a bottle, extrusion from a tube, or passage through a syringe needle.
- Can affect patient acceptability, physical stability, and even biological availability.

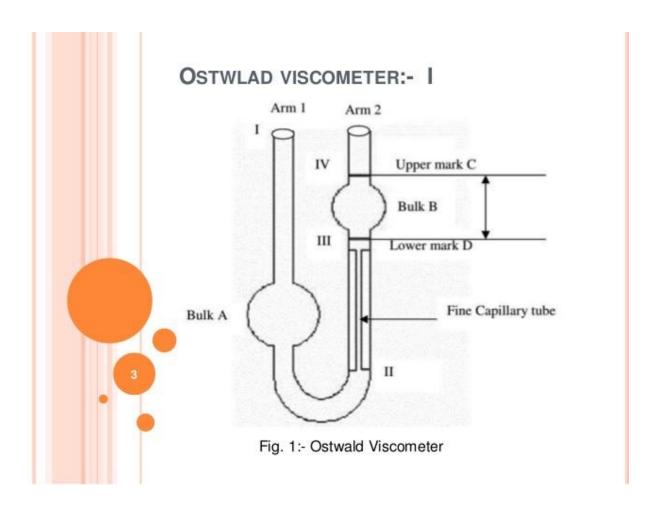
Rheogram



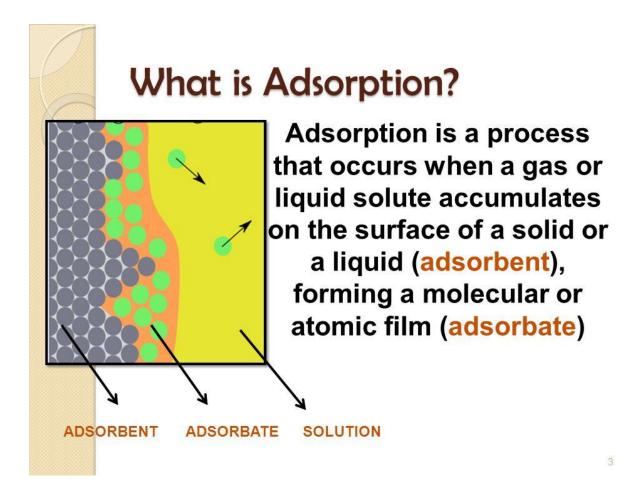
Rheogram: Rheogram is a plot of rate of shear Vs shearing stress. For Newtonian liquid if G is plotted Vs F the flow curve gives straight line passing through the origin and the slope is the coefficient of viscosity and is equivalent to 1

SINK CONDITION

- It is the state in which the concentration in the receptor compartment is maintained at lower level compared to its concentration in the donor compartment
- This can be maintained by connecting receptor compartment to a large reservoir from which solution is reticulated
- It is easy to maintain sink condition than steady state condition due to maintaining constant gradient in donor compartment is difficult



melt evaporate steam solidify condense



Why do metastable phases form?



Ostwald's Step Rule:

The first solid phase to precipitate is most soluble phase (i.e. the least stable, or metastable, phase)

Wilhelm Ostwald (1853 –1932)

- Aragonite instead of calcite
- •SiO₂. x(H₂O) instead of quartz
- •FeS instead of pyrite
- •Ferrihydrite instead of hematite