The Hashemite University

The Faculty of Pharmaceutical Science

Jordan - Zarqa

Laboratory Manual

Course code: 1917011334

Course Name: Physical pharmacy lab

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Preface

There are a lot of rules and guidelines that accompany working in a laboratory, as there are chemicals and equipments that can be dangerous if handled improperly. Thus:

1. Beware of the specific hazards and protect yourself accordingly;
2. Think about the exercises as you are doing them, and learn the techniques and principles behind them;
3. Have fun! A lab is a refreshing change from the class room, where you have an opportunity to observe concepts in action, rather than just being told how they work.

COURSE OBJECTIVES

Upon completion of this laboratory course, the student should be able to perform the following objectives at the specified level:

1. Develop skills and techniques related to the actual use of equipment and instruments.
2. Demonstrate the effect of the physico-chemical properties phenomena on pharmaceutical systems.
3. Clarify theoretical concepts learned in physical pharmacy theoretical courses.
4. Be able to interpret scientific data and represent the data graphically
5. Be able to present and discuss the results and conclusions orally

Laboratory Safety Rules

The following rules are very important for your safety as well as the safety of other students**.**

Please read them carefully and follow them in each laboratory period.

A. Laboratory Safety

- Do not eat, drink or smoke in the laboratory
- Avoid rubbing your eyes during your work unless you know that your hands are clean
- If chemicals come into contact with your eyes or skin, wash immediately with water and consult your instructor
- Know where to find and how to use safety and first-aid equipment
- Learn the location and use of fire protection devices
- When in doubt, treat all chemicals as hazardous, until you get familiar with their properties. Consult the Material Safety Data Sheets (MSDS) or Merck Index or your Lab instructor
- Perform all reactions producing gases or unpleasant odor in the fume hood
- Wear a white lab coat to protect your clothing
- Never taste anything. Never directly smell the source of any vapor
- Never point a test tube during heating toward yourself or your neighbor
- Do not perform any chemical test without being instructed
- In case of an accident notify your instructor immediately
- Clean up all broken glassware immediately
- Always pour acids into water and not vice versa
- Do not use flammable reagents (alcohol, acetone, and others) near open flame
- Do not put a sealed container over any heat source, as it may explode
- If you are not sure how to use something ask your lab instructor
- Observe all special precautions maintained in the experimental procedures
- Do not work alone, always work in the presence of the laboratory instructor

B. Instructions for Laboratory Work:

- Read the experiment carefully before coming to the laboratory
- Perform your experiment with full attention to avoid accidents

Dealing with reagents and chemicals

- Never return any excess material from to the original stock bottle unless advised to do so by the instructor
- Read the warning label or consult the MSDS before using a chemical
- Read the label twice before removing any thing from the bench
- Never exchange the stoppers of different bottles
- Leave reagent bottles on the shelf where you found them
- When weighing, do not place chemicals directly on the balance
- Never return reagents to the reagent bottle. Dispose excess reagent in the waste bottle provided by your instructor
- Use only the amount of reagent specified in the procedure, avoid excesses
- Whenever instructed to use water, always use distilled water unless instructed to do otherwise

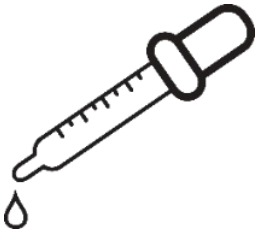
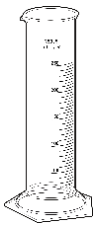
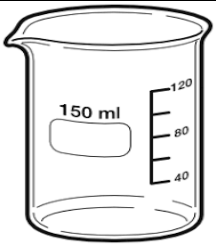
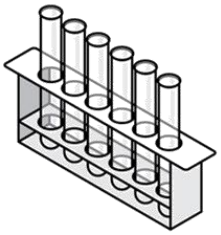
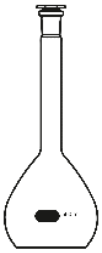
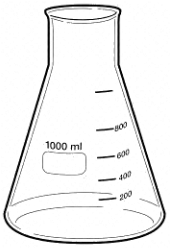
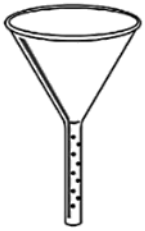
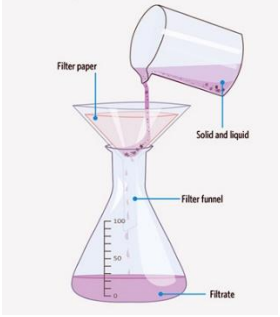
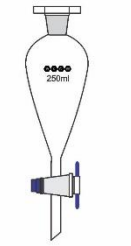
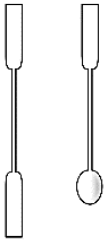
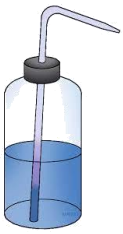
Dealing with wastes

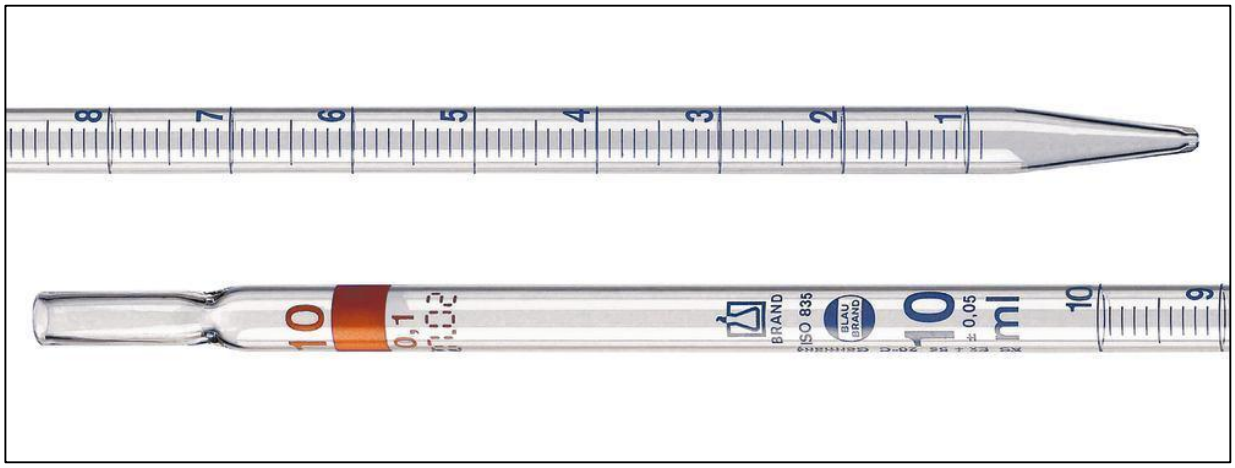
- Throw all solids and paper to be discarded into waste paper basket
- Never throw matches, filter paper, broken glass or any insoluble materials into the sinks.
- When disposing chemicals, avoid accidental mixing of incompatible chemicals such as acids and bases, flammables and toxics, flammables and oxidizers, oxidizers and reducers.

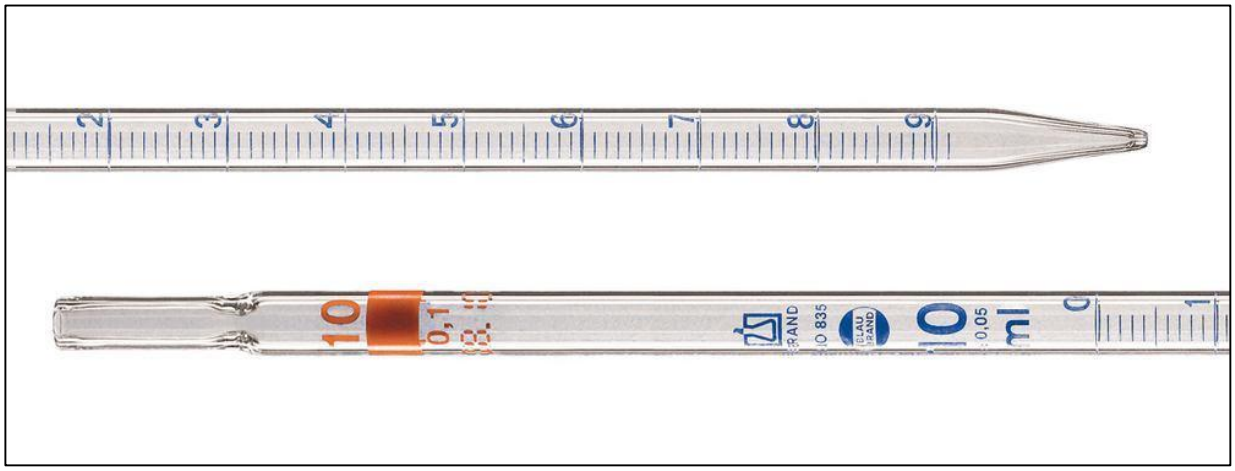
Dealing with the working area

- Keep your area clean
- Do not put hot objects on the desk top. Place them on a wire gauze or heat- resistant pad.
- At the end of each lab. Period leave your glass ware clean and dry on the top of your bench

Commonly used glass wares and lab tools

			
dropper	Graduated cylinder	Beaker	Test tube
			
Volumetric flask	Erlymer flask	funnal	Filtration unit
			
Burrit	Stand	Separatory funnal	Glass rod
			
Spatula	Weighting boat	Wash bottle	Volumetric pipette





Graduated pipette

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Experiment 1

Rheology

Rheology is the study of the flow and deformation of matter under stress. Since Rheo (to flow) and Logos (science), Rheology is the science that concerns with the flow of liquid and the deformation of solids.

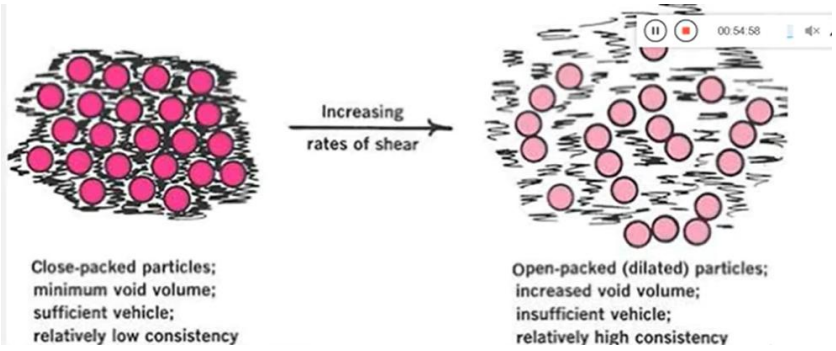
Study of flow properties of liquid is important for pharmacist working in the manufacture of several dosage forms: simple liquid, gel, ointment, cream, and paste. These systems change their flow behavior when exposed to different stress conditions.

Importance of rheology

- Formulation of medicinal and cosmetic creams, pastes and lotion.
- Formulation of emulsions, and suspensions.
- In mixing and flow of materials, their packaging into the containers, their removal prior to use, the pouring from the bottle.
- Passage of the liquid to a syringe needle.
- Can affect the patient's acceptability of the product, physical stability, biologic availability, absorption rate of drugs in the GIT

Rheology concept

- The basic concept of rheology is that of stress and strain or deformation. When a body is subjected to an external stress or force, the body tends to be deformed. If the deformation is temporary and disappears when the stress is removed. It is referred to as flow. The measure of a fluid resistance to flow is termed as its viscosity.

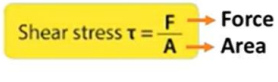


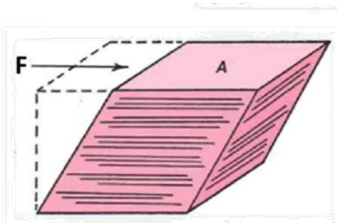
- Such types of deformation and flow include Newtonian (or simple) flow and non-Newtonian (or complex) flow.

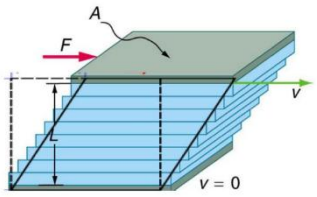
Newton law

Newton was the first to study flow properties of liquids in a quantitative way. He recognized that the higher the viscosity of liquid, the greater is the force per unit area (shearing stress) required to produce a certain rate of shear.

Shear stress is the force divided by area parallel to the surface, F/A. The SI unit is the Pascal, Pa. The effect (shear strain) is quantified by the displacement per unit height (D/H) and the rate of this effect (strain rate) is the velocity per unit height (V/H), where the height is the distance to a relatively unaffected position.



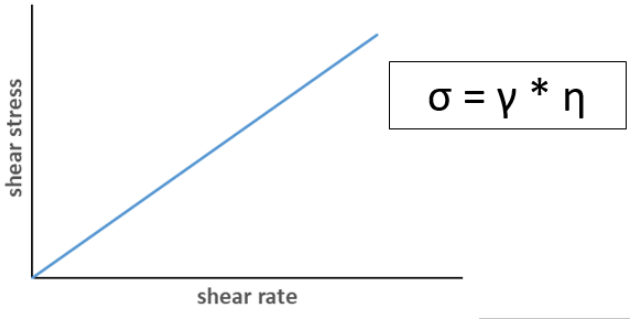




Newtonian flow

- Newtonian flow represents an ideal situation, in which viscous liquids would obey Newton's law of viscous flow, according to which the flow rate depends on the applied stress. These liquids are called Newtonian and include most solvents such as water, alcohol, benzene, true solutions, and very dilute colloidal solutions.

- Newtonian fluids exhibit a straight line relationship between shear stress (σ) and shear rate (γ) and are described in terms of absolute viscosity (η).



The viscosity (η) is the tendency of the fluid to resist flow and is defined by:

$$\eta = \frac{\text{shear stress}}{\text{strain rate}} \quad (\text{Pa s})$$

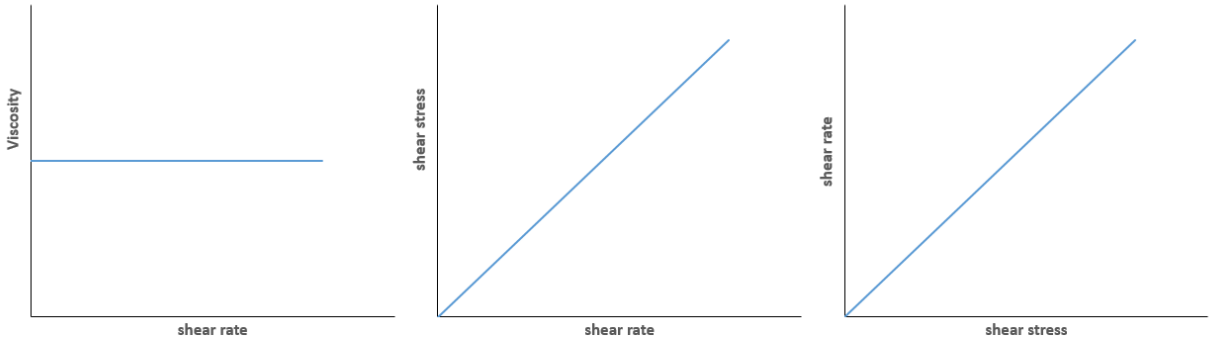
The unit of viscosity:

1. Pa s
2. poise (dyne.sec/cm2 or g/cm.sec)

Since the poise is a large unit, it is often convenient to use the centipoise, cp, (1cp = 0.01 poise) or millipoise, mp,(1 mp = 0.001 poise).

The opposite of viscosity is fluidity which measures the ease of flow and its equal $\frac{1}{\eta}$

Newtonian fluids exhibit the following relationships:



Slop = η

Slop = 1/η

Non Newtonian flow

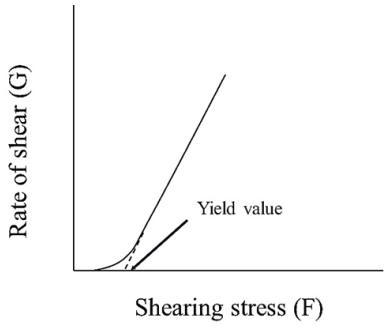
- Other fluids do not obey Newton's law of flow and are referred to as non-Newtonian fluids. These fluids do not exhibit a linear relationship between shear rate and shear stress and are usually described in terms of apparent viscosity.
- In other words when the shear rate is varied, the shear stress is no varied in the same proportion
- It can be seen In liquids and solid heterogeneous dispersions such as emulsions, suspensions, colloids and ointments. However, some Newtonian fluids could behave none linearly at higher concentrations.

Non-Newtonian fluids classified in three type of flow

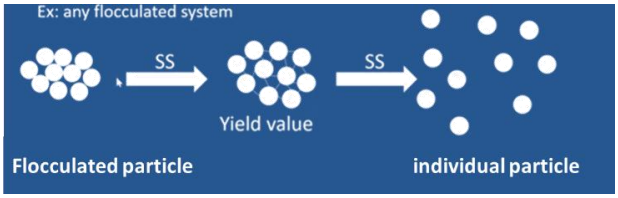
1. plastic flow
2. Pseudo plastic flow " shear thinning"
3. Dilatant " shear thickening"

➢ Plastic flow

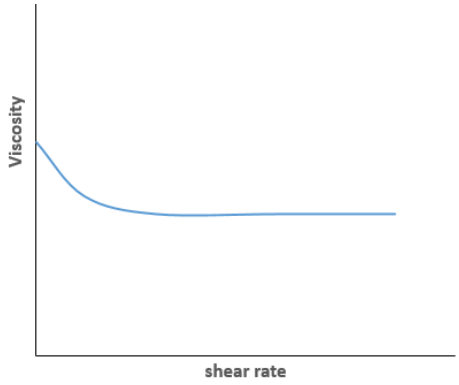
Substances that exhibit plastic flow are called Bingham bodies. Plastic flow does not begin until a shearing stress corresponding to a certain yield value is exceeded. The flow curve intersects the shearing stress axis and does not pass through the origin. The materials are elastic below the yield value.

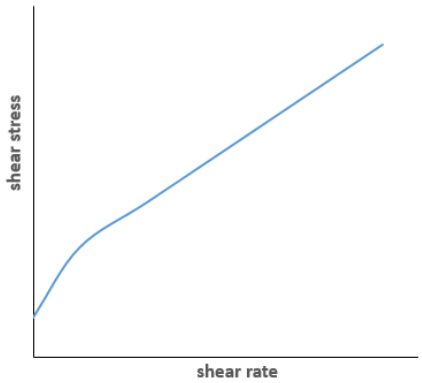


Example: flocculated suspensions, some ointments and pastes



Newtonian fluids exhibit the following relationships:





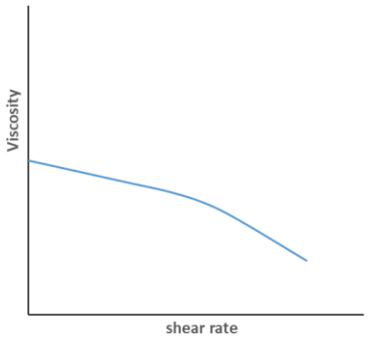
➢ Pseudo plastic flow "shear thinning"

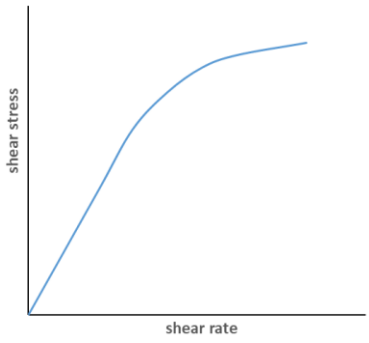
Materials instantaneously decrease in viscosity with increase in shear strain rate (for example, flow) and are therefore easier to pump and mix. They are shear-thinning.

Example: Polymer in water (Tragacan, methyl cellulose, sodium alginate)

This is often a consequence of high molecular weight molecules being untangled and oriented by the flow. Generally, this behavior increases with concentration

Pseudo plastic fluids exhibit the following relationships:

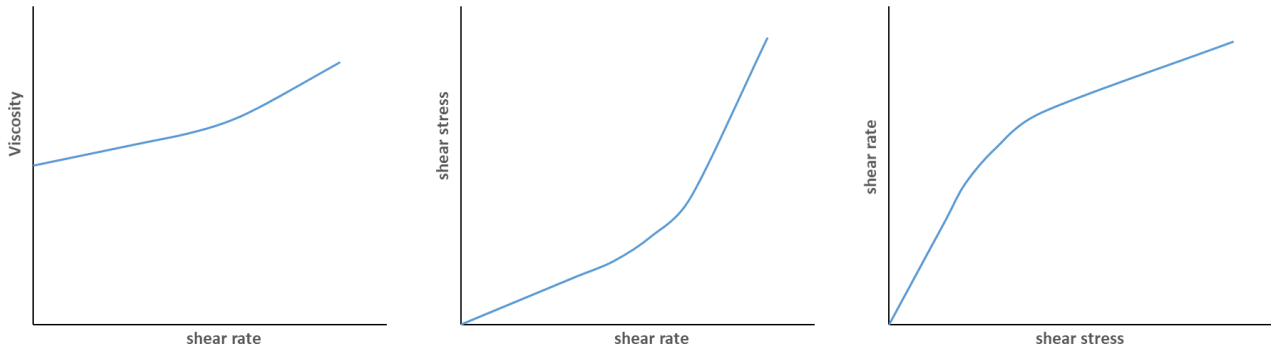




➢ Dilatant flow " shear thickening"

Shows an increase in viscosity with shear stress and strain due to structural enhancement.

An example is corn starch paste where shear stress squeezes the water from between the starch granules allowing them to grind against each other.



Factors affecting viscosity

1. **Temperature:** The viscosity of a liquid usually decreases as the temperature is raised. The opposite effect may, however, occur in certain systems, such as cold starch and block co-polymers.
2. **The shape of particles** of the dispersed phases in colloid dispersion: spherical colloid form dispersion of relatively low viscosity when compared with systems containing linear particles.
3. **Concentration:** as the concentration increases the number of particle of certain substance in a certain volume is also increased these mean higher frictional forces between particles resulting in higher resistance to flow and hence higher viscosity.

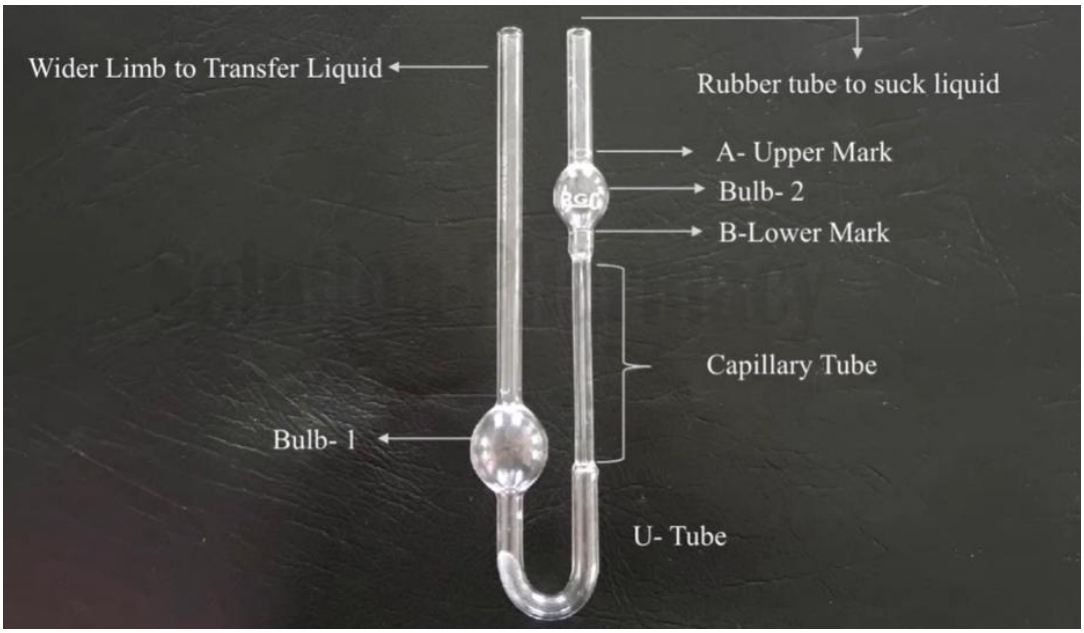
Determination of viscosity

The instruments used to measure the flow properties of fluids are called viscometer or rheometer.

Type	Single point Viscometer	Multi point viscometer
Example	Ostwald viscometer Falling sphere viscometer	Cup and bob viscometer Cone and plate viscometer
Principle	Stress α rate of shear Equipment works at Single rate of shear	Viscosity det. at several rates of shear to get consistency curves
Application	Newtonian flow	non -Newtonian flow Newtonian flow

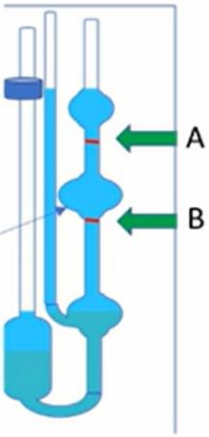
Ostwald viscometer

- simple capillary viscometer (e.g. Ostwald viscometer), determine the flow properties under a single rate of shear and are usually used with Newtonian fluids.
- The Ostwald viscometer has the form of a U-tube.
- Principle: Its use based on measuring the time required for a liquid to flow between two marks. The time of flow of the liquid under test is compared with time required for a liquid of known viscosity (Water).



- Calculation

$$\text{Viscosity}(\eta_s) = \frac{(\eta_w \times \rho_s \times t_s)}{(\rho_w \times t_w)}$$



η_s = Viscosity of given sample

η_w = Viscosity of triple distilled water at given temperature.

ρ_s = Density of given sample at given temperature.

t_s = time required in sec. by sample to cover distance (A to B) on viscometer.

ρ_w = Density of triple distilled water at given temperature.

t_w = time required in sec. by triple distilled water to cover distance (A to B) on viscometer.

Example: viscosity of turpentine oil

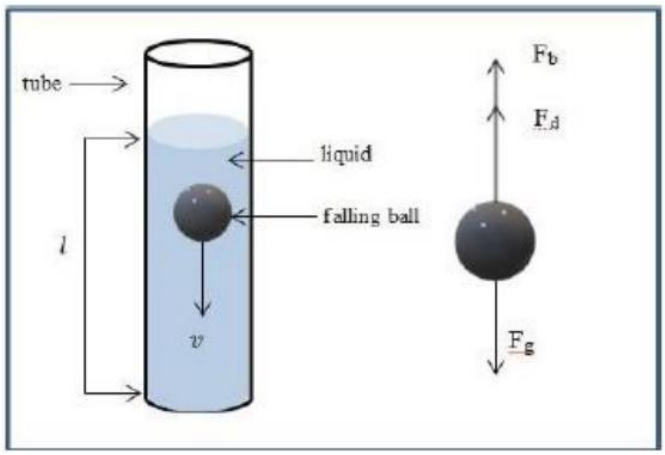
- Viscosity of water at room temperature η1 = 0.8937 cp
- Density of water ρ1= 0.997g/ml
- Density of turpentine oil ρ2= 0.852 g/ml

Liquid sample	Time of Flow (Sec.)			Mean Time (t) (Sec.)	Density (ρ) (g/ml)	Viscosity (η) (Centipoise)
	1	2	3			
Distilled Water	21.94	21.37	21.13	t_1 = 21.48 sec	0.997 g/ml	0.8937 cp
Turpentine oil	26.33	25.91	25.75	t_2 = 25.99 sec	0.852 g/ml	0.9240 cp

$$\eta = \frac{0.8937 \times 0.852 \times 25.99}{0.997 \times 21.48} = 0.9240 \text{ cp}$$

Falling ball viscometers

- Principle: A ball rolls down in vertical glass tube containing the test liquid at a known constant temperature.
- It is shown that there are three forces acting on the ball, these are gravity force , upward floating and the force of viscous (internal) friction .



- The rate (velocity) at which the ball of particular density and diameter falls is an inverse function of viscosity of sample.
- Method:
  1. Place the sphere near the top of the fluid reservoir. Try to get the sphere as close as possible to the air-fluid interface.
  2. Release the sphere and start the stopwatch as soon as the sphere reaches the top line marked on the glass tube and stop it as it reaches the bottom marked line.
  3. As the sphere settles, record its position as a function of time. (it may be more efficient to have one person drop the sphere, one person run the stopwatch, and the third to read the time off the stopwatch).

- Calculations:

$$\eta = \frac{D^2 (\rho_B - \rho_L)\, g}{18\, v}$$

η =viscosity (poise)
D = ball diameter (cm)
ρ_B = ball density (g/ml)
ρ_L= liquid density (g/ml)
g = accelerated gravity (m/s^2)
V= falling ball velocity (m/s)

$$v = \frac{H}{t}$$

H = liquid hight (m)
t = falling time (s)

Ball density calculation →

$$Density = \frac{mass\ (g)}{volume\ (ml)}$$

$$volume = \frac{4}{3}\,\pi\, r^3$$

Example:

- Liquid density = 1.05 g/ml
- Ball diameter = 2.5 cm → r = 1.25 cm
- Ball weight = 9.232 g
- Liquid height = 14 cm = 0.14 m
- Falling time:

time 1 (s)	time 2 (s)	time 3 (s)	Average time (s)
8.03	7.87	8.09	8.00

- Ball density calculation →

$$volume = \frac{4}{3}\,\pi\, r^3$$

$$= \frac{4}{3} \times 3.14 \times 1.25^3$$

$$= 8.18\ cm^3 = 8.18\ ml$$

$$Density = \frac{mass\ (g)}{volume\ (ml)} = \frac{9.232}{1.13} = 1.13\ g/ml$$

- Velocity calculation →

$$v = \frac{H}{t} = \frac{0.14}{8.00} = 0.018\ m/s$$

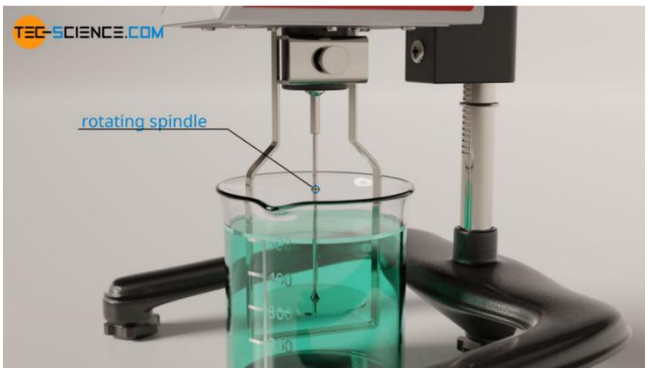
- Viscosity →

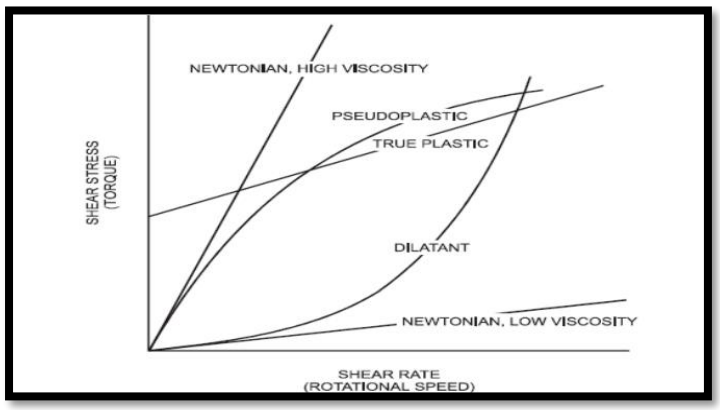
$$\eta = \frac{\boldsymbol{D^2\,(\rho_B - \rho_L)\,g}}{\boldsymbol{18\,v}}$$

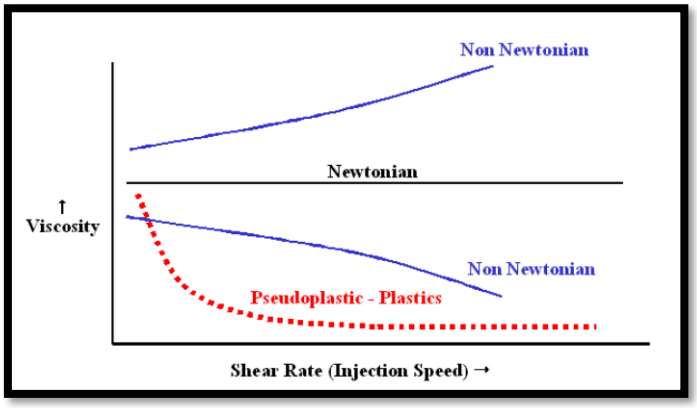
$$\eta = \frac{\boldsymbol{2.5^2 \times (1.13 - 1.05) \times 9.8}}{\boldsymbol{18 \times 0.018}} = 16.11\ poise$$

Rotational viscometer

Multipoint instruments, such as rotational viscometer determine the flow properties under a number of different shear rates.





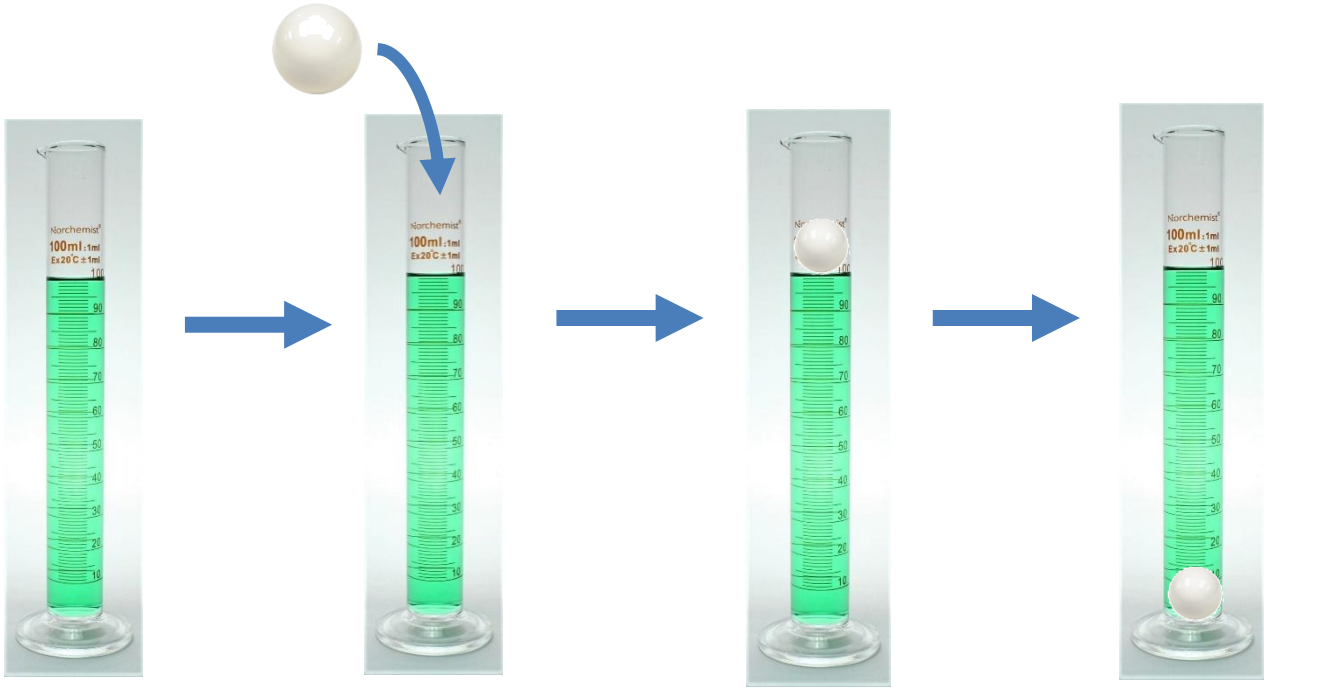


Objective:

To Study the flow properties and calculate the viscosity of different liquids using falling ball method and Ostwald viscometer

Experimental part:

1. Measure the ball weight
2. Place **100 ml** of liquid in a 100 ml graduate cylinder
3. Place the ball near the top of the fluid reservoir. Try to get the sphere as close as possible to the air-fluid interface.
4. Release the ball and start the stopwatch as soon as the ball reaches the top line marked on the glass tube "100 ml mark" and stop it as it reaches the cylinder bottom marked line.
5. As the ball settles, record the falling time in (s)
6. Repeat step (2 to 5) three times for each liquid



Data analysis and calculation:

- Liquid height: 14 cm
- Ball diameter: 25 mm
- Ball weight: ……..
- Ball volume (ml): ……..
- Ball density (g/ml): ……..

Name of the liquid	Liquid density (g/ml)	Time 1 (sec)	Time 2 (sec)	Time 3 (sec)	Average flow time (sec)	Viscosity η (cp)
Water						
20% glycerin						
40% glycerin						
Propylene glycol						

Experiment 2

Determination of partition coefficient

Introduction:

When a liquid or a solid is added to a mixture of two immiscible solvents, it will distribute itself between the two layers in a definite concentration ratio, which is called distribution coefficient (K). If we considering an aqueous (w) and an organic (o) phase, then the partition coefficient (K) would be expressed either as:

$$K=C_w/C_o \quad \text{.....(1)}$$

or as

$$K=C_o/C_w \quad \text{.....(2)}$$

Where C_o and C_w are the concentration of solute in the organic and the aqueous phase, respectively. There has been no convention with regard to whether the concentration in the aqueous phase or in the organic phase should be placed in the numerator. Thus, one should always specify in which of these two ways the distribution coefficient is being expressed. Equation (2) is the most commonly used form, where the concentration in the organic phase is divided by the concentration in the aqueous phase. The above relation is known as the distribution law.

The ratio, in which the solute distributes itself between the two solvents is constant at constant temperatures. In the presence of different solutes, the distribution of each solute usually take place independently of the others. It is also important to mention that the distribution law is strictly applicable in dilute solutions in which the activity coefficients are neglected.

A knowledge of partition coefficient is important in pharmaceutical applications for the principle is involved in several areas of pharmaceutical interest, these include preservation of oil-water system, drug action at non-specific sites, and the absorption and distribution of drugs throughout the body.

Objectives:

To determine the partition coefficient of iodine between aqueous and organic layer.

Experimental part:

Chemicals:

- Saturated solution of iodine in chloroform
- Distilled water
- 2.5% starch mucilage
- 0.05 M and 0.005 M Sodium thiosulfate solution Na2S2O3

Methods:

1. In a 250ml separatory funnel :
   Pipette 10 ml of saturated iodine solution in chloroform and 50 ml distilled water
2. Shake well for 15 minutes.
3. Separate organic layer and aqueous layer each in 100 ml beaker or E.flask.

4. Analyze the content of iodine in the **organic phase** as follows:
   a. Using a pipette, pipette **5.0 ml** of chloroform layer into 100 ml Erlenmeyer flask containing about 25 ml of distilled water.
   b. Titrate with **0.05 M** Na2S2O3 using 1 ml of starch solution as an indicator (added when the end point is near -close to yellow color) until the colorless point.
   c. Calculate the concentration of iodine in the organic phase (Co)

5. Analyze the content of iodine in the **aqueous phase** as follows
   a. Using a pipette or a graduated cylinder, withdraw **25 ml** of the aqueous layer into 100 ml Erlynmeyer flask
   b. Titrate the iodine with **0.005 M** Na2S2O3 until you get a very pale yellow, straw color (just before reaching the end point), then add 1 ml of starch mucilage.
   c. Continue titration until the color disappears completely.
   d. Calculate the concentration of iodine in the aqueous phase (cw).

Data analysis and calculations:

Iodine is distributed between the aqueous phase and the chloroform phase.

The (mls) of sodium thiosulfate consumed in the titration of aqueous and organic solutions is equivalent to the amount of iodine present.

$$I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$$

Then,

Phase	End point (ml)	Conc. I_2 (M)	K(w/o)	K(o/w)
Organic	V_O	C_O		
Aqueous	V_W	C_W		

$$Mole\ S_2O_3^{-2} = 2 \times Mole\ I_2$$

$$M \times V = 2 \times M \times V$$

$$0.05 \times V_O = 2 \times M \times 5$$

$$M = \frac{0.05 \times V_O}{2 \times 5} = C_O$$

$$Mole\ S_2O_3^{-2} = 2 \times Mole\ I_2$$

$$M \times V = 2 \times M \times V$$

$$0.005 \times V_W = 2 \times M \times 25$$

$$M = \frac{0.005 \times V_O}{2 \times 25} = C_W$$

$$K\ (W/O) = \frac{C_W}{C_O}$$

$$K\ (O/W) = \frac{C_O}{C_W}$$

Experiment 3

Surface Tension

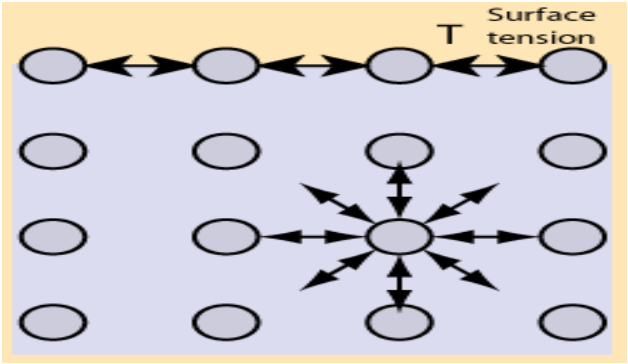
Surface tension: the molecules at the surface of a liquid are much more strongly attracted to their counterparts below or adjacent to them than to air, leading them to experience a net inward drag force into the bulk. This force pulls the surface molecules together contracting the surface and so giving rise to surface tension.

Surface tension can be **defined as** the force per unit length that has to be applied parallel to surface in order to counterbalance the aforementioned pull force. Or, it could be defined as the work (surface free energy increase in this case) per unit increase in surface area required for expanding the area of the liquid surface.

Surface tension is a measurement of the cohesive energy present at an interface. The molecules of a liquid attract each other. The interactions of a molecule in the bulk of a liquid are balanced by an equal attractive force in all directions. Molecules on the surface of a liquid experience an imbalance of forces as indicated below.

The cohesive forces between liquid molecules are responsible for the surface tension. The molecules at the surface do not have other like molecules on all sides of them and consequently they cohere more strongly to those directly associated with them on the surface. This forms a surface "film" which makes it more difficult to move an object through the surface than to move it when it is completely submersed.

The cohesive forces between molecules down into a liquid are shared with all neighboring atoms. Those on the surface have no neighboring atoms above and exhibit stronger attractive forces upon their nearest neighbors on the surface. This enhancement of the intermolecular attractive forces at the surface is called surface tension.

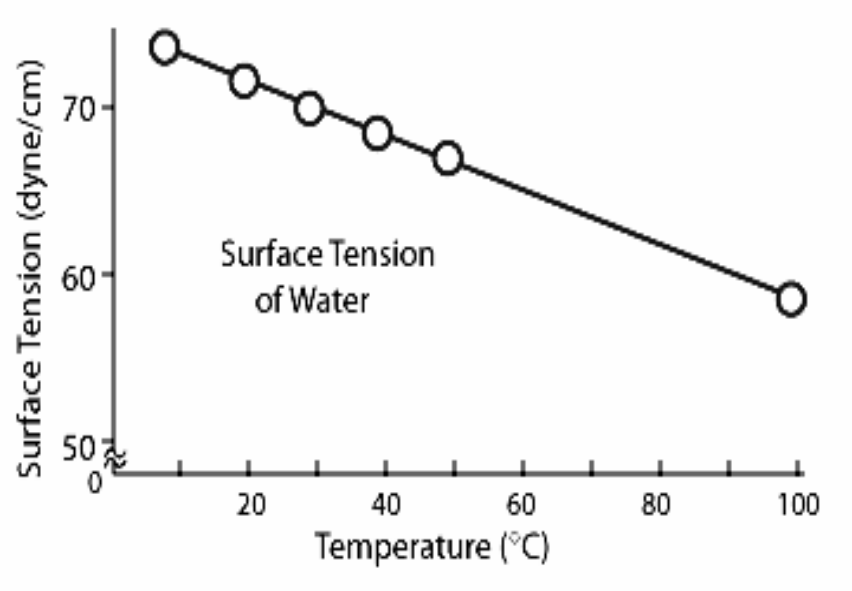


Surface tension is typically measured in dynes/cm, the force in dynes required to break a film of length 1 cm. equivalently, it can be stated as surface energy in ergs per square centimeter. Water at 20°C has a surface tension of 72.8 dynes/cm compared to 22.3 for ethyl alcohol and 465 for mercury.

Substance	**Surface tension Dyne/cm**
water H(OH)	72.7
diethyl ether (CH3-CH2)2O	17.0
benzene C6H6	40.0
glycerin C3H2(OH)3	63
mercury (15°C)	487
n-octane	21.8
sodium chloride solution (6M in water)	82.5
sucrose solution (85% in water)	76.4
sodium oleate (soap) solution in water	25

Surface Tension of Water and effect of temperature on the surface tension

The surface tension of water is 72 dynes/cm at 25°C . It would take a force of 72 dynes to break a surface film of water 1 cm long. The surface tension of water decreases significantly with temperature as shown in the graph. The surface tension arises from the polar nature of the water molecule.



Hot water is a better cleaning agent because the lower surface tension makes it a better "wetting agent" to get into pores and fissures rather than bridging them with surface tension. Soaps and detergents further lower the surface tension

How is surface tension measured?

Surface tension can be measure using force tensiometers or optical tensiomters (also known as contact angle meter or goniometer). Specific technologies such as volumetric tensiometry and bubble tensiometry can also be used.

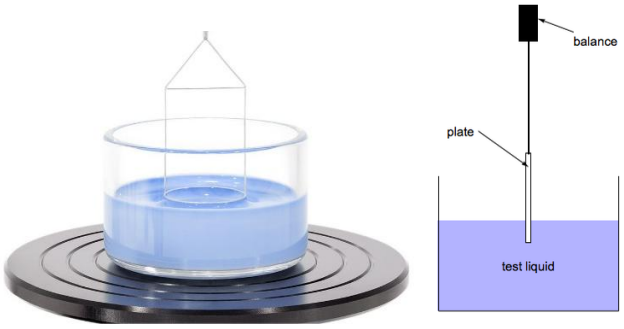
A. Force Tensiometry

The measurement of surface and interfacial tension as performed by a force tensiometer is based on force measurements of the interaction of a probe with the surface of interface of two fluids. In these experiments a probe is hung on a balance and brought into contact with the liquid interface tested. The forces experienced by the balance as the probe interacts with the surface of the liquid can be used to calculate surface tension.

The forces present in this situation depend on the following factors; size and shape of the probe, contact angle of the liquid/solid interaction and surface tension of the liquid. The size and shape of the probe are easily controlled. The contact angle is controlled to be zero (complete wetting).

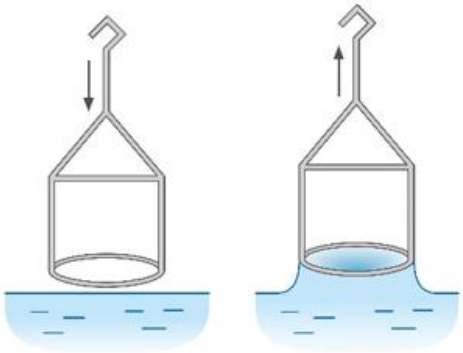
This is achieved by using probes with high energy surfaces. probes are made of a platinum/iridium alloy which insures complete wetting and easy and reliable cleaning.

The mathematical interpretation of the force measurements depends on the shape of the probe used. Two types of probes are commonly used, the **Du Noüy ring** and the **Wilhelmy plate.** A metal rod can also be used to limit the liquid sample volume.

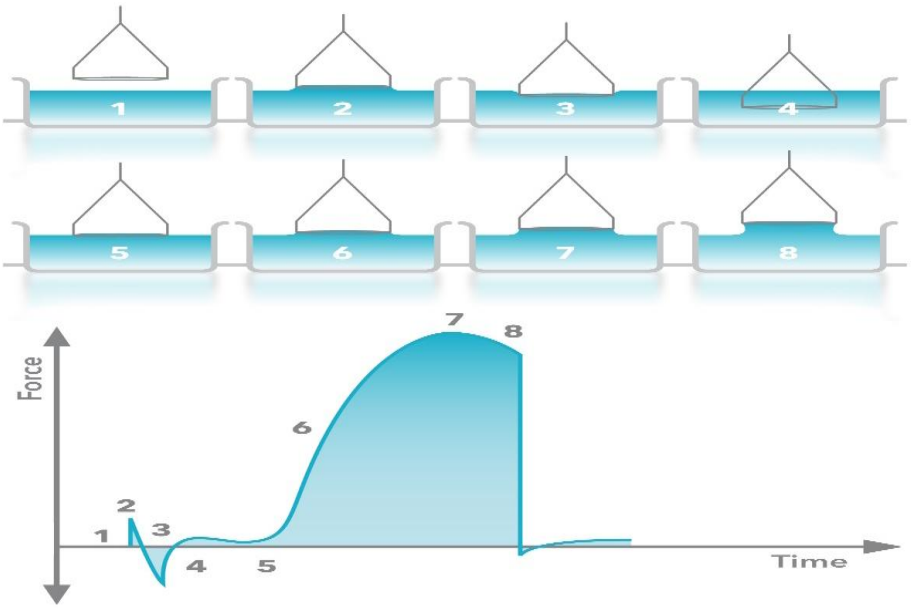


Du Noüy ring

The Du Nouy tensiometer will measure the force required to detach a platinum-iridium ring immersed at the surface which is directly proportional to the surface tension.

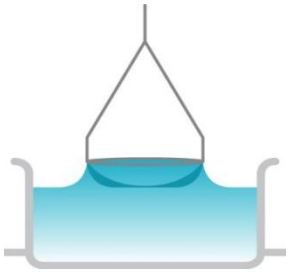


This method utilizes the interaction of a platinum ring with the surface being tested. The ring is submerged below the interface and subsequently raised upwards. As the ring moves upwards it raises a meniscus of the liquid. Eventually this meniscus tears from the ring and returns to its original position. Prior to this event, the volume, and thus the force exerted, of the meniscus passes through a maximum value and begins to diminish prior to the actually tearing event. The process is shown in the diagram below:



1. The ring is above the surface and the force is zeroed.
2. The ring hits the surface and there is a slight positive force due to the adhesive force between ring and surface.
3. The ring must be pushed through the surface (due to the surface tension) which causes a small negative force.
4. The ring breaks through the surface and a small positive force is measured due to the supporting wires of the ring.
5. When lifted through the surface the measured force starts to increase.
6. The force keeps increasing until the maximum force is reached
7. After the maximum there is a small decrease of in the force until the lamella breaks.

The calculation of surface or interfacial tension by this technique is based on the measurement of this maximum force. The depth of immersion of the ring and the level to which it is raised when it experiences the maximum pull are irrelevant to this technique. The original calculations based on the ring technique were based on theories which apply to rings of infinite diameter and do not consider an additional volume of liquid which is raised due to the proximity of one side of the ring to the other. This additional liquid lifted is diagrammed below as the darker turquoise portion:



Basic rule for Du Noüy ring measurements:

- All parts of the apparatus must to be coming in to contact with the liquid to be measured have to be kept meticulously clean since the interfacial tension reacts in a very sensitive way to all kinds of contamination.
- The enrichment of molecule active in the surface or the interface generally takes place very slowly, that is to say the parameter age and temperature. influence the measurements significantly, during any measuring series its therefore essential to maintain constant test condition like temperature.
- The Du Noüy ring is highly sensitive prop which gets useless when deformed (Don't ever touch the ring itself with your fingers it can easily get deformed by even low forces) to handle the ring take the opening between your fingers so that the ring can fall in to the palm of your hand, clean the ring you must rinse it under warm flowing water and D.W

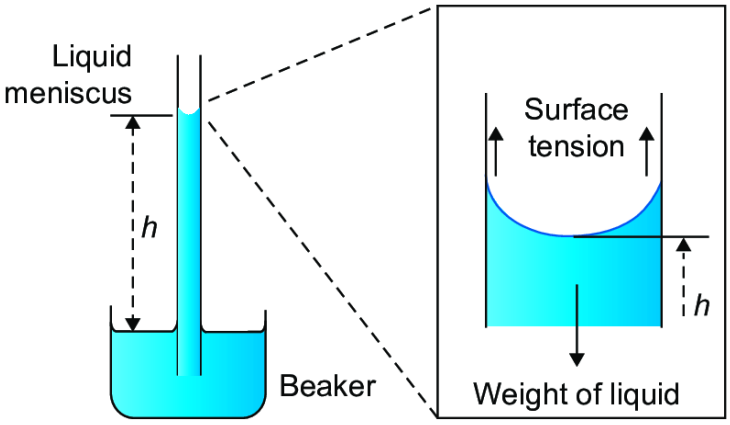
B. Capillary rise method

When a capillary tube is placed in a liquid contained in a beaker, the liquid rises up the tube a certain distance because the liquid molecules and capillary wall is greater than cohesion between liquid molecules.

The liquid continues to rise in the tube due to the surface tension, until the upward movement is balanced by downward force of gravity due to the weight of the liquid.

The best known method for determining surface tension, and one which is capable of considerable accuracy depend on the measurement of the rise of the liquid surface in a capillary tube if the height h to which the liquid ascends is ascertained and the radius r of the tube is known the surface tension can be calculated by means of equation.

Capillary rise method is based on the fact that if the forces of adhesion between the liquid molecules and the glass surface exceed the cohesive forces among the liquid molecules, the liquid will spread over the capillary wall and its surface tension will result in an upward drag force resulting in the liquid level rising through the capillary until this upward force is balanced by the downward gravitational force. That's why water rises and forms a concave surface in glass capillaries. It is clear that the greater the surface tension, the greater is the capillary rise.



Surface tension can be calculated from capillary rise by the following equation:

$$\gamma = 1/2\ r h \rho g$$

Where Ɣ is the surface tension (Dyne/cm)

r is the capillary radius (cm)

p is the density of the liquid (g/ml)

g is the acceleration due to gravity

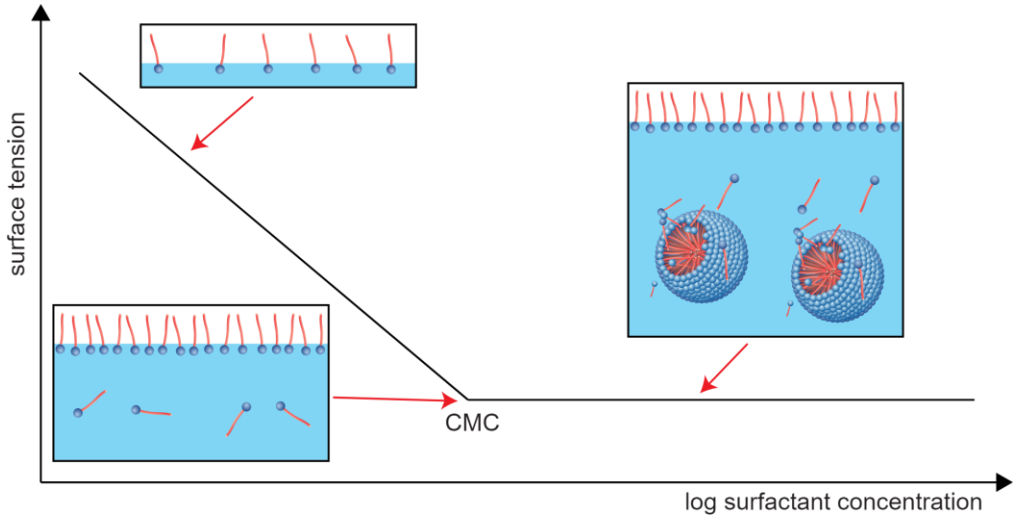
and h is the capillary rise (cm)

(make sure to use the right units)

If the surface tension of any material, like water in our case, is known, and its capillary rise is determined at the same conditions as our solution of interest, then:

$$Ɣ_{solution} / Ɣ_{water} = p_{solution}\ h_{solution} / p_{water}\ h_{water}$$

Upon adding surfactant, the surface tension will decrease as the surfactant molecules accumulate at the surface because the attractive forces between the hydrophobic groups are less than that between water molecules, so that the surface tension of water will be decreased as more surfactant molecules are added to the surface until the CMC is reached. The decrease in surface tension will be linear in relation to the logarithm of surfactant concentration. But, after reaching CMC, most of the added surfactant molecules will go to the micelles in the bulk resulting in a drastically reduced slope of the decrease.



Experimental part:

- **Part 1: Du Nouy tensiometer demonstration**
- **Part 2: Capillary rise method**

Materials and equipment:

Capillary tubes, beakers, graduated ruler, rubber band, v. pipette, pipette filler, volumetric flasks 50 ml, graduated cylinder 25 ml.

Procedure:

1. Prepare the following concentrations of sodium lauryl sulfate solutions: 0 mM, 1mM, 2 mM, 4 mM, 6 mM, 8 mM, 10 mM
2. Clean the ruler very well with distilled and dry it very well.
3. Attach a perfectly clean capillary to the ruler using a rubber band.
4. Place the capillary attached to the ruler in a 50 ml beaker containing 25 ml of the liquid.
5. Measure the **difference** in height **(h)** between the liquid surface in the beaker **($h_{surface}$)** and the capillary **($h_{Capillary}$)** and record it.
6. Repeat for the other solutions.
7. Estimate the density of each solution by measuring the weight of a 10 ml volumetric flask before and after filling it with the solution.
8. Arrange your results in the following table

Data analysis and calculation:

concentraction mM	Log Concentration	Weight (g)	Volume (ml)	Density (g/ml)	h surface (cm)	h Capillary (cm)	Height (cm)	Radius (cm)	Calculated Surface tension (Dyne/cm)
0			10						
1			10						
2			10						
4			10						
6			10						
8			10						
10			10						

$= \log Concentration$

$Density = \frac{weight}{volume}$

$= h\ Capillary - h\ Surface$

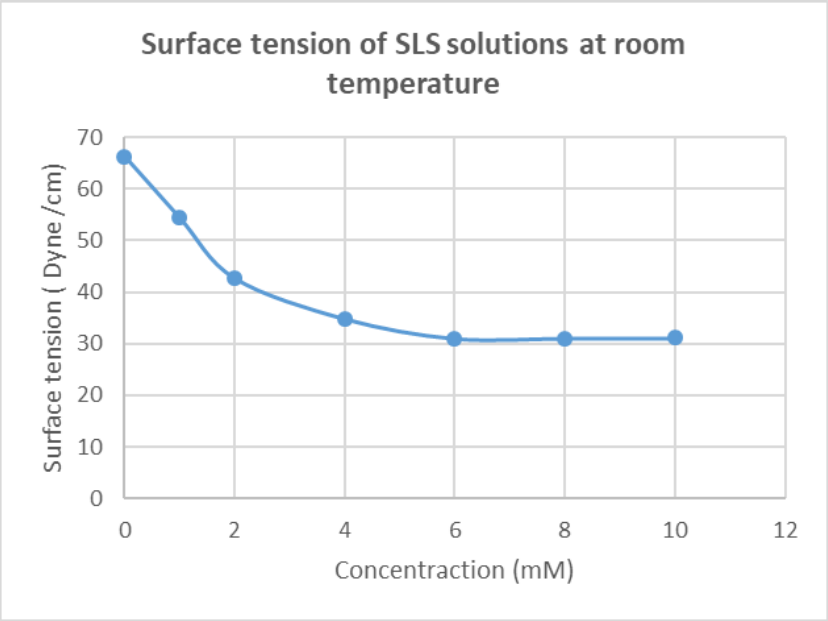
$= \frac{Capillary\ tube\ internal\ Diameter}{2}$

$= \frac{1}{2} \times raduis \times hight \times density \times Gravitational\ acceleration$

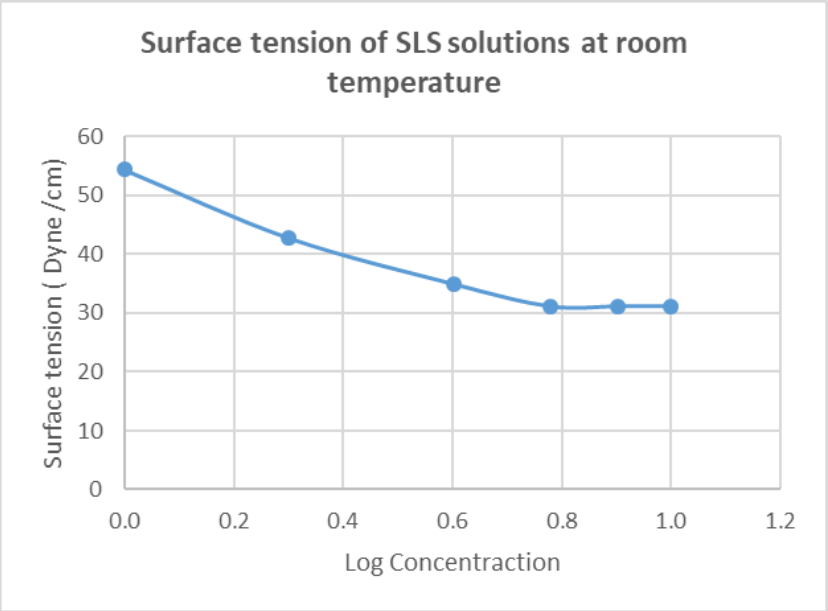
$= \frac{1}{2} \times r \times h \times \rho \times 980$

SLS concentration	Density measurements		Height measurements		
	Volume (ml)	Weight (g)	h surface (cm)	h Capillary (cm)	h (cm)
0					
1					
2					
4					
6					
8					
10					

- ***Plot surface tension Vs. surfactant concentration***



- ***Plot surface tension Vs. log surfactant concentration and determine the CMC value of SLS***



Experiment 4

Preparation of buffers and effect of pH on drug solubility

Background

When a solute dissolve in a solvent the solute–solute forces and the solvent–solvent forces break to achieve the solute–solvent attraction.

The **solubility** of an agent in a particular solvent indicates the maximum concentration to which a solution may be prepared with that agent and that solvent. When a solvent at a given temperature has dissolved all of the solute possible, it is said to be **saturated solubility.**

Remember, the solubility is expressed in any concentration unit, for example g/ml (grams of solute dissolving in milliliters of solvent).

Enhancement of solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development, nearly 40% of the new chemical entities currently being discovered are poorly water soluble drugs. Aqueous solubility of any therapeutically active substance is a key property as it governs dissolution, absorption and thus the in vivo efficacy. Orally administered drugs completely absorb only when they show fair solubility in gastric medium and such drugs shows good bioavailability. The solubility and dissolution properties of drugs play an important role in the process of formulation development. Problem of solubility is a major challenge for formulation scientist which can be solved by different technological approaches during the pharmaceutical product development work.

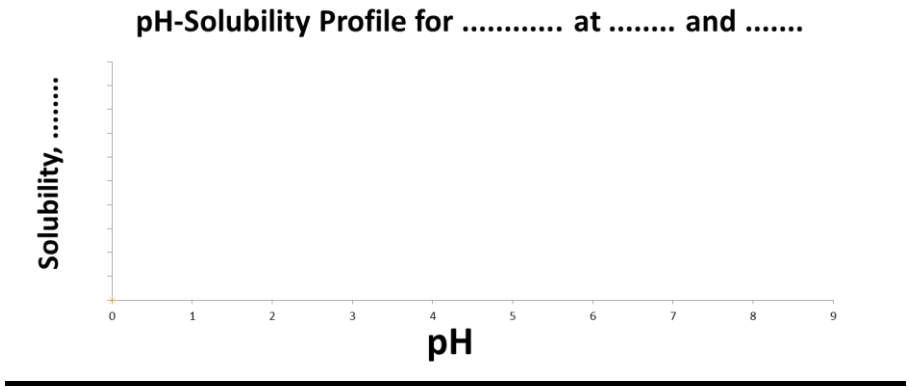
Objectives

The objective of this lab is to evaluate an approaches to solubilize a weakly acidic drug (Salicylic acid).

pH-solubility profile: the solubility will be checked in different buffer systems. For this purpose, different buffers with different pH values will be prepared and the drug solubility will be determined in the different buffers.

pH-Solubility Profile of salicylic Acid

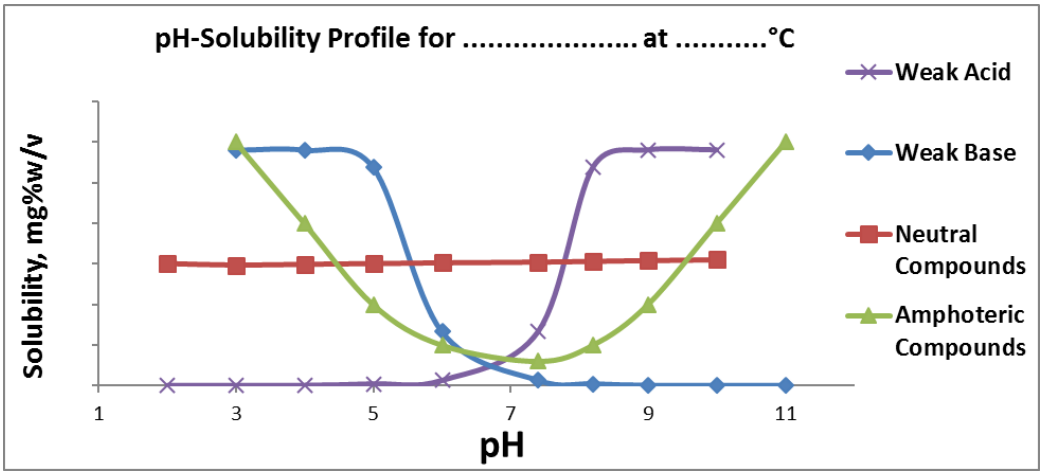
Is plotted as solubility (using any suitable solubility expression) versus pH (using the correct pH range for each studied material/drug).



Drugs are either:

1. Weak Acids (have functionalities like Carboxylic, Imide, Sulfonamides, Phosphate groups), e.g. Mefenamic acid, Salicylic Acid, and Ibuprofen.
2. Weak Bases (have functionalities like Amine group), e.g. Tetracycline.
3. Neutral, e.g. Paracetamol.
4. Amphoteric contains both acidic & basic groups (--COOH & --NH2), e.g. Ciprofloxacin.

The following plot represent the pH-solubility profile for each of the above classes. (Hint: soluble when ionized, in which medium/media would each class be ionized?)



Buffer and buffer calculation:

A **buffer solution** is an aqueous solution consisting of a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid. It has the property that the pH of the solution changes very little when a small amount of strong acid or base is added to it. Buffer solutions are used as a means of keeping pH at a nearly constant value in a wide variety of chemical applications as well as many life forms succeed only in a relatively small pH range. For example, blood is a buffer solution at pH 7.4.

A compound can buffer the pH of a solution only when its concentration is sufficient and when the pH of the solution is close (within about one pH unit) to its pK_a. To make a buffer you must first pick a compound whose pK_a is close to the pH you want for the solution, and then decide what the buffer concentration should be. Typically, buffer concentrations are between 1 mM and 200 mM, depending on the desired ionic strength and the buffering capacity required. If the pH is expected to decrease during the experiment, choose a buffer with a pK_a slightly below the working pH. Conversely, if the pH is expected to increase during the experiment, select a buffer with a pK_a slightly above the working pH. Having decided on the total buffer concentration, you must adjust the ratio of the protonated and unprotonated forms of the buffer in your solution soas to give the desired pH. Typically, buffers are composed of weak acids and their salts, or weak bases and their salts. If the protonated form is uncharged, it is an acid (like acetic acid), and its unprotonated form is a salt (e.g., sodium acetate). Conversely, if theunprotonated form is uncharged it is a base (like Tris-base), and its protonated form is a salt (e.g., TrisHCl).

<u>Two practical ways to make a buffer are described below:</u>

A. **The Slow and Stupid Method -** To avoid adding extra salt to a solution, prepare a buffer composed of an acid and its salt by dissolving the acid form of the buffer in about ~60% of the water required for the final solution volume. Adjust the pH using a strong base, such as NaOH. When preparing a buffer composed of a base and its salt, start with the base form and adjust the pH with strong acid, such as HCl. After the pH is correct, dilute to just under the final solution volume. Check the pH and correct if necessary, then add water to the final volume.

Advantages: Easy to understand.

Disadvantages: Slow, may require lots of base (or acid), If the base (or acid) is concentrated, it

is easy to overshoot the pH, If the base (or acid) is dilute; it is easy to overshoot the volume, Ionic strength will be unknown, adding a strong acid or base can result in temperature changes, which will make pH readings inaccurate (due to itsdependence on temperature) unless the solution is brought back to its initial temperature.

B. **The Mentally Taxing Method -** Using the buffer pK_a, calculate the amounts (in moles) of acid/salt or base/salt present in the buffer at the desired pH. If both forms (i.e., the acid and the salt) are available, convert the amount required from moles to grams, using the molecular weight of that component, and then weigh out the correct amountsof both forms. Decide what the total concentration of buffer will be in the solution, and convert the concentration to amount (in moles) using the volume of solution, and then to grams, using the molecular weight of the buffer form available. Then calculate the amounts (in moles) of each form that will be present in the final solution, using the buffer pK_a and the desired pH.

Advantages: Fast, Easy to prepare, Additional pH adjustment is rarely necessary, and when necessary, the adjustment is small. Ionic strength easily calculated.

Disadvantages: Requires the buffer pK_a and solving two equations.

The following is further illustration on how to prepare a buffer according to the Mentally Taxing Method

1. Decide on the Buffer Properties

Before making a buffer, you must know what molarity you want it to be, what volume to make and what the desired pH is. Most buffers work best at concentrations between 0.1 M and 10 M. The pH should be within 1 pH unit of the acid/ conjugate base pKa. For simplicity, this sample calculation will be for 1 L of buffer. The following table (Table 1) shows some of acid-base conjugates and their pKa value. If you need a buffer of pH 5 you can use acetic acid and sodium acetate or benzoic acid and sodium benzoate. If youneed a pH of 3.5 you can use citric acid and sodium citrate (mono). If you need a pH of 7.4 you can use $H_2PO_4^-$ (di-hydrogen phosphate such as potassium phosphate monobasic) HPO_4^{-2} (hydrogen phosphate such as potassium phosphate

dibasic).

Table 1: Weak Acids, K_a, and pK_a values

Acid	HA	A^-	K_a	pK_a
Acetic	CH_3COOH	CH_3COO^-	$1.74 * 10^{-5}$	4.76
Ammonium	NH_4^+	NH_3	$5.60 * 10^{-10}$	9.25
Benzoic	C_6H_5COOH	$C_6H_5COO^-$	$6.46 * 10^{-5}$	4.19
Carbonic	H_2CO_3	HCO_3^-	$4.30 * 10^{-7}$	6.37
	HCO_3^-	CO_3^{-2}	$4.80 * 10^{-11}$	10.32
Chloroacetic	$CH_2ClCOOH$	CH_2ClCOO^-	$1.40 * 10^{-3}$	2.85
Citric	$C_6O_7H_8$	$C_6O_7H_7^-$	$7.41 * 10^{-4}$	3.13
	$C_6O_7H_7^-$	$C_6O_7H_6^{-2}$	$1.74 * 10^{-5}$	4.76
	$C_6O_7H_6^{-2}$	$C_6O_7H_5^{-3}$	$3.98 * 10^{-7}$	6.40
Formic	$HCOOH$	$HCOO^-$	$1.77 * 10^{-4}$	3.75
Phosphoric	H_3PO_4	$H_2PO_4^-$	$7.52 * 10^{-3}$	2.12
	$H_2PO_4^-$	HPO_4^{-2}	$6.23 * 10^{-8}$	7.21
	HPO_4^{-2}	PO_4^{-3}	$2.20 * 10^{-13}$	12.00

2. Determine the Ratio of Acid to Base

Use the Henderson-Hasselbalch equation to determine what ratio of acid to base is required to make a buffer of the desired pH. Use the pKa value nearest your desired pH and the ratio will refer to the acid-base conjugate pair that corresponds to that pKa.

Example:

Prepare 500 mL of a 0.1 M buffer solution with a pH of 5.0 using acetic acid and sodiumacetate.

Solution:

The Mass Method will be used here. The conjugate acid-base pair to be used is acetic acid, $C_2H_3CO_2H$ and acetate ion, $C_2H_3CO_2^-$, to be represented as HA and A^-, respectively. From the Henderson-Hasselbach Equation we have:

$$\text{pH} = pK_a + Log\frac{[A^-]}{[HA]}$$

$$Log\frac{[A^-]}{[HA]} = pH - pK_a$$

where, pKa is the pKa of the conjugate acid , acetic acid, in this case. Therefore:

pKa = - Log($1.74 * 10^{-5}$) = 4.76

And now, substitution into the equation above gives:

$$Log\frac{[A^-]}{[HA]} = 5.00 - 4.76 = 0.24$$

$$\Downarrow$$

$$\frac{[A^-]}{[HA]} = 10^{0.24} = 1.738$$

We must prepare a solution with this ratio of concentrations. Note that this is also a moleratio:

$$\frac{n_{A-}}{n_{HA}} = 1.738$$

The total concentration of conjugate acid and conjugate base is 0.10 M. Therefore:

$$\frac{n_{A-} + n_{HA}}{0.500\ L} = 0.10\ M$$

and from the previous equation:

$$n_{A-} = 1.738 * n_{HA}$$

this lead us to:

$$\frac{1.738 * n_{HA} + n_{HA}}{0.500\ L} = 0.10\ M$$

$$\Downarrow$$

$$2.738 * n_{HA} = 0.050\ M$$

solving for nHA gives:

$$n_{HA} = 0.0183\ moles$$

and

$$n_{A-} = 0.0183 * 1.738 = 0.0317\ moles$$

In this case, nHA and nA- are the moles of acetic acid and acetate ion, respectively, that must be added to 500 mL of solution. Note that although the conjugate base is acetate ion, it must be weighed out as sodium acetate.

The molar masses of acetic acid and sodium acetate are 60.05 g mol^{-1} and 82.03 g mol^{-1}, respectively. The masses of acetic acid and sodium acetate that mustbe dissolved in 500 mL of solution are:

Mass of Acetic Acid = 0.0183 mol * 60.05 g mol^{-1} = 1.0970

gm Mass of Sodium Acetate = 0.0317 mol * 82.03 g mol^{-1}

= 2.6040 gm

The procedure for preparing this buffer solution is to add the above masses of acetic acid and sodium acetate to a 500 mL volumetric flask and diluting to the mark with de-ionized water.

Buffer capacity

Buffer capacity is the quantity of strong acid or base that can be added to change the pH of one liter of buffer solution by one pH unit

Buffer Capacity (β) can be calculated by the following equation:

$$\beta = 2.3C\frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2}$$

C: is the total buffer concentration (the sum of the molar concentrations of the acid and the salt), [H3O+] can be calculated from the pH of solution**.**

Practical part

First:

make your calculations to make 100 ml (0.1 M) of the following buffers (Justify the type of buffers used and determine the type of HA and A^- to be used).

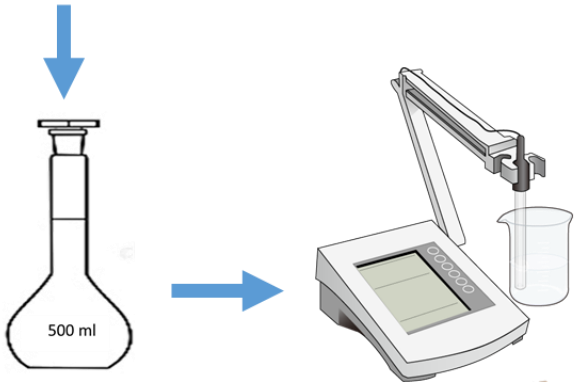
pH	Buffer type	HA (g)	A^- (g)
3.0	**Citrate**		
4.0	**Citrate**		
5.0	**Acetate**		
6.2	**Phosphate**		
7.4	**Phosphate**		
8.2	**Phosphate**		

Second:

1. Into glass bottles add 50 mL of each buffer
2. Add an amount of Ibuprofen to each bottle (1g)
3. Put the bottles on a shaker and observe the bottles for excess drug and ifneeded add more solid drug
4. Filter the mixtures then make suitable dilution with 0.1 M NaOH and measure the UV absorbance at 222.4 nm. Make further dilution with 0.1 M NaOH if needed." As seen in the following chart"
5. Convert the absorbance value to concentration using calibration curve equation and then calculate the solubility
6. Plot the solubility versus buffer pH
7. Comment on the obtained plot

Part 1
Buffer preparation

Dissolve the required amount of HA and A^- in 500 ml distill water.



Measure the PH of the solution

Adjust the pH with 0.1 M HCl or 0.1 M NaOH if required

Volume = 500 mL, Concentration = 0.100 Molar

pH	Amount, grams	
	Citric acid	Sodium citrate
3	5.516	4.557

pH	Volume, ml	Amount, grams
	Acetic acid	Sodium acetate
4	2.44	1.007
5	1.04	4.319

pH	Amount, grams	
	Potassium dihydrogen phosphate	Di-potassium hydrogen phosphate
6.2	6.199	1.016
7.4	2.670	6.934
8.2	0.632	10.352

Part 2
Solubility study

50 ml buffer

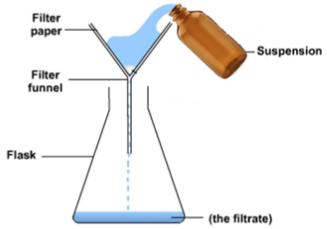
+

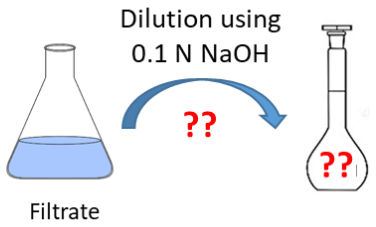
1 g Ibuprofen

Repeat the same step using different type of buffer

Put the bottles on a shaker for 24 hour

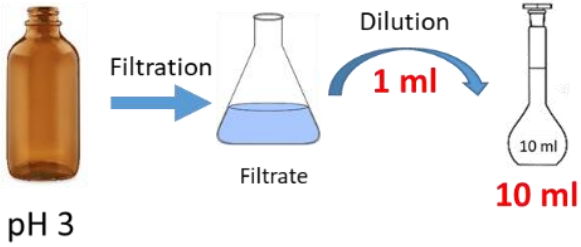
Part 3
Sample analysis

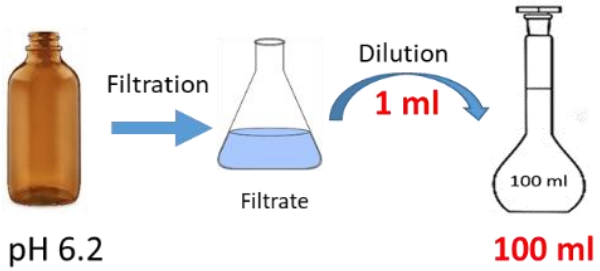


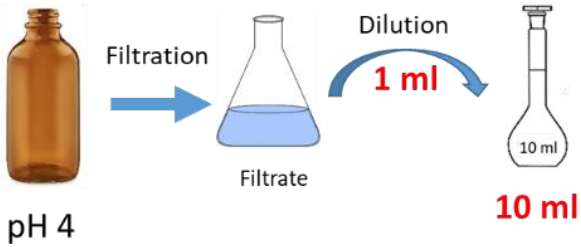


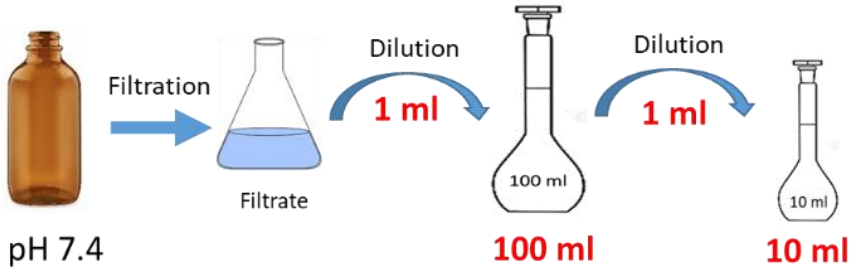
AS seen in next page

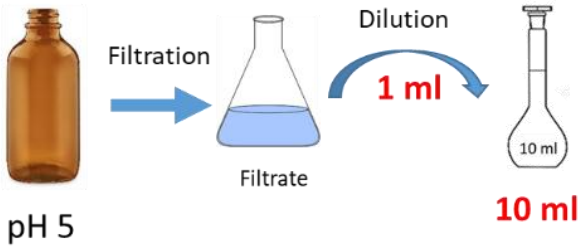
Measure the absorbance of your samples using UV spectrophotometer at 222.4 nm using 0.1 N NaOH as a blank

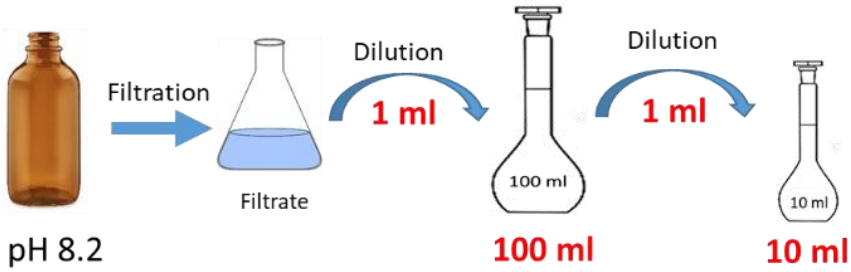

Filtration
Filtrate
Dilution
1 ml
10 ml
10 ml
pH 3


Filtration
Filtrate
Dilution
1 ml
100 ml
pH 6.2
100 ml


Filtration
Filtrate
Dilution
1 ml
10 ml
10 ml
pH 4


Filtration
Filtrate
Dilution
1 ml
100 ml
Dilution
1 ml
10 ml
pH 7.4
100 ml
10 ml


Filtration
Filtrate
Dilution
1 ml
10 ml
10 ml
pH 5

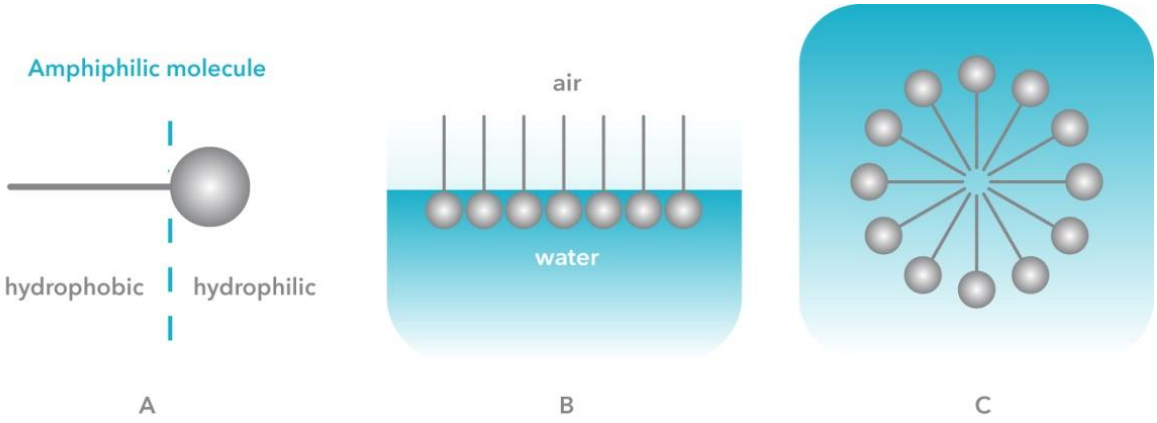

Filtration
Filtrate
Dilution
1 ml
100 ml
Dilution
1 ml
10 ml
pH 8.2
100 ml
10 ml

Experiment 5

Solubility: Effect of surfactant

Introduction:

Certain molecules may be said to contain two distinct components, differing in their affinity for solutes. The part of the molecule which has an affinity for polar solutes, such as water, is said to be hydrophilic. The part of the molecule which has an affinity for non-polar solutes, such as hydrocarbons, is said to be hydrophobic. Molecules containing both types of components are said to be amphiphilic (illustration A).

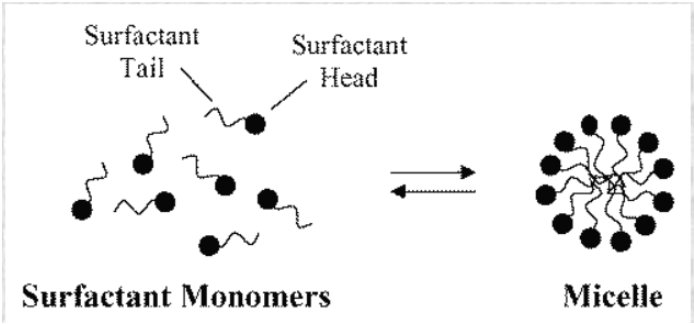


Such molecules display distinct behavior when interacting with water. The polar part of the molecule seeks to interact with water while the non-polar part shuns interaction with water. There are two ways in which such a molecule achieve both these states. An amphiphilic molecule can arrange itself at the surface of the water such that the polar part interacts with the water and the non-polar part is held above the surface (either in the air or in a non-polar liquid) as shown in **Figure B** above. The presence of these molecules on the surface disrupts the cohesive energy at the surface and thus lowers the surface tension. Such molecules are called **'surface active' molecules or surfactants**.

Another arrangement of these molecules can allow each component to interact with its favored environment. Molecules can form aggregates in which the hydrophobic portions are oriented within the cluster and the hydrophilic portions are exposed to the solvent. Such aggregates are called **micelles**. An example of a spherical micelle is diagrammed above (illustration C).

The proportion of molecules present at the surface or as micelles in the bulk of the liquid depends on the concentration of the amphiphile. At **low concentrations** surfactants will favor arrangement on the surface. As the surface becomes crowded with surfactant more molecules will arrange into micelles. At some concentration the surface becomes completely loaded with surfactant and any further additions must arrange as micelles. This concentration is called the **Critical Micelle Concentration (CMC).**

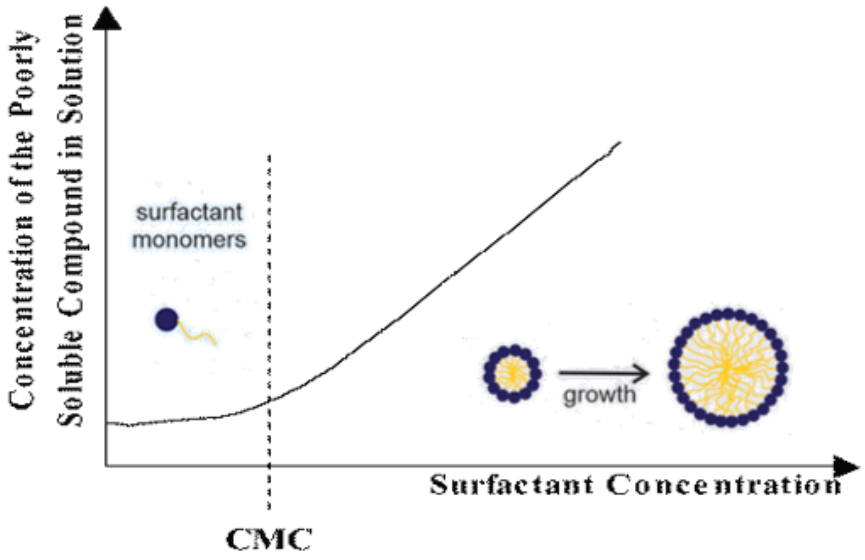
Surface-active agents (surfactants) form micelles in aqueous solution above a critical concentration called the critical micelle concentration (CMC). Since the surfactant molecules would much rather live at an interface than be in either solution alone, when the interface is saturated, the surfactant molecules create more interface by increasing the surface area real estate by creating micelles. In aqueous solution, the micelle has a hydrophobic core and a dielectric gradient towards the surface of the micelle making the micelle surface hydrophilic.



Thus, the micelle can act as a soluble phase for non-polar solutes (core), semi-polar solutes (palisade layers) and polar solutes (surface). As a result, the efficiency of a particular surfactant as a solubilizing agent varies from substance to substance. The process of increasing the water solubility of a solute (drug) using a surfactant is called micellar solubilization.

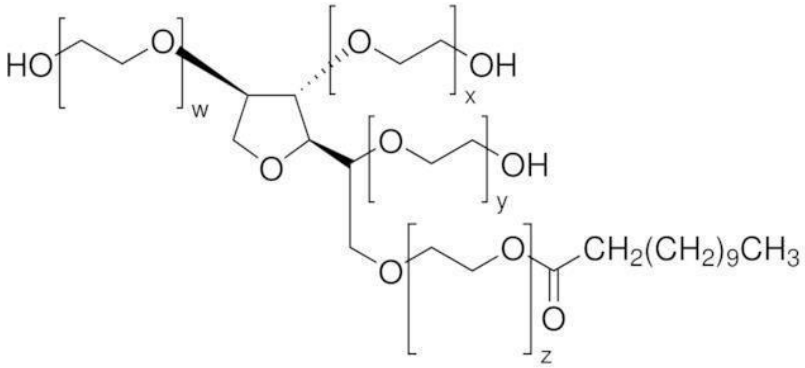
The solubilizing power of water surfactant solutions is of great importance in the preparation of dosage forms containing sparingly soluble drug. The factors affecting micellar solubilization are many and their interrelationship is complex. In general, the degree of solubilization is a function of the physiochemical properties of the surfactant and solubilizate.

If we plot the solubility of a poorly soluble compound as a function of the concentration of surfactant, usually what happens is that the solubility is very low until the surfactant concentration reaches the CMC. At surfactant concentrations above the CMC the solubility increases linearly with the concentration of surfactant, indicating that solubilization is related to micellization.



Objective:

In this experiment, the effect of surfactant on the solubility of undissociated salicylic acid will be investigated. The surfactant used will be nonionic – Tween 20 (polyoxyethelene (20) sorbitan monopalmitate).



Experimental part:

1. Prepare 100 ml of the following tween 20 solution

   (0%w/v, 0.5%w/v, 1.0 %w/v, 1.5%w/v, 3.0% w/v, 5.0%w/v)

   (use equation $c_1v_1=c_2v_2$ to prepare the above tween 20 solutions using Tween 20 solution at 20%w/v)

2. Add few drops of 0.1 M HCL to each sample to ensure that the salicylic acid remains undissociated in solution.

3. Prepare saturated salicylic acid in tween 20 solution:

   Add 1.0 g of salicylic acid to100 ml of prepared solution in step 1 in stoppered bottle and shake them using a shaker for 24 hours.

4. Take sample from your instructor from the following concentration

   (0%w/v ,0.5%w/v, 1.0 %w/v, 1.5%w/v ,3.0% w/v, 5.0%w/v) tween 20 solution

5. Take 20 ml sample of the supersaturated solution using cylinder and filter sample using funnel in Erlenmeyer flask.

6. Take 10 ml of the filtrate using graduated pipette in 100 ml Erlenmyer flask

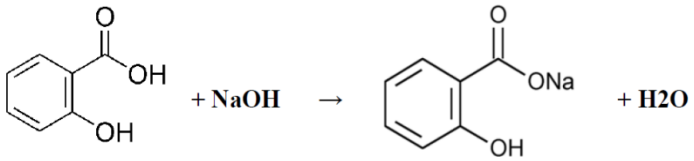
7. Titrate with 0.05 M NaOH using 2 drops of phenolphthalein solution as indicator.

8. Record the end point

Data analysis and calculation:

Calculate solubility in (% w/v):

The following equation represent the interaction between salicylic acid and NaOH :



Then,

Example:

Tween 20 (% w/v)	Volume of 0.05M NaOH (ml) (End point)	Concentration mmole	Concentration (mg/ml)	Solubility (%w/v)
0	1.5			
0.5				
1.0				
1.5				
3.0				
5.0				

mmole salicylic acid = mmole NaOH

mmole Salicylic acid = M × Volume in ml

= 0.05 * end point

= 0.05 × 1.5

= 0.075 mmol

$$= \frac{\text{mmole Salicylic acid} \times \text{MWT}}{Volume\ in\ ml}$$

$$= \frac{0.075 \times 138.1\ \text{g/mole}}{10\ ml}$$

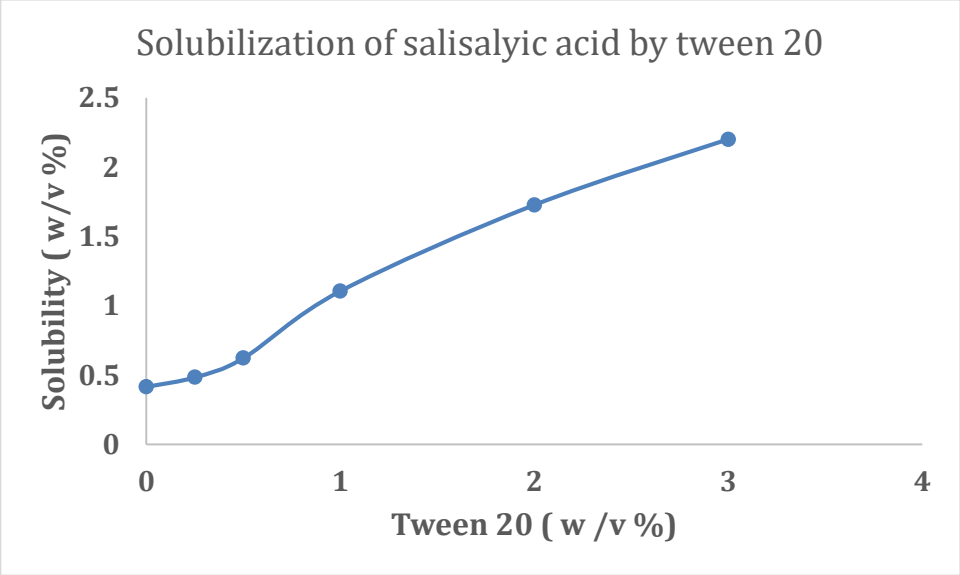
= 1.036 mg/ml

1.036 mg → ml

?? g → 100 ml

$$\frac{1.036\ mg \times 100\ ml}{1\ ml} \times \frac{1}{1000} = 0.1036\ \%\ (w/v)$$

Plot the solubility (w/v%) of salicylic acid versus concentration (w/v%) of Tween 20 and discuss your results.



Experiment 6

Part 1 (Solubility : Effect of cosolvent)

Cosolvency

Cosolvent is a second solvent added in small quantities to enhance the solvent power of the primary solvent. The solubility of a weak electrolyte or non-polar compound in water can often be improved by altering the polarity of the solvent. This can be achieved by the addition of another solvent that is both miscible with water and in which the compound is also soluble. Often the solubility in this mixed system is greater than can be predicted from the material's solubility in each individual solvent.

The choice of suitable cosolvents is somewhat limited for pharmaceutical use because of possible toxicity and irritancy, particularly if required for oral or parenteral use. Ideally, suitable blends should possess values of dielectric constant between 25 and 80. The most widely used system that will cover this range is a water/ethanol blend. Other suitable solvents for use with water include sorbitol, glycerol, propylene glycol and syrup. For example, a blend of propylene glycol and water is used to improve the solubility of co-trimoxazole, and paracetamol is formulated as an elixir by the use of alcohol, propylene glycol and syrup. For external application to the scalp, betamethasone valerate is available dissolved in a water/isopropyl alcohol mixture.

Prediction of solubility

Speculation on what is likely to be a good solvent is usually based on the 'like dissolves like' principle, that is, a solute dissolves best in a solvent with similar chemical properties. The concept traditionally follows two rules:

1. Polar solutes dissolve in polar solvents.
2. Non-polar solutes dissolve in non-polar solvents.

To rationalize the above rules, consider the forces of attraction between solute and solvent molecules. If the solvent is A and the solute B and the forces of attraction are represented by A-A, B-B and A-B, one of three conditions will arise:

1. If A-A >> A-B, i.e. the affinity of a solvent molecule for its own kind is markedly greater than its affinity for a solute molecule, the solvent molecules will be attracted to each other and form aggregations from which the solute is excluded. As an example, benzene is almost completely insoluble in water. Attraction between water molecules is very strong, so that water exists as aggregates, which have a similar form to ice, floating in a matrix of free molecules. It may be visualized as 'icebergs' floating in a 'sea' of free water molecules. Molecules are continually moving from sea to icebergs and from icebergs to sea. The attraction between benzene molecules arises from weak van der Waals forces, so that although very little energy is required to disperse benzene molecules, discrete benzene molecules are unable to penetrate the closely bound water aggregates.

2. If B—B >> A—A, the solvent will not be able to break the binding forces between solute molecules and disperse them. This situation would apply if you tried to dissolve sodium chloride in benzene. The sodium chloride crystal is held together by strong electrovalent forces which cannot be broken by benzene. A conducting solvent, such as water, would be required to overcome the attraction between solute molecules.

3. If A—B > A—A or B—B, or the three forces are of the same order, the solute will disperse and form a solution.

The attractive forces exerted between polar molecules are much stronger, however, than those that exist between polar and non-polar molecules, or between non-polar molecules themselves. Consequently, a polar solute will dissolve to a greater extent in a polar solvent, where the strength of the solute—solvent interaction will be comparable to that between solute molecules, than in a non-polar solvent, where the solute—solvent interaction will be relatively weak. In addition, the forces of attraction between the molecules of a polar solvent will be too great to facilitate the separation of these molecules by the insertion of a non-polar solute between them, because the solute—solvent forces will again be relatively weak. Thus, solvents for non-polar solutes tend to be restricted to non-polar liquids. The above considerations are often expressed very generally as 'like dissolves like', i.e. a polar substance will dissolve in a polar solvent and a non-polar sub-stance will dissolve in a non-polar

solvent. Such a generalization should be treated with caution, because the intermolecular forces involved in the process of dissolution are influenced by factors that are not obvious from a consideration of the overall polarity of a molecule. For example, the possibility of intermolecular hydrogen-bond formation between solute and solvent may be more significant than polarity

Solubility determination

A saturated solution is obtained by stirring excess powdered solute with solvent for several hours at the required temperature until equilibrium has been attained. It is essential that some undissolved solid should be present at the completion of this stage in order to ensure that the solution is saturated.

A sample of the saturated solution is obtained for analysis by separating it from the undissolved solid. Filtration is usually used, but precautions should be taken to ensure that:

1. it is carried out at the temperature of the solubility determination, in order to prevent any change in the equilibrium between dissolved and undissolved solute; and
2. loss of a volatile component does not occur.

The amount of solute contained in the sample of saturated solution may be determined by a variety of methods, e.g. gravimetric or volumetric analysis, electrical conductivity measurements, ultraviolet (UV) spectrophotometry and chromatographic methods. The selection of an appropriate method is affected by the natures of the solute and the solvent and by the concentration of the solution.

Part 1 (solubility: effect of cosolvent)

1. Prepare 100 ml of one of the following

   (0%v/v , 5%v/v ,7.5%v/v, 10%v/v , 15%v/v , 20% v/v) hydroethanoic mixture (Ethanol in Water), (use equation $c_1v_1=c_2v_2$)

2. Prepare one sample of saturated salicylic acid in hydroethanoic mixture :

   Add 1.0 g of salicylic acid to100 ml of prepared mixture in step 1 in stoppered bottle and shake them using a shaker for 24 hours.

3. Take 3 sample from your instructor from the following concentration

   (0%v/v ,5%v/v , 7.5 %v/v , 10%v/v ,15% v/v, 20% v/v) hydroethanoic mixture.

4. Take 10 ml sample of the supersaturated solution using cylinder and filter it using funnel in Erlenmeyer flask .

5. Dilute **1.0 ml** of filtrate to **100.0 ml** volumetric flask with water.

6. Read absorbance of final diluted sample by UV spectroscopy at 310 nm using Quartz Cuvette.

Data analysis and calculation:

Calculate solubility in (% w/v):

Example,

Ethanol (% w/v)	Absorbance	Concentration (mg/ml)	Dilution factor	Solubility (mg/ml)	Solubility (%w/v)
0	0.215	0.000356	100	0.0356	0.00356
5					
7.5					
10					
15					
20					

Calibration Curve Equation:

Y = 604 X

Knowing that the concentration (X) is in (mg/ml)

Example,

0.215 = 604 X → X = 0.000356 mg/ml

$$dillution\ factor = \frac{final\ volume}{initial\ volume}$$

Example,

$$\frac{100}{1} = 100$$

$$Solubility = dilluted\ concentraction \times dillution\ factor$$

Example,

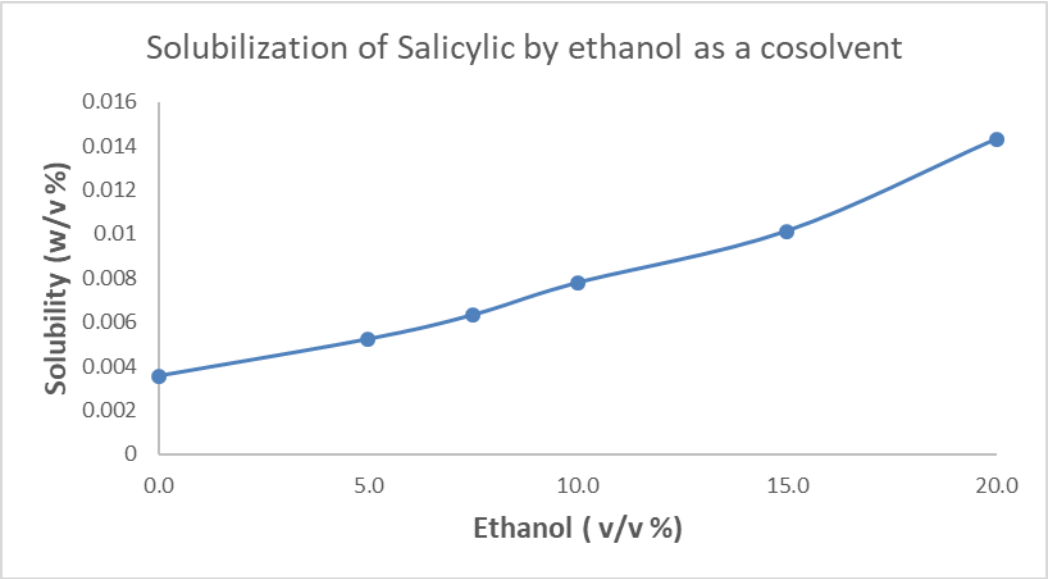
$$= 0.000356 \times 100 = 0.0356\ mg/ml$$

0.0356 mg → ml

?? g → 100 ml

$$\frac{0.0356\ mg \times 100\ ml}{1\ ml} \times \frac{1}{1000} = 0.00356\ \%\ (w/v)$$

Plot the solubility (w/v%) of salicylic acid versus concentration (w/v%) of ethanol and discuss your results.



Experiment 6

Part 2 (Solubility : Effect of temperature)

The solubility of a substance fundamentally depends on the used **solvent** as well as on **temperature** and **pressure**.

Other Factors affecting solubility

1. **Temperature**

   The solubility of a given solute in a given solvent typically depends on temperature. For many solids dissolved in liquid water, the solubility increases with temperature up to 100 °C. In liquid water at high temperatures, (e.g., that approaching the critical temperature), the solubility of ionic solutes tends to decrease due to the change of properties and structure of liquid water; the lower dielectric constant results in a less polar solvent.

   The solubility of organic compounds nearly always increases with temperature. The technique of recrystallization, used for purification of solids, depends on a solute's different solubilities in hot and cold solvent. A few exceptions exist, such as certain cyclodextrins

2. **Pressure**

   For condensed phases (solids and liquids), the pressure dependence of solubility is typically weak and usually neglected in practice. Assuming an ideal solution, the dependence can be quantified as.

3. **Chemical and physical properties of solute**

   The chemical structure of the solute usually determines the solute major properties which can influence its dissolution and bioavailability. The physical properties of the solute such as the crystalline state and particle size are important in determining its solubility, so minor modifications in the drug molecules (e.g salt formation or esterfication, micronization to decrease particle size and to increase the effective surface area, and complexation with inert water soluble materials), are strategies that have been used to enhance the aqueous solubility of these drugs.

Studying the effect of temperature on solubility

The preparation of solutions is one of the most frequent tasks required of a pharmacist. Knowledge of the enthalpy change accompanying a solution process allows the pharmacist to rationalize solvent –solute interactions and thereby obtain better control over the behavior of the finished product.

An example of this additional control would be the ability to predict changes in drug solubility with temperature. If a sparingly soluble drug dissolves exothermically at 25 C, it is obvious that the pharmacist shouldn't make the concentration of the drug in the preparation very close to it 25C solubility since precipitation of the drug would occur upon injection into the body (37C).

In this experiment you will determine the heat of solution of salicylic acid in distilled water. This will be accomplished by determining solubility of salicylic acid in distilled water at different temperatures and treating this data according to the **Vant Hoff relationship:**

$$\textbf{Log S} = (-\Delta \textbf{H} / 2.303\ \textbf{R})\ (1/\textbf{T}) + \textbf{constant}$$

Where:

S is the solubility in mole fraction

R is the molar gas constant (1.987cal/mol.deg)

T is the absolute temperature (K)

H is the heat of solution (K.cal/mol)

According to Vant Hoff equation, if you plot **log S** versus **1/T** should yield a straight line with a slope of **(-ΔH /20303R).** A knowledge of ΔH makes it possible to predict S at versus temperatures using the following equation.

$$\textbf{Log } S_1/S_2 = (-\Delta \textbf{H} /2.303\textbf{R}) *((T_1-T_2)/ T_1T_2)$$

Where:

S_2 is the unknown solubility at T_2

S_1 is the known solubility at T_1

Objective:

Study the effect of temperature on the solubility of salicylic acid

Experimental part:

1. Prepare three samples of over saturated solution of salicylic acid in water at 25C◦, 50 C◦ and 70 C◦
   a. Weigh about **0.5gm** salicylic acid in bottle , Add **50ml** distilled water , put on stirring hot plate at **25 C** for 20 minutes
   b. Weigh about **0.9gm** salicylic acid in bottle, Add **50ml** distilled water, and Shake the solution, in water bath, at **50 C** for 20 min.
   c. Weigh about **2.0 gm** salicylic acid in bottle, Add **50ml** distilled water, and Shake the solution, in water bath, at **70 C** for 20 min.
2. Filter 10 ml using funnel and filter paper to get rid of the excess (insoluble) salicylic acid
3. Dilute **1.0 ml of the filtrate in 100 ml volumetric flask** with distilled water.
4. Measure the absorbance of diluted salicylic acid at 310nm, using distilled water as solvent.

Data analysis and calculation:

$$dillution\ factor = \frac{final\ volume}{initial\ volume}$$

Example,

$$\frac{100}{1} = 100$$

$$Solubility = dilluted\ concentraction \times dillution\ factor$$

Example,

$$= 0.00048 \times 100 = 0.048\ mg/ml$$

T (C˚)	T (K)	Absorbance	Diluted concentration (mg/ml)	Dilution factor	solubility (mg/ml)	mole salicylic acid in 1 ml (mmole)	mole water in 1 ml (mmole)	solubility (mole fraction)	1/T	log S
25	298.15	0.287	0.00048	100	0.048	0.00034	55.56	0.000006	0.00336	-5.2078
50										
70										

1 C ^{O} = 274.15 K

Example,

T = 25 + 274.15

= 298.15 K

Calibration Curve Equation:

Y = 604 X

Knowing that the concentration (X) is in (mg/ml)

Example,

0.287 = 604 X

X = 0.00048 mg/ml

$$= \frac{Solubility\ (mg/ml)}{Molecular\ weight}$$

Example,

$$= \frac{0.048}{138}$$

$$= 0.00034\ mmole$$

$$water,$$

$$1\ ml = 1\ g = 1000$$

$$= \frac{weight\ (mg/ml)}{Molecular\ weight}$$

Example,

$$= \frac{1000}{18}$$

$$= 55.56\ mmole$$

$$= \frac{1}{Temperature\ (K)}$$

Example,

$$= \frac{1}{298.15}$$

$$= 0.00336\ K^{-1}$$

$$= \log Solubility$$

Example,

$$= \log 6 \times 10^{-6}$$

$$= -5.2078$$

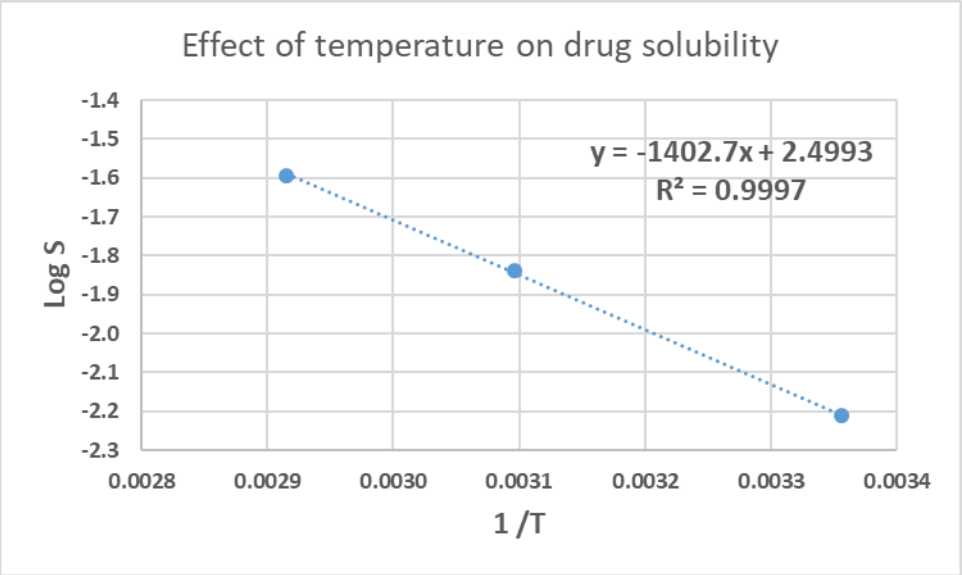
$$= \frac{moles\ of\ SA}{moles\ of\ SA + moles\ of\ water}$$

Example,

$$= \frac{0.00034}{0.00034 + 55.56}$$

$$= 6 \times 10^{-6}$$

Plot log S versus 1/T and calculate ΔH value



$$\boldsymbol{Slop} = \frac{-\Delta H}{2.303\ R}$$

Then,

$$-\Delta \boldsymbol{H} = \boldsymbol{Slop} \times \boldsymbol{R} \times 2.303$$

Example,

$$-\Delta \boldsymbol{H} = -1402.7 \times 1.987 \times 2.303 = -7230.63$$

$$\Delta \boldsymbol{H} = 7230.63\ \boldsymbol{K.cal/mol}$$

Experiment 7

Solubility curve for a ternary system of liquids

Theory

Phase rule

The *phase rule* is a relationship for determining the least number of intensive variables (independent variables that do not depend on the volume or size of the phase. e.g., temperature, pressure, density, and concentration) that can be changed without changing the equilibrium state of the system. or, alternately, the least number required to define the state of the system. This critical number is called F, the number of degrees of freedom of the system, and the rule is expressed as follows:

$$F = C - P + 2$$

where *C is* the number of components and ***P*** is the number of phases present.

Phase equilibria in three-component systems

In systems containing three components but only one phase, F = 3 - 1 + 2 = 4 for a noncondensed system. The four degrees of freedom are temperature, pressure, and the concentrations of two of the three components. Only two concentration terms are required because the sum of these subtracted from the total will give the concentration of the third component, If we regard the system as condensed and hold the temperature constant, then F = 2, and we can again use a planar diagram *to* illustrate the phase equilibria. Because we are dealing with a three-component system, it is more convenient to use triangular coordinate graphs, although it is possible to use rectangular coordinate.

Rules relating to Triangular Diagrams

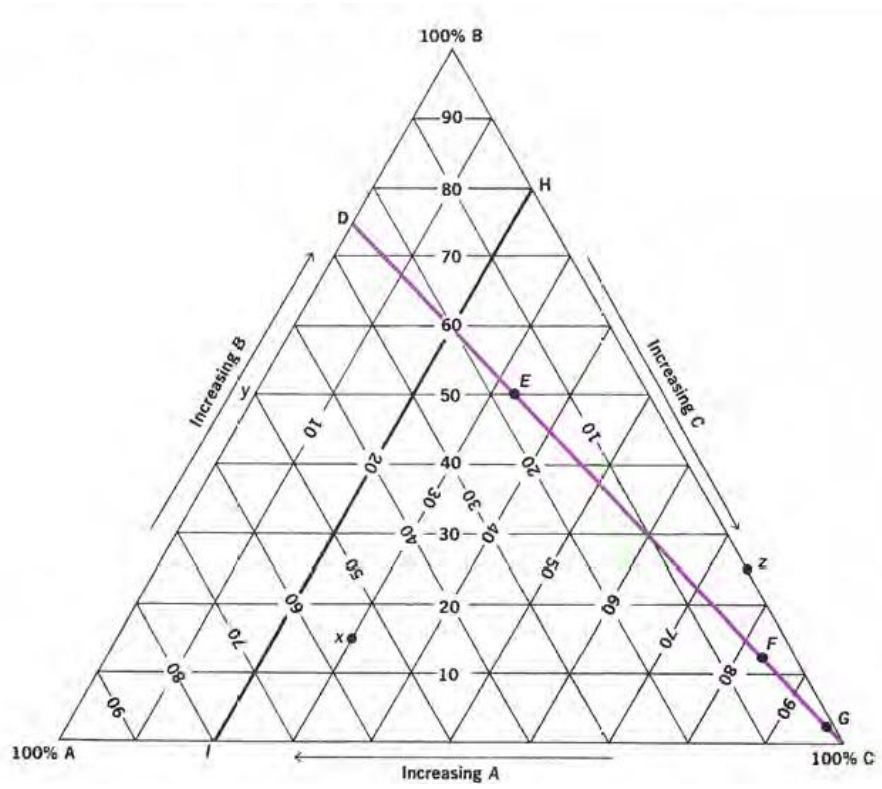


Figure 1.The triangular diagram for three-componentsystems.

1) Each of the *three* corners or apexes of the triangle represent 100% by weight of one component (A. *B,* or *C).* As a result, that same apex will represent 0% of the other two components.
2) The three lines joining the corner points represent two-component mixtures of the three possible combinations of *A, B.* and *C,* Thus the lines *AB, BC,* and CA are used for two-component mixtures of *A* and *B, B* and *C,* and *C* and A, respectively. By dividing each line into 100 equal units, we can directly relate the location of a point along the line to the percent concentration of one component in a two-component system. For example, pointy, midway between A and *B* on the line *AB,* represents a system containing 50% of *B* (and hence 50% of A also). Point z, three fourths of the way along *BC,* signifies a system containing 75% of *C* in *B.*
3) In going along a line bounding the triangle so as to represent the concentration in a two-component system, it does not matter whether we proceed in a clockwise or a counterclockwise direction around the triangle, provided we are consistent. The more

usual convention is clockwise and has been adopted here. Hence, as we move along *AB* in the direction of *B,* we are signifying systems of *A* and *B* containing increasing concentrations of *B, and* correspondingly smaller amounts of *A.* Moving along *BC* toward *C* will represent systems of *B* and *C* containing more and more of *C;* the closer we approach A on the line *CA,* the greater will be the concentration of A in systems of A and *C.*

4) The area within the triangle represents all the possible combinations of *A, B,* and *C* to give three-component systems. The location of a particular three-component system within the triangle, for example, point *X* in Figure 1, can be undertaken as follows:

   The line *AC* opposite apex *B* represents systems containing *A* and *C.* Component *B* is absent, that is, *B* = 0. The horizontal lines running across the triangle parallel to *AC* denote increasing percentages of *B* from *B* = 0 (on line *AC) to B* = 100 (at point *B).* The line parallel to *AC* that cuts point *x* is equivalent to 15% *B;* consequently, the system contains 15% of *B* and 85% of A and *C* together. 100%c

   Applying similar arguments to the other two components in the system, we can say that along the *line AB, C* = 0. As we proceed from the line *AB* toward *C* across the diagram, the concentration of *C* increases until at the apex, *C* = 100%. The point x lies on the line parallel to *AB* that is equivalent to 30% of *C.* It follows, therefore, that the concentration of A is 100 — *(B* = 100 — (15 30) = 55%. This is readily confirmed by proceeding across *the* diagram from the line *BC* toward apex A; point x lies on the line equivalent to 55% of A.

5) If a line is drawn through any apex to a point on the opposite side (e.g., line *DC* in Figure 1), then all systems represented by points on such a line have a constant ratio of two components, in this case *A* and *B.* Furthermore, the continual addition of C to a mixture of A and *B* will produce systems that lie progressively closer to apex *C (100%* of component *C).*

6) Any line drawn parallel to one side of the triangle, for example. line *HI* in Figure 1, represents ternary system in which the proportion (or percent by weight) of *one* component is constant. In this instance, all systems prepared along *HI* will contain 20% of *C* and varying concentrations of A and *B.*

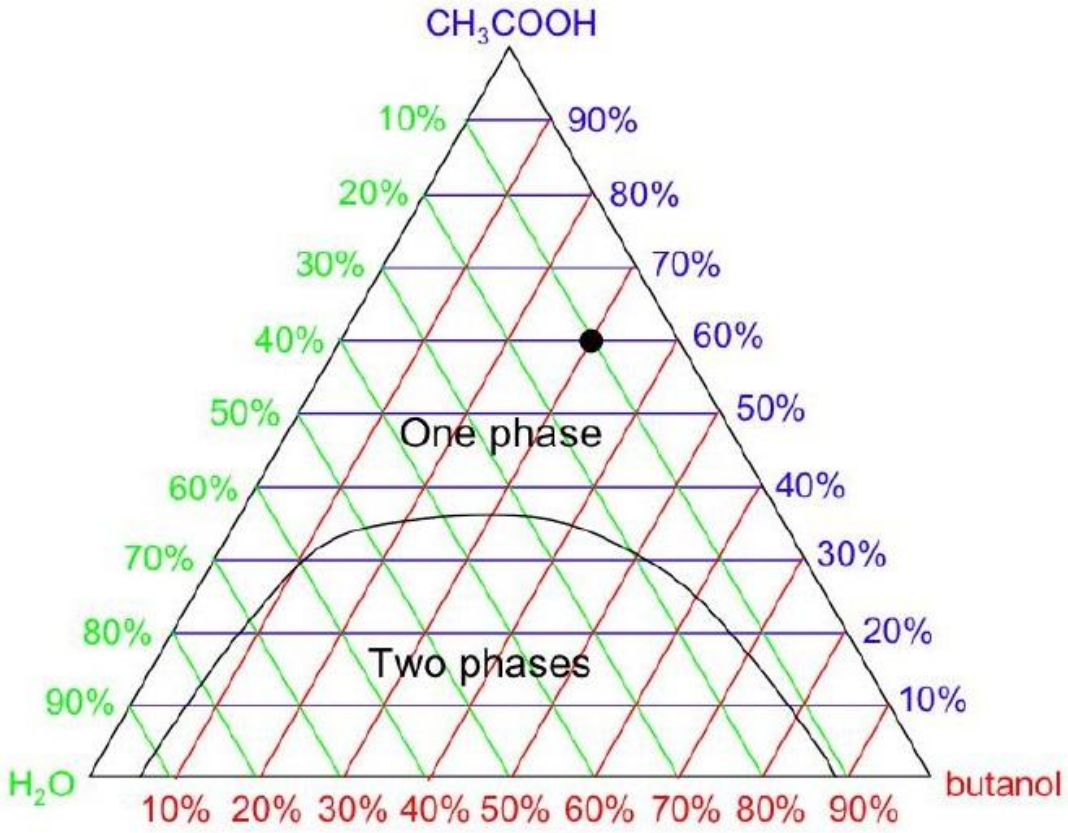


Figure 2 : A triangular phase diagram showing the representation of the mass fractions for ternary systems. The colours indicate how concentrations for different species should be read from the diagram. The point marked in the diagram (•) represents 30% 1-butanol, 10% water and 60% acetic acid. The one-phase and two-phase regions have been separated by a black line. Pressure and temperature are assumed to be fixed.

Regions where one or two phases appear have also been indicated in Figure 2. Note that the line drawn is hypothetical, the real curve will be determined in this experiment. When the solution is stirred, the transition from one region to another can be observed by appearance (or disappearance) of cloudiness or turbidity in the solution. The turbidity results from scattering of light by the large number of very small "oily" droplets of the second phase that are produced when the system is stirred.

Objective

To determine the solubility curve for a ternary system of two immiscible liquids and a third liquid which is miscible with each of them.

Experimental part

Apparatus and Chemicals: 250 ml Erlenmeyer flasks, 5 ml pipette, 2 burettes and holders. distilled water, ethyl acetate, chloroform and absolute ethanol.

Procedure

1. Using the 5 ml pipette, introduce 5 ml of chloroform or ethyl acetate into the 250 ml Erlenmeyer flask.
2. Add water from one burette drop wise and slowly with vigorous shaking until turbidity appears. Record the volume added
3. Then continue adding water from burette to reach 1 ml of water added and shake vigorously.
4. From the other burette add ethanol slowly, until, after vigorous shaking, a clear (non-cloudy) solution is obtained which is saturated with respect to the three components. Record the volumes added.
5. Add another 1- ml of water to the liquid, shake vigorously, and repeat the addition of ethanol until the mixture again becomes homogeneous.
6. Add successively 1 ml of water for three times,2-ml for one time, 3-ml for one time, 5 ml for two times and 15 ml two times, and in each case add enough ethanol to produce a clear liquid. Record and tabulate all the results using the following table.

Results:

	Volume		
	Chloroform (ml)	**Water (ml)**	**Ethanol (ml)**
1	**5**	**??**	**0**
2	**5**	**1**	
3	**5**	**2**	
4	**5**	**3**	
5	**5**	**4**	
6	**5**	**5**	
7	**5**	**7**	
8	**5**	**10**	
9	**5**	**15**	
10	**5**	**20**	
11	**5**	**35**	
12	**5**	**50**	

.

Data analysis and calculations:

	Chloroform	Ethanol	Water
Molar mass (g/mol)	**119.4**	**46.1**	**18.0**
Specific gravity (g/ml)	**1.489**	**0.789**	**1.000**

- ***Weight % calculation:***

Point	Chloroform			Water			Ethanol		
	V (ml)	W (g)	W% (%)	V (ml)	W (g)	W% (%)	V (ml)	W (g)	W% (%)
1	5	a	A		B	B	0	c	C
2	5			1					
3	5			2					
4	5			3					
5	5			4					
6	5			5					
7	5			7					
8	5			10					
9	5			15					
10	5			20					
11	5			35					
12	5			50					

$weight = volume \times density$

Example:

a = V × 1.489

$weight = volume \times density$

Example:

b = V × 1

$weight = volume \times density$

Example:

c = V × 0.789

$$weight\ \% = \frac{a}{a+b+c} \times 100 = A$$

Or

$$weight\ \% = 100 - (B + C) = A$$

$$weight\ \% = \frac{b}{a+b+c} \times 100 = B$$

Or

$$weight\ \% = 100 - (A + C) = B$$

$$weight\ \% = \frac{c}{a+b+c} \times 100 = C$$

Or

$$weight\ \% = 100 - (A + B) = C$$

- ***Mole % calculation:***

Point	Chloroform				Water				Ethanol			
	V (ml)	W (g)	mole	mole(%)	V (ml)	W (g)	mole	mole(%)	V (ml)	W (g)	mole	mole(%)
1	5	a	X	X'		B	Y	Y'	0	c	Z	Z'
2	5				1							
3	5				2							
4	5				3							
5	5				4							
6	5				5							
7	5				7							
8	5				10							
9	5				15							
10	5				20							
11	5				35							
12	5				50							

$$mole = \frac{mass}{molecular\ weight}$$

Example:

$$X = \frac{a}{119.4}$$

$$mole = \frac{mass}{molecular\ weight}$$

Example:

$$Y = \frac{b}{18}$$

$$mole = \frac{mass}{molecular\ weight}$$

Example:

$$Z = \frac{c}{46.1}$$

$$Mole\ \% = \frac{X}{X+Y+Z} \times 100 = X'$$

Or

$$Mole\ \% = 100 - (y' + z') = x'$$

$$Mole\ \% = \frac{Y}{X+Y+Z} \times 100 = Y'$$

Or

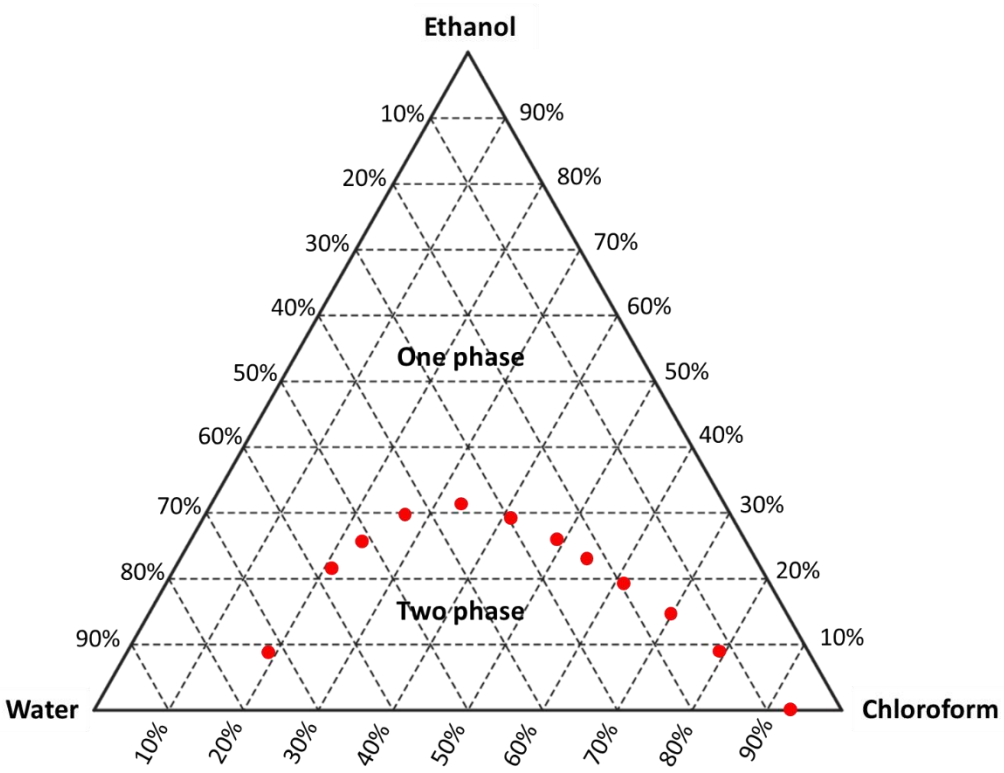
$$Mole\ \% = 100 - (X' + Z') = Y'$$

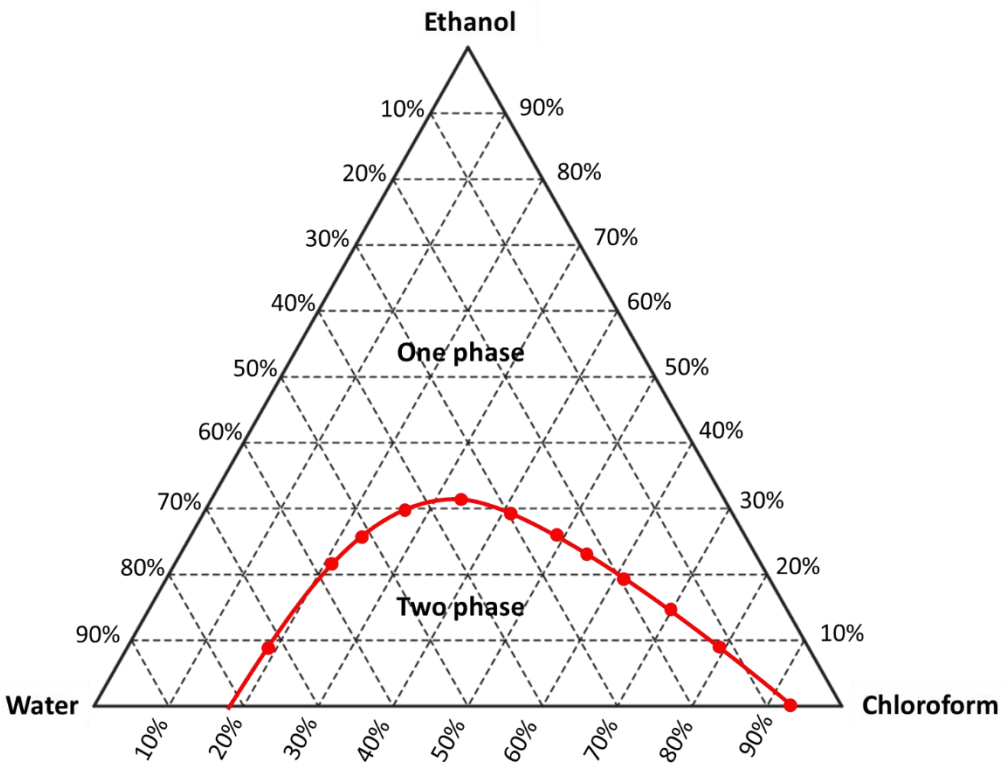
$$Mole\ \% = \frac{Z}{X+Y+Z} \times 100 = Z'$$

Or

$$Mole\ \% = 100 - (X' + Y') = Z'$$

- ***Draw the ternary diagram using weight % or mole %***





Experiment 8

Kinetics of Hydrolysis of aspirin

Kinetics is the study of the rates of chemical processes in an effort to understand what it is that influences these rates and to develop theories which can be used to predict them. Knowledge of reaction rates has many practical applications, for example in designing an industrial process, in understanding the complex dynamics of the atmosphere and in understanding the intricate interplay of the chemical reactions that are the basis of life.

Rate of reaction

The rate is defined as = Δconcentration /Δtime

We can talk about the rate of formation or loss of any species – reactant, intermediate or product. It is, however, important to specify which species we are talking about. The rate can be positive or negative: a positive rate means that the concentration is increasing with time e.g. a product; a negative rate means that the concentration is falling with time e.g. a reactant.

Half-Life ($t_{0.5}$ or $t_{50\%}$) is the time required for one-half of the material to disappear.

Zero Order Reaction

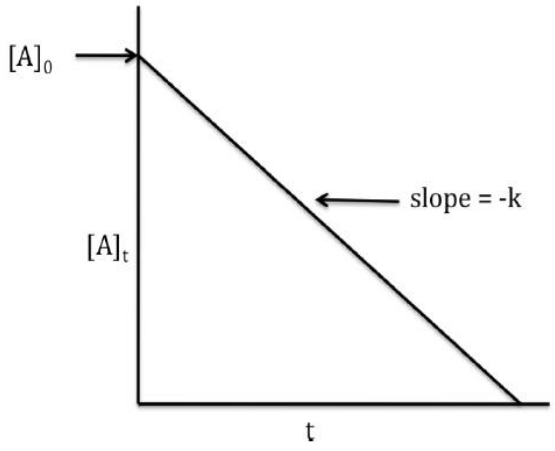
A reaction is of zero order when the rate of reaction is independent of the concentration of materials. The rate of reaction is a constant. When the limiting reactant is completely consumed, the reaction stops abruptly. Hydrolysis of aqueous drug suspensions follows zero-order kInetics. The equation for zero-order kinetics is:

$$[A]_t = [A]_0 - K_0 t$$

$[A]_t$: remaining amount of substance at time *t*

K_0: zero order rate constant (unit is *concentration. time^{-1}).*

A plot of $[A]_t$ against t is linear with a slope of $-K_0$ and an intercept of $[A]_0$.



First Order Reaction

The rate depends on the concentration of one reactant. Degradation of aqueous solutions (hydrolysis) of many drugs (e.g. aspirin) and excipients follows first order Kinetics.

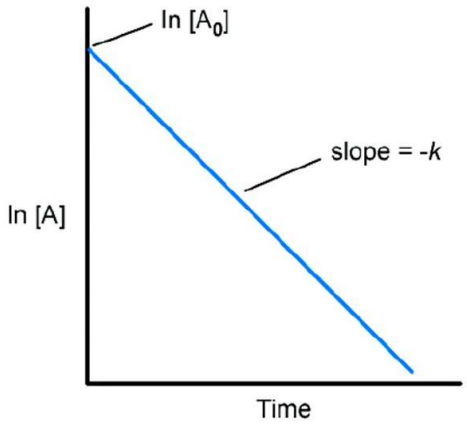
The integrated rate equation is:

$$\boldsymbol{ln[A]_t = In[A]_0 — K_1 t}$$

$[A]_0$: initial amount of substance

K_1: first order rate constant (units are $time^{-1}$).

A plot of $\ln[A]_t$ against t is linear with a slope of $-K_1$ and an intercept of $\ln[A]_0$.



Second Order Reaction

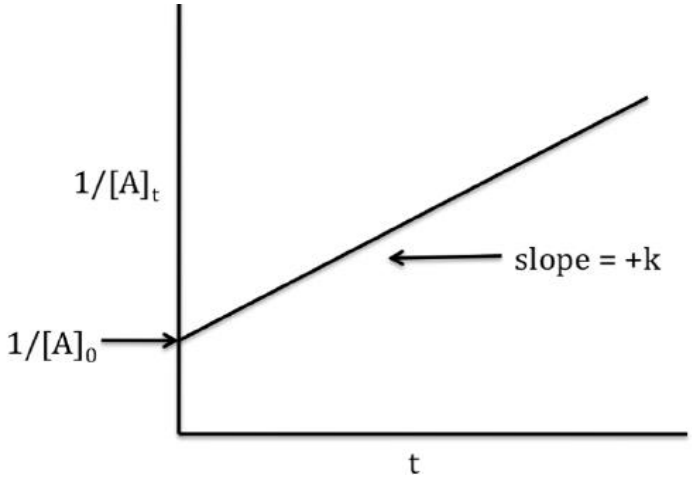
The rate of a second order reaction is proportional to either the concentration of a reactant squared, or the product of concentrations of two reactants.

If initial concentrations of the two reactants are equal or in reactions when similar molecules react together the integrated rate equation is:

$$1/[A]_t = 1/[A]_0 + k_2t$$

K_2: second order rate constant (unit is *concentration^{-1}. time^{-1}).*

A plot of 1 / [A] vs. t produces a straight line with slope k and intercept 1 / [A]o.



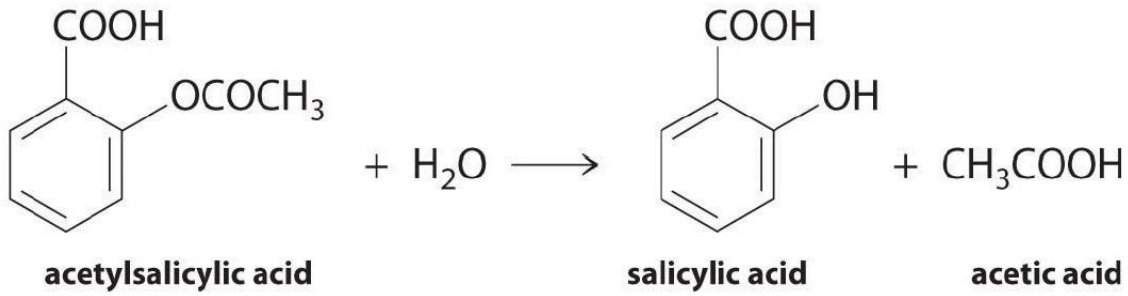
Summary

Reaction Order	Rate Law	Linear Plot	Slope	Units of Rate Constant	Half-life
0	**[A]= [A]o - kt**	**[A] vs t**	**- k**	***concentration. time^{-1}***	**$t_{50\%} = [A]_0/ 2K_0$**
1	***$ln[A]_t = In[A]_0$ — K_1t***	**ln [A] vs t**	**- k**	***time^{-1}***	**$t_{50\%} = 0.693/K_1$**
2	**$1/[A]_t = 1/[A]_0 + k_2t$**	**1 /[A] vs t**	**k**	***concentration^{-1}. time^{-1}***	**$1/k_2[A]_0$**

Hydrolysis of aspirin

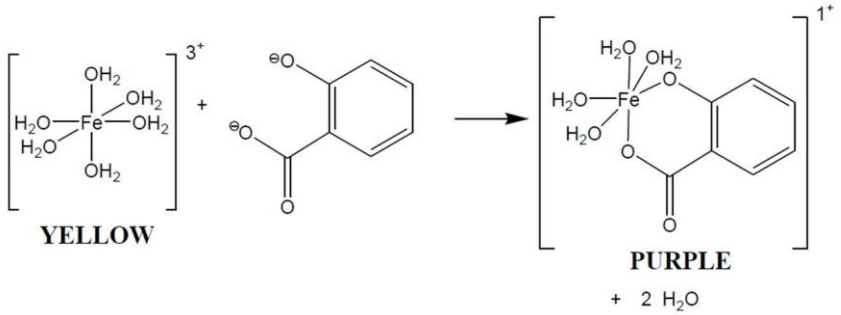
Aspirin is in a group of drugs called salicylates. It works by reducing substances in the body that cause pain, fever, and inflammation.

Aspirin is used to treat mild to moderate pain, and also to reduce fever or inflammation. It is sometimes used to treat or prevent heart attacks, strokes, and angina. Aspirin should be used for cardiovascular conditions only under the supervision of a doctor.



Ferric chloride test for phenolic groups

In solution, ferric chloride becomes the $Fe(H_2O)_{6+3}$ ion. This ion can bind to salicylic acid because water is exchangeable in iron complexes. One water can be replaced by the negative carboxylic acid oxygen ion in salicylic acid. Because of the chelate effect and the formation of a new six membered ring, the phenolic oxygen of salicylic acid can also replace one of the waters in the iron complex. This new iron complex has an intense violet color.

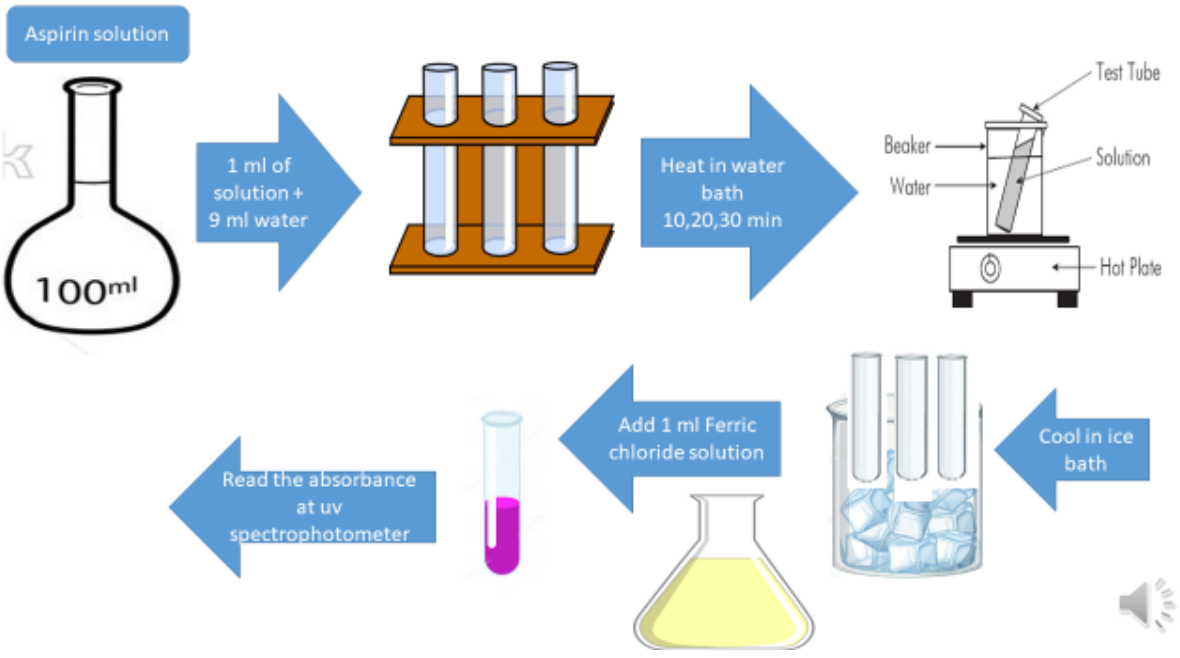


Materials and Equipment

- Aspirin, ethanol, ethanol, 5% $FeCl_3$
- Volumetric flask, measuring cylinder, ice bath, water bath, and UV spectroscopy.

Procedure

1. **Dissolve 0.3 g of aspirin in a 100 ml volumetric flask complete the volume to 100 ml with ethanol.**
2. **Transfer 1 mL of the aspirin solution into 3 test tubes.**
3. **Add 9 mL of distilled water to each test tube and record the time.**
4. **Place the test tubes in a water bath with at temperature =70 °C.**
5. **Remove one tube at 10, 20, and 30 min.**
6. **Place the removed tube in an ice bath for 3 min.**
7. **Add 1 mL of 5% $FeCl_3$**
8. **Determine the concentration by UV spectroscopy at 540 nm after suitable dilution using Quartz Cuvette.**
9. **Calculate the percentage of aspirin remaining**



Experiment 9

Emulsions: Preparation and Stabilization

An emulsion is a thermodynamically unstable two-phase system consisting of at least two immiscible liquids, one of which is dispersed in the form of small droplets throughout the other, and an emulsifying agent. The dispersed liquid is known as the internal or discontinuous phase, whereas the dispersion medium is known as the external or continuous phase.

Where oils, petroleum hydrocarbons, and/or waxes are the dispersed phase, and water or an aqueous solution is the continuous phase, the system is called an oil-in- water (o/w) emulsion. An o/w emulsion is generally formed if the aqueous phase constitutes > 45% of the total weight, and a hydrophilic emulsifier is used.

Conversely, where water or aqueous solutions are dispersed in anoleaginous medium, the system is known as water-in-oil (w/o) emulsion. W/O emulsions are generally formed if the aqueous phase constitutes < 45% of the total weight and a lipophilic emulsifier is used.

Emulsion stability

1. ***Thermodynamic stability;***

Emulsion is a thermodynamic unstable system. The reason for that is the positive surface free energy, which equal to interfacial tension times the surface area of the dispersed phase.

$$Surface\ Free\ Energy = \gamma * SA$$

Where: SA is surface area and γ is surface tension

Any system tends to reduce its free energy, and it cannot be thermodynamically stable unless the free energy is reduced to zero, which is not applicable to emulsions, because of the interfacial tension between the two phases. However, solutions (such as water and ethanol) are thermodynamically stable because of zero interfacial tension. Notice according to the equation, as the dispersed droplet size decreases, the free energy increases, thus the system becomes more thermodynamically unstable. Accordingly, dispersed droplets tend to flocculate and then coalesce and to form larger droplets,

reduce surface area and consequently reduce the surface free energy. Why the dispersed droplets in an emulsion are spherical?

2. ***Physical stability***

Sedimentation / Creaming

The dispersed droplets in emulsion are subjected to gravitational force. Accordingly, they tend to move upward or down word. Upward movement is called creaming, while downward movement is called sedimentation. For O/W emulsions, creaming happens, while sedimentation occurs in W/O emulsion (Why?!). Sedimentation or creaming rate (V) is depicted by Stokes Law.

$$Vt = \frac{d^2\,(\rho - \rho_0)*g}{18\eta}$$

Where:

- Vt: Sedimentation/Creaming rate (cm/sec)
- t: time (sec)
- d: particle diameter (cm)
- ρ: density of the dispersed phase (gm cm-3 or gm ml-1)
- ρ_0: density of the dispersing medium
- η: Viscosity of the dispersing medium

Stokes law suggests that rate of sed. or creaming is proportional to particle size, difference in density between the two media, and gravitational force, while it is disproportional to viscosity. However, size would have the highest effect on the rate (Why?!).

Sedimentation or creaming would affect the homogeneity of an emulsion as it would bring the dispersed phase droplets closer to each other. Accordingly, in the case of O/W emulsion, creaming would transfer the freshly homogenous emulsion, into two layers: the bottom layer as aqueous phase depleted of oil droplets (Translucent), while the upper layer is creamy rich in oil droplets. The droplets in the creamy layer are folliculated. In flocculation two droplets are attached to each other, but still separated

by a thin film of liquid (Figure 1), when more droplets are added, agglomerate is formed; here a cluster of individual droplets formed but with retained thin film between them. Upon flocculation, coalescence could happen as two or more droplets unite or coalesce to form larger single droplet (Figure 1).

As the film between the flocculated droplets would be stronger and more continuous, such as in the case of the presence of surfactant or hydrocolloid polymer, the coalescence is less likely to happen. Conversely, if the film is discontinuous or broken and removed because of weakness, coalescence happens easily. As coalescence proceeds, phase separation happens.

Coalescence is more serious problem than flocculation, because coalescence means phase separation and is irreversible by gentle agitation, while flocculation is reversible by agitation as the droplets are still separated by a film. Consequently, phase separation as result of coalescence is pharmaceutically unacceptable, while flocculation is pharmaceutically acceptable. However, flocculation is still not appealing to the patients, andthus not desirable.

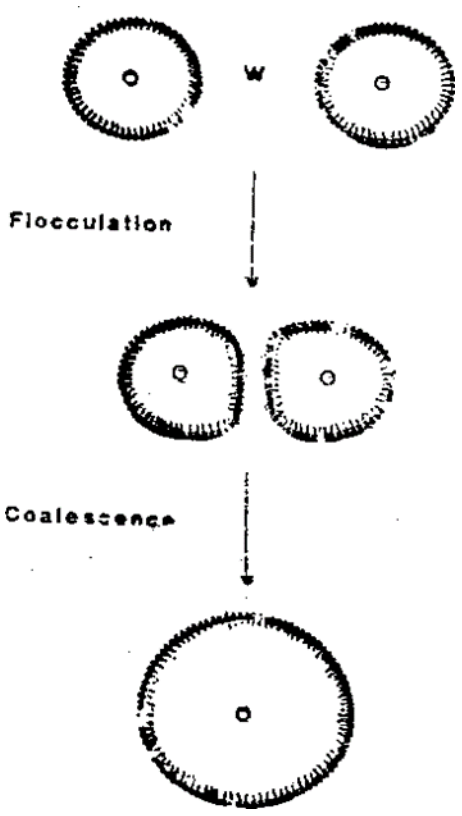
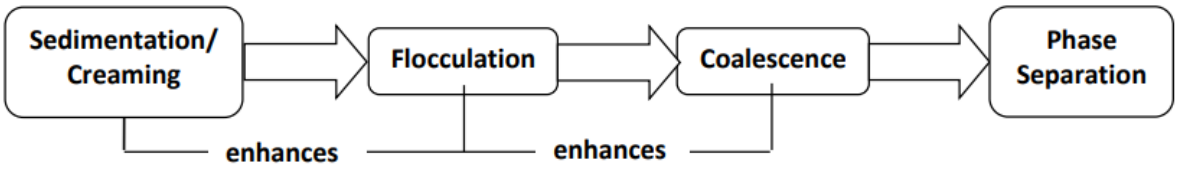


Figure 1: In flocculation, the two droplets are attached to each other, but still separated by thin film. In coalescence, the two droplets are united into a larger droplet.

Sedimentation or creaming would encourage flocculation and coalescence because it brings the dispersed droplets closer to each other. On the other hand, Flocculation or coalescence would also accelerate creaming and sedimentation, because of increase in particle size. Therefore, after certain period of time, complete phase separation would happen because of these processes. The less the emulsion is physically stable, the less the time for phase separation to happen. The sequence of phase separation is illustrated as the following



It imperative to point out that coalescence and flocculation destabilizes emulsion physically, but stabilizes emulsion thermodynamically (Why?!).

Microscopical examination is one way to detect flocculation and coalescence. Flocculation is seen under the microscope as clusters of particles (Figure 2a), while coalescence is shown by the presence of wide particle distribution, indicating that some small droplets coalesced into larger ones (Figure 2b).

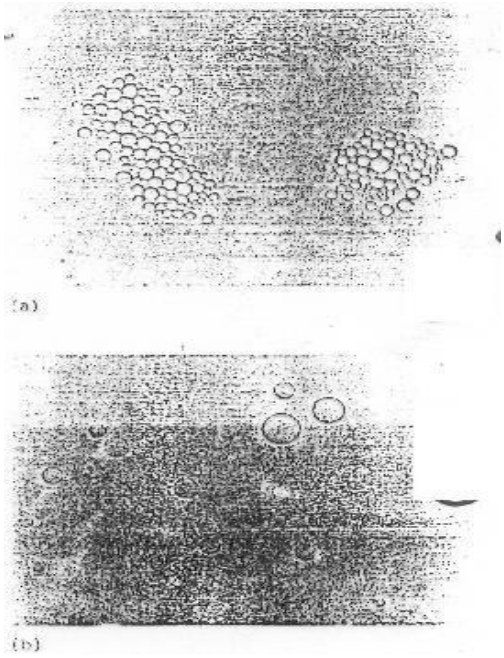


Figure 2: An emulsion showed (a) flocculated droplets indicated as agglomerates and an emulsion showed (b) coalesced droplet indicated as variety of droplet sizes.

If the problem is apparent, it can be noticed visually by following a shelf- standing emulsion for certain period of time. Figure 3 shows unstable emulsion to the right and stable emulsion to the left. The unstable emulsion has three distinct layers: upper transparent layer, middle creamy layer and bottom transparent layer. If the emulsion is O/W, the upper layer would be coalesced oil droplet s (separated oil phase layer), the middle layer represents flocculated oil droplets with thin aqueous phase among them and the bottom layer is transparent aqueous phase depleted from the oil droplets as a result of creaming of single or flocculated oil droplets.

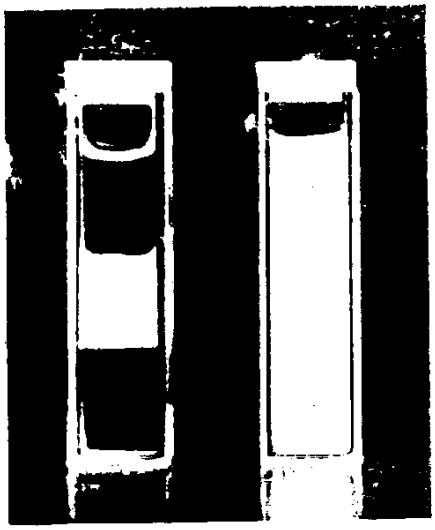


Figure 3. Destabilized O/W emulsion (to the left) with upper oil layer, flocculated layer (creamy) in the middle and aqueous phase is left at the bottom. A stable emulsion is shown to the right.

Hydrophilic-Lipophilic Balance and Emulsion stability

The most used approach by formulators to pick up surfactants is based on Hydrophilic Lipophilic balance (HLB). A system was developed to assist in making systemic decisions about the types of surfactants needed in stable products. HLB is a numeric value that represents the hydrophilic and hydrophobic tendencies of the material. HLB numbers are experimentally determined for the different emulsifiers (Table 1).

For every oil or fat, it requires an optimum HLB to form stable O/W emulsion and a different optimum HLB to form stable W/O emulsion (Table 2). If there are several oil ingredients the required HLB is calculated as a sum of their respective required HLB multiplied by the fraction of each. The following example explains

Table 1: Commonly Used Emulsifiers and Their HLB Values

Commercial Name	Chemical Name	HLB Value
Potassium oleate	Potassium oleate	20
Sodium lauryl sulfate	Sodium lauryl sulfate	40
Sodium oleate	Sodium oleate	18
Span® 20	Sorbitan monolaurate	8.6
Span® 40	Sorbitan monopalmitate	6.7
Span® 60	Sorbitan monostearate	4.7
Span® 65	Sorbitan tristearate	2.1
Span® 80	Sorbitan monooleate	4.3
Span® 85	Sorbitan trioleate	1.8
Triethanolamine oleate	Triethanolamine oleate	12
Tween® 20	Polyoxyethylene sorbitan monolaurate	16.7
Tween® 21	Polyoxyethylene sorbitan monolaurate	13.3
Tween® 40	Polyoxyethylene sorbitan monopalmitate	15.6
Tween® 60	Polyoxyethylene sorbitan monostearate	14.9
Tween® 61	Polyoxyethylene sorbitan monostearate	9.6
Tween® 65	Polyoxyethylene sorbitan tristearate	10.5
Tween® 80	Polyoxyethylene sorbitan monooleate	15.0
Tween® 81	Polyoxyethylene sorbitan monooleate	10.0
Tween® 85	Polyoxyethylene sorbitan trioleate	11.0

Table 2: Required HLB for some oils to make both o/w and w/o emulsion

Oil Type	o/w	w/o
Cottonseed oil	7	--
Petrolatum	8	3
Beeswax	11	5
Paraffin wax	10	4
Mineral oil	12	6
Methyl silicon	11	--
Lanolin anhydrous	14	8
Carnauba wax	13	8
Lauryl alcohol	14	--
Castor oil	14	--
Kerosene	13	--
Cetyl alcohol	15	--
Stearyl alcohol	16	--
Carbon tetrachloride	16	--
Lauric acid	16	9
Oleic acid	17	--
Stearic acid	17	--
Wool Fat	10	8
Soft Parrafin	12	4

<u>Example 1</u>: Calculate the required HLB for the oil phase of the following o/w emulsion: cetyl alcohol 15 g., paraffin wax 1g. Lanolin 2 g, emulsifier (q.s.), glycerin 5 g. water 100 g.

	Required HLB		Fraction		Required
Cetyl Alcohol	15	x	15/18	=	12.5
Parrafin Wax	10	x	1/18	=	0.6
Lanolin	13	x	2/18	=	1.4
	Total Required HLB			=	14.5

Once we determined the optimum required HLB for emulsification, we need to determine which surfactant to use. It is better to use combination of emulsifiers with overall HLB equivalent to that required than using a single emulsifier with the same HLB number; mixed surfactants produce higher interfacial coverage, and consequently, more continuous (with less spaces) and integrate film. For example, suppose that the calculated overall HLB for an emulsion is The HLB value of a combination of emulsifiers is determined according to the proportion of each emulsifier in their total weight the following examples explain that

<u>Example 2:</u> What is the HLB of the mixture of 40 % Span 60 (HLB = 4.7) and 60 % Tween 60 (HLB = 14.9)?

HLB of mixture= 4.7 x 0.4 + 14.9 x 0.6 = 10.8

<u>Example 3:</u> What is the HLB value of a surfactant system composed of 20 g Span 20 (HLB = 8.6) and 5 g Tween 21 (HLB = 13.3)?

$$\text{HLB} = \frac{(\text{Quantity of surfactant 1})(\text{HLB surfactant 1}) + (\text{quantity of surfactant 2})(\text{HLB surfactant 2})}{\text{quantity of surfactant 1} + \text{quantity of surfactant 2}}$$

$$\text{HLB} = \frac{(20\text{ g})(8.6) + (5\text{ g})(13.3)}{(20\text{ g} + 5\text{ g})} = 9.54$$

<u>Example 4:</u> In what proportion should Span 80 (HLB = 4.3) and Tween 80 (HLB = 15.0) be mixed to obtain "required" HLB of 12.0?

4.3*(1-x) + 15*x = 12

x = 0.72

Then the" Emulsifying System" should contain: 72 % Tween® 80 and 28 % Span® 80

Effect of Hydrophilic-Lipophilic (HLB) on emulsion stability

Objective:

To prepare a series of emulsions using the "Hydrophile- Lipophile Balance Method" by using different ratios of Surface Active Agents then to study the stability of these emulsions along standing on shelf over a week (for 7 days)

Materials

1. Mineral oil
2. dye
3. Tween® 80
4. Span® 80
5. Test tubes
6. Marker
7. Ruler

Procedure

1. Prepare 100 ml of 0.1% of the dye in de-ionized water to givecolored water
2. Prepare the following Tabulated emulsions according to the procedure afterTable 3

Table 3: Formulations of mineral oil in water

Emulsion Number	***1***	***2***	***3***	***4***	***5***	***6***	***7***	***8***
Colored Water (gm)	*7*	*7*	*7*	*7*	*7*	*7*	*7*	*7*
Mineral Oil (gm)	*3*	*3*	*3*	*3*	*3*	*3*	*3*	*3*
*Tween® 80 (grams)** *HLB = ……*	*0*	*0*	*0.3*	*0.4*	*0.5*	*0.6*	*0.7*	*1*
*Span® 80 (grams)** *HLB = ……*	*0*	*1*	*0.7*	*0.6*	*0.5*	*0.4*	*0.3*	*0*

* Each drop is equivalent to 0.1 gm

a. Mark 8 test tubes differently from 1 to 8.
b. Into each test tube add the colored water
c. If not zero, add Tween® 80 (drops) to the previous tube and vortex for 30 seconds. Mark the top of the aqueous phase inside the tube with a line on the outside of the tube.
d. Into each previous tube add mineral oil.
e. If not zero, add Span® 80 (drops) above the mineral oil in each tube
f. Vortex the oil phase and aqueous phase for 1 minutes
g. Put on shelf-standing and watch them for 1 hr at 15 minutes interval. At each time point observe the emulsions for the following (see tables)

A. *15 minutes*

Tube Number	Separation (Yes or No) If Yes go to the next column	Number of Separated Layer	Height of the bottom layer (mm)	Did the separation of the bottom layer reach the mark? (Yes or No)
1				
2				
3				
4				
5				
6				
7				
8				

B. 30 minutes

Tube Number	Separation (Yes or No) If Yes go to the next column	Number of Separated Layer	Height of the bottom layer (mm)	Did the separation of the bottom layer reach the mark? (Yes or No)
1				
2				
3				
4				
5				
6				
7				
8				

C. *45 minutes*

Tube Number	Separation (Yes or No) If Yes go to the next column	Number of Separated Layer	Height of the bottom layer (mm)	Did the separation of the bottom layer reach the mark? (Yes or No)
1				
2				
3				
4				
5				
6				
7				
8				

D. 60 minutes

Tube Number	Separation (Yes or No) If Yes go to the next column	Number of Separated Layer	Height of the bottom layer (mm)	Did the separation of the bottom layer reach the mark? (Yes or No)
1				
2				
3				
4				
5				
6				
7				
8				

3. Leave the tubes for the next practical session and observe the Emulsions for the following

E. One week

Tube Number	Separation (Yes or No) If Yes go to the next Column	Number of Separated Layer	Height of the bottom layer (mm)	Did the separation of the bottom layer reach the mark? (Yes or No)
1				
2				
3				
4				
5				
6				
7				
8				

4. Calculate the HLB of the different surfactant systems used for the different formulations. Compare the values versus the RHLB value needed to make O/W emulsion of mineral oil. Correlate these comparisons with the observed stabilityof the emulsions.

Experiment No. 10

Adsorption Isotherm

Objective

Determine the residual equilibrium concentrations of acetic acid after stirring solutions of differing initial concentrations with a constant mass of active carbon. Using the measured results, determining the adsorption isotherm, that is valid for the given system.

Introduction:

Phenomenon whereby molecules or ions are adhered to surface of a solid due to forces of attraction is called adsorption. The solid phase is called the adsorbent and the molecules that are adsorbed on the adsorbent are called the adsorbed phase or adsorbate. The adsorbate can be either a gas (molecules) or a solute (molecules or ions) in solution. There are two types of adsorption i.e. physical adsorption in which the particles are held by physical forces such as dipole and Van der Waals forces and chemical adsorption (or chemisorption) where chemical bonds are formed between the particles and the surface.

The adsorption of acetic acid on charcoal is studied using both the Freundlich isotherm and the Langmuir isotherm. This is an example of physical adsorption, where dipole and van der Waals forces are the predominant sources of attraction, and the heat of adsorption is typically less than 50 kJ/mol.

The amount of acetic acid (adsorbate) adsorbed per gram of charcoal (adsorbent) will depend on the surface area of the charcoal, the temperature of the solution, and the adsorbate concentration in solution. The adsorption will be followed by titrating the acetic acid not adsorbed by the charcoal, then determining the amount adsorbed by difference. Isotherms (plots of moles of adsorbate adsorbed per gram of adsorbent versus solution concentration) will be constructed, then compared with two models: The Freundlich isotherm and the Langmuir isotherm.

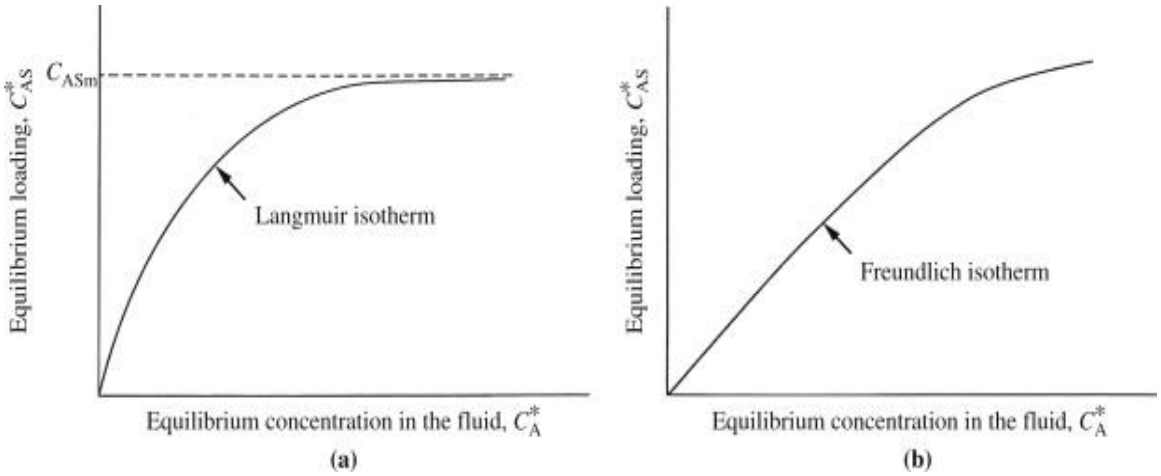
The degree of adsorption depends on:

1- Chemical nature of the adsorbate and adsorbent
2- Total surface area of the adsorbent
3- Temperature
4- Concentration (if liquid) or pressure (if gas) ofadsorbate.

Types of adsorption:

1- Physical adsorption: where the adsorbate is attached to the adsorbent by weak bonds (van der waal forces, hydrogen bonding,……)
2- Chemical adsorption: where adsorbate is attached to the adsorbent by primary chemical bonds(i.e. covalent bonds); so it is an irreversible process.

Adsorption isotherm:



1- Langmuir isotherm: (for monolayer adsorption)

$$x/m = abCeq / (1+bCeq)$$

which can be written as :

$$Ceq/(x/m) = 1/ab + (1/a)Ceq$$

Where:

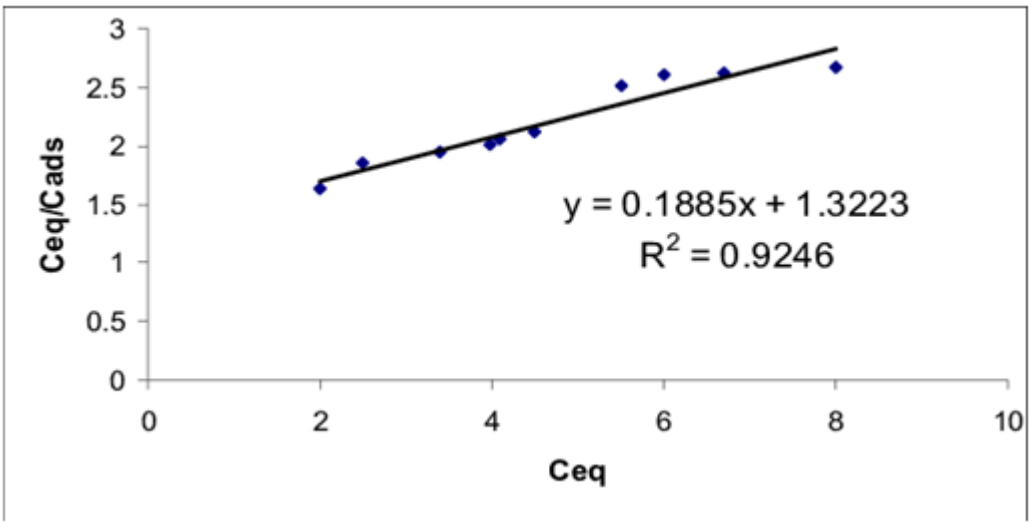
x is the amount of adsorbate adsorbed

m is the mass of adsorbent

C*eq* is the adsorbate concentration at equilibrium

a & b are constants related to the system

According to this equation, when a plot of Ceq/(x/m) versus Ceq gives a linear relationship, monolayer adsorption is assumed.



2- Freundlich isotherm: (for multilayer adsorption)

$$x/m = a*Ceq^{1/n}$$

which can be written as:

$$\log (x/m) = \log a + 1/n \log Ceq$$

where:

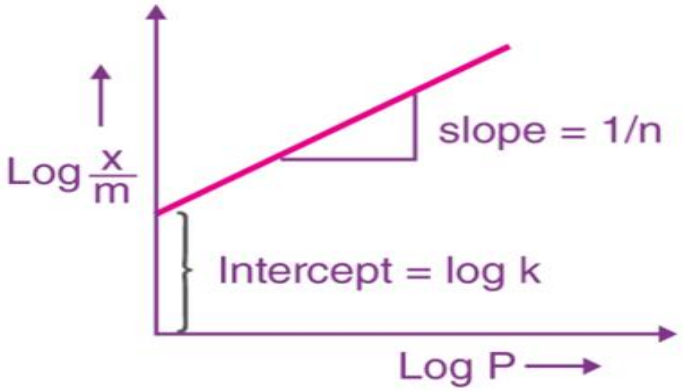
x is the amount of adsorbate adsorbed

m is the mass of adsorbent

C*eq* is the adsorbate concentration at equilibrium

a & n are constants related to the system

according to this equation, when a plot of log (x/m) versus log Ceq gives a linear relationship, multilayer adsorption is assumed.



Experimental Part:

Materials:
Charcoal, 0.50 m acetic acid solution,

Glassware:

Erlenmeyer flasks 250 ml, funnels, burette, beakers, pipettes, pipette fillers, parafilm, filter papers and volumetric flasks 250 and 100 ml.

Procedure:

1. **Prepare 0.50M acetic acid solution in 250ml volumetric flask, and then prepare the following solutions of acetic acid in 100 ml volumetric flask by dilution: 0.20, 0.15, 0.09, 0.05, 0.03M.**
2. **Transfer each of the above solutions to an Erlenmeyer flask, and then add 1.0g of activated charcoal to each flask. Stopper the flasks, shake the contents.**
3. **Shake the flasks well for 15 minutes. Allow to stand for 10 minutes.**

4. **Separate the acetic acid solution in each flask from charcoal by using a filter paper into another flask (discard the first 5-10 ml of each filtrate sample).**

5. **Take 10.0 ml sample of each filtrate and titrate with standard 0.10M NaOH using phenolphthalein as an indicator, record the volume of NaOH needed.**