As Per PCI Regulations
Second Year B. Pharm. • Semester-III & IV

A PRACTICAL BOOK OF PHYSICAL PHARMACEUTICS

SUDIP DAS
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RAVI SHANKAR

NIRALI PRAKASHAN
ADVANCEMENT OF KNOWLEDGE

A Practical Book of

PHYSICAL PHARMACEUTICS

As Per PCI Regulations

SECOND YEAR B. PHARM.

Semester III AND IV

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Preface

Pharmacy Council of India (PCI) setup for co-ordinating the standards of technical education has done a commendable job by bringing about a model syllabus for the B. Pharm. course.

Physical Pharmacy is the process of applying physics and chemistry to the study of pharmaceutics. Physical pharmacy integrates knowledge of mathematics, physics and chemistry and applies them to the pharmaceutical dosage form development. It focuses on the theories behind the phenomena needed for dosage form design. It has enable the pharmacist to make rational decisions on scientific basis concerning the art and technology of solutions, suspensions, emulsions, colloids, etc. It provides the basis for understanding the chemical and physical phenomena that govern the *in-vivo* and *in-vitro* actions of pharmaceutical products.

This book is our first edition textbook "A Practical Book of Physical Pharmaceutics", published by Nirali Prakashan, in the year 2018. This book consisted twenty two experiments as per PCI new syllabus. Our teaching experience in pharmaceutics and physical pharmacy over many years, guided us in deciding the chapter and their contents.

Sincere efforts have been made to make it an ideal practical book on physical pharmacy and the book is also useful for science graduates studying physical chemistry. The book is published in simple language with suitable diagram as per the need of the experiment.

We are grateful to Mr. Amit Jha, Mr. Malik Shaikh and Mrs. Roshan Khan of Nirali Prakashan publishers for their enthusiasm in bringing out this book. We are also grateful to Dr. H. P. Chhetri, founder director of Himalayan Pharmacy Institute, Sikkim, for his continued encouragement and for his valuable suggestion to prepare this book. We are also thankful to Dr. Nihar Ranjan Bhuyan for his valuable guidance to prepare this book.

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Syllabus

Physical Pharmaceutics - I (Practical)

1. Determination of the solubility of drug at room temperature.
2. Determination of pKa value by Half Neutralization/ Henderson Hasselbalch equation.
3. Determination of Partition co-efficient of benzoic acid in benzene and water.
4. Determination of Partition co-efficient of Iodine in CCl_4 and water.
5. Determination of % composition of NaCl in a solution using phenol-water system by CST method.
6. Determination of surface tension of given liquids by drop count and drop weight method.
7. Determination of HLB number of a surfactant by saponification method.
8. Determination of Freundlich and Langmuir constants using activated char coal.
9. Determination of critical micellar concentration of surfactants.
10. Determination of stability constant and donor acceptor ratio of PABA-Caffeine complex by solubility method.
11. Determination of stability constant and donor acceptor ratio of Cupric-Glycine complex by pH titration method.

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Physical Pharmaceutics - II (Practical)

1. Determination of particle size, particle size distribution using sieving method.
2. Determination of particle size, particle size distribution using Microscopic method.
3. Determination of bulk density, true density and porosity.
4. Determine the angle of repose and influence of lubricant on angle of repose.
5. Determination of viscosity of liquid using Ostwald's viscometer.
6. Determination of sedimentation volume with effect of different suspending agent.
7. Determination of sedimentation volume with effect of different concentration of single. suspending agent.
8. Determination of viscosity of semisolid by using Brookfield viscometer.
9. Determination of reaction rate constant first order.
10. Determination of reaction rate constant second order.
11. Accelerated stability studies.

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Physical Pharmaceutics - I (Practical)

Experiment No. 01

Determination of the Solubility of Drug at Room Temperature

Aim: To determine the solubility of drug at room temperature.

Theory:

One of the primary physicochemical considerations of preparing pharmaceutical solutions is the solubility of the drug in a suitable solvent.

Solubility is the property of a solid, liquid or gaseous chemical substance (solute) to dissolve in a solid, liquid or gaseous solvent. Solubility of a substance depends on the physicochemical properties of the solute and solvent as well as on temperature, pressure and the pH of the solution.

The solubility of any substance is a function of temperature. Most substances are endothermic in nature (absorbing heat), in the process of dissolution. For these substances, an increase in temperature results in an increase in solubility. A few substances, such as Calcium hydroxide and Sodium carbenicillin are exothermic (releasing the heat) and give off heat in the process of dissolution. The solubility of such substances would decrease with an increase in temperature. Oral preparation is the most convenient and common route of drug delivery. However, the major challenge with the design of oral dosage form lies within their poor bioavailability. The cause of low oral bioavailability is the poor solubility of the drug and low permeability of the drug.

In this experiment, sodium chloride is used as an electrolyte necessary for many body functions. It can be mixed with water to form normal saline. It is given by I.V. route to replace lost fluids and correct electrolyte imbalances. It can be used in a solution as wound rinse.

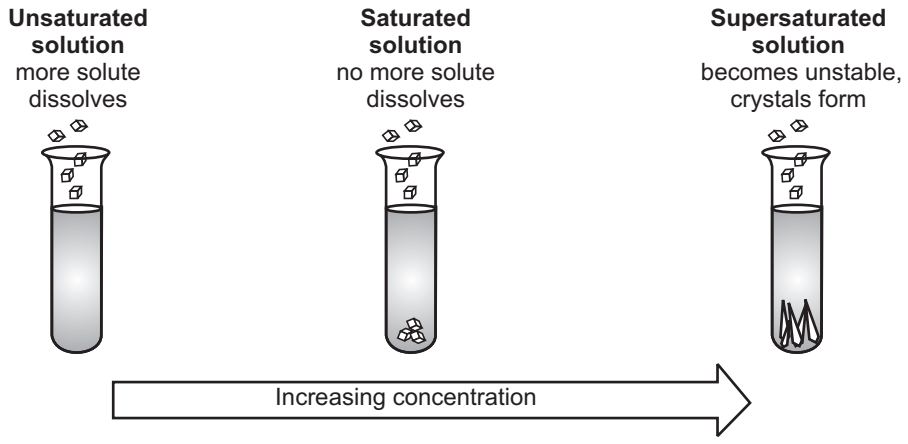

Fig. 1: Different types of solutions

Table 1: General terms used for expressing solubility

Descriptive terms	Parts of solvent needed for 1 part solute
Very soluble	< 1
Freely soluble	1-10
Soluble	10-30
Sparingly soluble	30-100
Slightly soluble	100-1000
Very slightly soluble	1000-10,000
Practically insoluble	> 10,000

Solubility is also expressed quantitatively in terms of percentage, molality and molarity. Molality is expressed as a number of moles of solute dissolved in 1000 g of solvent and molarity is expressed as a number of moles (gram molecular weight) of solute dissolved in 1000 g of solvent. There are three concentration terms are used in the pharmaceutical field. These are:

1. % w/w is the number of grams of solute dissolved in 100 g of solution.
2. % v/v is the number of ml of solute dissolved in 100 g of solution.
3. % w/v is the number of gram of solute dissolved in 100 ml of solution.

For the determination of the solubility of a solid in liquids, it can be divided into two steps:

1. Preparation of saturated solution:

Saturated solution of substance can be prepared by the three methods:

(a) In the first method, the substance is added in the solvent slowly at a particular temperature and solute is not added more than the saturation.

(b) The second method is based on the effect of temperature, if solubility increases with increasing temperature. Again if the solubility is to be studied at 30°C, then the solvent is to be heated at 35°C to 40°C with excess amount of solute. The amount of solute required is more at higher temperature for the preparation of saturated solution. When this solution is cooled at the previous temperature, the excess amount of solute is separated out in the solution. It can be separated by the filtration method. The filtrate solution is considered as saturated solution at the previous temperature.

(c) In the third method, excess amount of the solute is added in solvent at the study temperature and shaken with continuous stirring, with occasional shaking and removing excess amount of solute by filtration. This solution is known as saturated solution.

2. Analysis of saturated solution:

Saturated solution can be determined by the following methods:

(a) Evaporation method: This method is suitable for those substances which do not decompose at a slightly higher temperature than the boiling point of a solvent. In this method known volume saturated solution is taken in porcelain dish is weighed and the solvent is evaporated till dryness. It is heated to get a final volume in an oven to a constant weight. Thus, the amount of the solid present in the solution can be calculated.

(b) Volumetric method: This method is based on the acid-base titration. In this method, a fixed volume of solution is treated with a suitable reagent using an indicator and determine amount of the solute present in the solution.

(c) Instrumental method: This method is very popular nowadays. The methods are:

(i) High Performance Liquid Chromatography (HPLC).

(ii) Thin Layer Chromatography (TLC).

(iii) Gas Chromatography (GC).

(iv) UV-Spectroscopy.

Requirement:

Chemicals: Distilled Water, Drug (Sodium chloride).

Apparatus: Conical flask, Weighing balance, Watch Glass, Hot Plate, Pipette, Thermometer, Glass rod, Hot air oven.

Procedure:

1. Clean all the glassware apparatus with detergent solution or chromic acid solution.
2. Wash all the glassware apparatus with distilled water (2 to 3 times).
3. Around 20 g of sodium chloride is added with 50 ml of water in a conical flask, with constant stirring using glass rod.
4. The stirring is continued till a saturated solution is obtained.
5. A part of solid is left undissolved in a conical flask.
6. The solution is filtered and 10 ml of the filtrate is pipetted out into a preweighed watch glass.

7. The watch glass containing 10 ml of filtrate (Saturated solution of Sodium chloride) is weighed.
8. Then the filtrate is evaporated and dried at about 100°C in a hot air oven.
9. Then it is cooled and weighed.
10. The drying is continued till a constant weight is obtained.

Observation:

Room temperature: _____°C.

- Weight of empty watch glass: W_1 g.
- Weight of watch glass + 10 ml sodium chloride solution: W_2 g.
- Weight of watch glass + Dry solution (dry sodium chloride): W_3 g.

Calculation:

Weight of solute in 10 ml solution = $(W_3 - W_1)$ g = W_4

Weight of solvent in 10 ml solution = $(W_2 - W_3)$ g = W_5

Volume of solvent in ml = $\frac{\text{Weight of solvent}}{\text{Density of solvent}} = \frac{W_5}{\text{Density of water}}$

Solubility is the parts of solvent required for 1 part of solute.

W_4 g of solute requires = $\frac{W_5}{\text{Density of water}}$ ml of water

1 g of solute will require = $\frac{W_5}{W_4 \times \text{Density of water}}$ ml of water

Report:

The solubility of drug (Sodium chloride) at …… **ºC** room temperature (specify) is 1 in …… ml.

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Experiment No. 02

Determination of the pK_a Value by Half-Neutralization / Handerson-Hasselbalch Equation

Aim: To determine the pK_a value by half-neutralization/Handerson-Hasselbalch equation.

Theory:

A common analysis of a weak acid or a weak base is to conduct a titration with a base or acid of known molar concentration to help to determine the equilibrium constant, pK_a for the weak acid or weak base. The results obtained by conducting this titration very carefully and precisely, can lead to a valid approximation of equilibrium constant.

The primary goal in this experiment is to calculate the pK_a of acetic acid and the data we use to complete the calculations, which will come from the reaction of acetic acid with a solution of NaOH in a weak acid-strong base titrations, the point at which a reaction is half-neutralized can be used to determine the pK_a of the weak acid. In this experiment, the half-neutralization point will exist when we have added half as many moles of CH_3COOH as moles of NaOH. Thus, hydroxyl ions will have reacted with half of the CH_3COOH, leaving the solution with equal moles of CH_3COOH and CH_3COO^- ion. At this point, according to the Handerson-Hasselbalch equation, if there are equal moles of CH_3COOH and CH_3COO^- at the half-neutralization point, then the pK_a is equal to the pH value of the solution.

$pH = pK_a + \log (CH_3COO^-) / (CH_3COOH)$

$pK_a = pH - \log (CH_3COO^-) / (CH_3COOH)$

In this experiment, we do not need to keep close track of the volume of NaOH (titrant) added as in most of other titrations. Therefore, half-neutralization is only important to know when equal amounts of OH^- and CH_3COOH have been added.

The pH of a buffer solution and the change in the pH upon addition of a acid or a base can be calculated based on the use of the buffer equation which is an expression developed by considering the effect of a salt on the ionization of a weak acid or a weak base when the salt and the acid or base have an ion in common.

Common ion effect: Now let us take an example of a mixture of a weak acid like acidic acid and its salt (sodium acetate). Acetic acid is very slightly dissociated in solution while sodium acetate being a salt is almost completely dissociated. The mixture thus consist of CH_3COOH molecules as well as CH_3COO^- and Na^+ ions. If a strong acid is added to the mixture, the H^+ ions supplied by the acid are immediately taking up by CH_3COO^- ions to form the very slightly dissociated CH_3COOH.

$$H^+ + CH_3COO^- \longrightarrow CH_3COOH$$

The H^+ ions are thus neutralized by the acetate ions present in the mixture and there is very little change in the pH value of the mixture.

If a strong base is added, the OH^- ion supplied by the base is neutralize by acetic acid present in the mixture and again there is very little change in the pH of the solution.

$$OH^- + CH_3COOH \longrightarrow CH_3COO^- + H_2O$$

A mixture of weak acid and its salt also behave in a similar manner. Let us take an example of a mixture containing equimolar solution of NH_4OH and its largely dissociated salt, ammonium chloride. The mixture contain undissociated NH_4OH as well as NH_4^+ and Cl^- ion. If a strong acid is added to this mixture, the H^+ ions supplied by the acid are neutralize by the base NH_4OH.

$$H^+ + NH_4OH \longrightarrow H_2O + NH_4^+$$

On the other hand if a strong base is added, the OH^- ion are neutralize by NH_4^+ ion forming vary slightly dissociated NH_4OH.

$$OH^- + NH_4^+ \longrightarrow NH_4OH$$

Let us take an example of the effect of addition of sodium acetate on the ionization of acetic acid. Both sodium acetate and acetic acid have an ion common between them i.e. CH_3COO^-.

The dissociation constant for the acid is given by

$$CH_3COOH \longrightarrow CH_3COO^- + H_2O$$

$$K_a = [CH_3COO^-]\,[H_3O^+] / [CH_3COOH]$$

If sodium acetate is added to the acetic acid solution, it ionizes to give acetate ions.

$$CH_3COONa \longrightarrow CH_3COO^- + Na^+$$

This causes a momentary increase in the concentration of CH_3COO^- in the solution. To reestablish the dissociation constant for the solution, the hydrogen ion term in the numerator is instantaneously decreased. This results in the increase of the concentration of CH_3COOH in the denominator. Thus the reaction,

$$H_3O^+ + CH_3COO^- \longrightarrow CH_3COOH + H_2O$$

Is favoured and the constant K_a remains unaltered. In other words, the ionization of acetic acid is replaced upon the addition of the common acetate ion to the solution and this is known as the common ion effect.

The pH of the buffer solution can be obtained by rearranging the above equation for dissociation constant:

$$H_3O = Ka\,[CH_3COOH] / [CH_3COO^-]$$

Since, acetic acid ionizes only slightly, the concentration of acetic acid may be consider to represent the total concentration of acid in the solution. Hence the term $[CH_3COOH]$ can be replaced by acid. Similarly the acetate ion is contributed almost entirely by the salt, sodium acetate, CH_3COO^- may be replaced by salt.

Therefore,

$$H_3O = Ka\,[acid] / [salt]$$

Expressing in logarithm form,

$$\log [H_3O^+] = \log K_a + \log [acid] - \log [salt]$$

We can write the above equation,

$$-\log [H_3O^+] = -\log K_a - \log [acid] + \log [salt]$$

Or

$$pH = pK_a + \log [salt] / [acid]$$

This is known as the buffer equation or the Handerson – Hasselbalch equation for a weak acid and its salt. The buffer capacity of a solution is a major of its magnitude of resistant to change in pH on addition of an acid or a base. It is also refer to as buffer index, buffer efficiency, buffer coefficient or buffer value.

Requirement:

Chemicals: 1 M sodium hydroxide (NaOH) solution, 1 M acetic acid (CH_3COOH) solution, phenolphthalein (indicator solution), Distilled water.

Apparatus: Burette stand, 250 ml conical flask, Magnetic stirrer, Bulb pipette.

Procedure:

Step I:

1. Wash all the glass apparatus with distilled water (2 – 3 times).
2. Fix the burette into the burette stand (taking care it is vertical and stable).
3. Rinse the burette with 1 M acetic acid solution.
4. Fill the burette with 1 M acetic acid solution.
5. Transfer precisely 25 ml of acetic acid solution from the burette to a 250 ml of conical flask.
6. Take 10 ml of bulb pipette, pipette out small volume of the 1 M acetic acid from the conical flask. Draw enough acetic acid into the pipette so that the bulb contains $1/4^{th}$ full of 1 M acetic acid in a 100 ml beaker and set aside to be used later.
7. Add 1-2 drops of phenolphthalein indicator solution to the conical flask.
8. Check the pH of the solution in the conical flask using pH meter.

Step II:

1. Take another burette.
2. Add 50 ml of 1 M NaOH solution in the burette.

Step III:

Begin the half titration:

1. Place the conical flask of acetic acid on a magnetic stirrer platform and add a magnetic bead in the conical flask.
2. Gently stir the acetic acid solution.
3. Determine the pH of the solution using pH meter.
4. Slowly add the 1 M NaOH solution from the burette (approximately 1 ml increment), to the conical flask of acetic acid solution.
5. Continue to check the pH simultaneously.

6. Conduct the titration carefully. As the reaction approaches the equivalence point, at about pH 6, add the NaOH solution drop by drop. When the equivalence point is reached, the pH will change rapidly (but not beyond equivalence point i.e. pH-10) and the indicator will change colour.
7. Add all of the acetic acid from the 100 ml beaker which we removed in step-6), to the conical flask of reaction mixture. Check the pH readings and observe the indicator colour. The mixture should be slightly acidic once again.
8. Carefully add NaOH, drop by drop, from the burette to the conical flask of reaction mixture, until you reach the equivalence point as precisely as possible. A very slight pink colour of the phenolphthalein indicator is visible. This is the half-neutralized solution, because we have neutralized precisely 25 ml of the original 50 ml of the acetic acid that we measured out into the burette.
9. Transfer the remaining 25 ml of acetic acid from the burette to the 250 ml conical flask of reaction mixture. Stir the solution in the conical flask thoroughly and record the final pH of the solution in the conical flask when it is stable.
10. Repeat the same procedure for other two more trials.

Observations and Calculations:

Titration results	Trial 1	Trial 2	Trial 3
Equivalence point pH			
pH of half-neutralized solution			

Using Handerson-Hasselbalch equation, calculate the pK_a from the above readings.

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

Report:

The pK_a of the given sample was found to be …….

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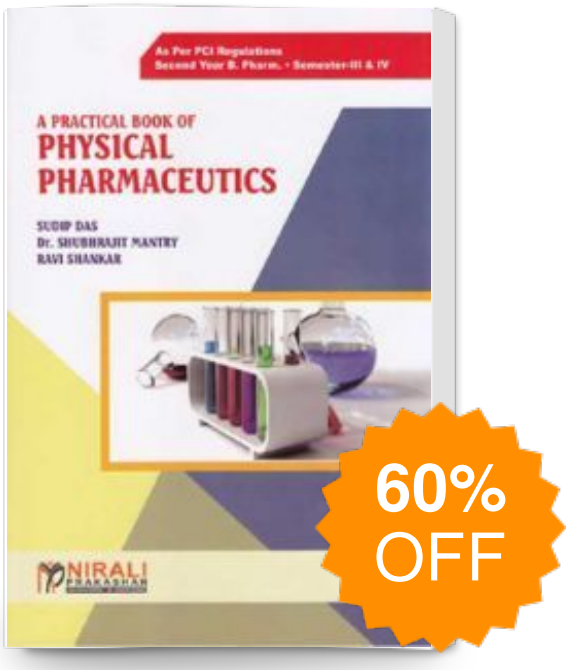
Physical Pharmaceutics



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