Shree H.N. Shukla Institute of Pharmaceutical Education and Research Rajkot

B.Pharm
Sem-1

Subject Name: Pharmaceutics
Subject code: BP103TP

2.1 PHARMACEUTICAL CALCULATION

Metrology

While dispensing of drug it is desirable for a pharmacist to have thorough knowledge regarding weights and measures which are used in calculations.

There are two types of system for weights and measures:

1. Imperial system
2. Metric system

1. Imperial System

This is an old system of weights and measures.

Weight is a measure of the gravitational force acting on a body and is directly proportional to mass.

The imperial system is divided in two parts for the purpose of measurement of weights. These are

(a) Avoirdupois system.

(b) Apothecaries system.

(a) Avoirdupois System: Primary unit of weight is pound (LB) and all measures of mass are derived from the imperial standard pound thus,

(a) 1 pound (lb) = 16 ounce (oz)

(b) 1 pound = 7000 grains

(c) 1 ounce (oz) = 7000/16 = 437.3 grains

Here only weight is primarily used for compounding.

437.5 grain = 1 oz = 28.35 gm

7000 grain = 1 lb = 16 oz = 454 gm

1 kg = 2.2 lb

1 gr = 64.8 mg

(b) Apothecary System: Comprised of both volume and weight. It is used for compounding and for preparing concentration for dilution. In this system, weight is measured in grain and volume in Minim.

(i) Volume:

1 teaspoonful (tsp) = 5 milliliters (ml) = 1 dram = 5 cubic centimeters (cc)

1 tablespoonful (tbsp) = 15 milliliters (ml)

29.57 milliliters (ml) = 1 fluid ounce (fl oz)

473 milliliters (ml) = 1 pint (pt) = 16 fluid ounce (fl oz)

946 milliliters = 1 quart = 2 pints

3784 milliliters = 1 gallon = 8 pints = 128 fl oz

(ii) Weight:

1 grain = 64.8 mg

1 ounce = 31.1 gm = 480 grain

2. Metric System

The metric system is used for the measurement of weight and capacity. The metric system in India was implemented from 1st April 1964 in pharmacy profession. This system was used the Indian pharmacopoeia. The metric system is an alternative system of measurement used in most countries, as well as in the United States. The metric system is based on joining one of a series of prefixes, including kilo-, hecto-, deka-, deci-, centi-, and milli-, with a base unit of measurement, such as meter, liter, or gram.

Measurement of weight in metric system: A kilogram is the standard unit for measurement of weight and all other measures are derived from it.

1 kilogram (kg) = 1000 grams

1 gram = 1000 mg

1 milligram (mg) = 0.001 gram

1 microgram (mcg) = 0.000,001 gram

1 hectogram (hg) = 100 grams

1 decagram (dag) = 10 grams

1 decigram (dg) = 0.1 gram

1 centigram (cg) = 0.01 gram

Measurement of volume or capacity: for measuring volume litre is used as the standard unit and the remaining measures can be derived from it.

1 litre (lt) = 1000 millitre (ml)

Convert the following apothecary problems using the ratio and proportion method:

1. 2,000 gr = 4.167 oz (AP)
2. 500 gm = 16.077 oz (AP)
3. 500 mg = 7.716 gr
4. 100 fl oz = 6.25 pt
5. 500 fl oz = 3.906 gal
6. 4.5 oz (AP) = 139.95 gm
7. 3 gr = 194.4 mg
8. 20,000 ml = 5.284 gal
9. 3 pt = 1,419 ml
10. 119 ml = 4.024 fl oz
11. 2.5 gal = 320 fl oz
12. 5,000 gr = 10.417 oz (AP)
13. 25 pt = 3.125 gal
14. 1,500 ml = 3.171 pt
15. 6 fl oz = 177.42 ml
16. 0.75 gal = 2,838.75 ml
17. 1,000 gr = 2.083 oz (AP)
18. 3.25 gal = 26 pt
19. 350 gr = 22,680 mg
20. 2.5 oz (AP) = 1,200 gr
21. 1.5 tsp = 7.5 ml
22. 12.5 ml = 2.5 tsp
23. 1.5 fl oz = 44.355 ml
24. 500 mg = 7.716 gr
25. 500 fl oz = 3.906 gal
26. 375 ml = 12.682 fl oz
27. 24 fl oz = 1.5 pt
28. 275 gm = 8.842 oz (AP)
29. 500 ml = 33.333 Tbsp
30. 1 drop = 0.05 ml
31. 1 tsp = 5 ml
32. 1 tbsp = 15 ml
33. 1 wineglass ful = 60 ml
34. 1 tumbler ful = 240 ml
35. 1 inch = 2.54 cm
36. 1 pint = 473ml
37. 1 gallon = 3785 ml
38. 1 quart= 946 ml

2.2 CALCULATION OF ISOTONOCITY

1. Freezing Point Method

The lachrymal secretion contains several solutes in it and has a freezing point of –0.52°C. All solutions, which freeze at –0.52°C, will be isotonic with the lachrymal fluid. Human blood plasma also freezes at this temperature and hence solutions having freezing point at – 0.52°C will be isotonic with blood plasma as well.

Adjustment of tonicity is simplified if the freezing points of the medicament and the inert salt (adjusting substance) are known for various strengths of their solutions. Freezing points are usually expressed in terms of 1% solutions and one can calculate the quantity by multiplying the freezing point with the factor.

The following equation is useful:

Freezing point of tear secretion Freezing point of drug + freezing or human Blood plasma = point of the adjusting substance.

Therefore, the amount of adjusting substance required may be calculated from the equation $W = \frac{(0.52 - a)}{b}$

Where,

W = Weight in g, of the added substance in 100 ml of the final solution;

a = Depression of the freezing point produced by the medicament already present in solution, calculated by multiplying the value for the medicament by the strength of the solution expressed as a percentage w/v; and

b = Depression of the freezing point of water produced by 1% of the adjusting substance.

Example 2.1:

How much boric acid is required to render 200 ml of eyewash containing 1% boric acid are to be dispensed.

(F.P. of 1% boric acid at – 0.29°C and F.P. of 1% solution of sodium chloride = – 0.58°C).

Applying the above equation:

Thus the working formula for 200 ml of the eyewash will be:

Boric acid (1%, for 200 lL) = 1 g × 2 = 2 g.

Sodium chloride (0.39%, for 200 ml) = 0.39 × 2 = 0.78 g.

Purified water q.s. 200 ml.

Solution:

However if the pharmacist has been asked to supply 200 ml of eyewash of boric acid, the calculation will be as follows:

Lowering of 0.29°C in F.P. is caused by 1 g of boric acid

Lowering of 0.52°C in F.P. will be caused by 1.8 g of boric acid

Therefore, 1.8 g of boric acid is required to make 100 ml of eyewash and the working formula will be : Boric acid (1.8%, for 200 ml) = 1.8 × 2 = 3.6 g. Purified water, q.s. 200 ml.

2. Molecular Weight Method

Freezing point of a solute depends on the concentration of the solute dissolved therein. Greater the concentration of the solute, lower is the freezing point. In other words, it depends on the number of ions (more correctly, the number of effective ions), the weight of the substance and its molecular weight. The concentration for 0.9% solution of sodium chloride can be expressed in the following manner:

Percentage w/v of adjusting substance required = 0.03 m/n

Where n = No. of effective ions (n)

m = molecular weight of substances (m)

Since 0.9% solution of sodium chloride (normal saline) is isotonic with body fluids, 0.03 will be the isotonicity or tonicity factor for tear secretion and blood plasma as well. Thus quantities for making eye solutions can be calculated by equating the value of 0.03 with the tonicity contributed by the drug and the additive(s).

The following equation is employed for calculating the quantity of the additive(s):

$$\text{Quantity of additive} = (g/m) \times n$$

where g, n and m denote the weight in gram, effective ion concentration and molecular weight of the medicament, respectively. Effective ionic concentration can be ascertained from the following generalizations;

n = 1 for non-ionizable substances, e.g. dextrose

n = 1.5 for partially ionizable solutes in two ions, e.g. silver nitrate

n = 2 for highly ionizable solutes in two ions e.g. sodium chloride

n = 2 for partially ionizable solutes in three ions, e.g. sodium sulfate

Example 2.2:

Find the concentration of sodium chloride required to produce a solution isoosmotic with blood plasma.

Solution:

Molecular weight of sodium chloride = 58.5

Sodium chloride is ionizing substance and hence it gets dissociated into two ions.

Therefore, the formula used is

$$W = 0.03\ m/n$$

$$= \frac{(0.03 \times 58.5)}{2}$$

$$= 0.88\ g/100\ ml$$

3. Sodium Chloride Equivalent Method

This is the simplest method and is based on the sodium chloride equivalents of various drugs. Sodium chloride equivalent of a drug represents the amount of sodium chloride equivalent to 1 g of the drug. The method avoids tedious calculation.

It can be memorized that 0.27 g of sodium chloride makes 30 ml of a 0.9% solution and that 4.1 grain of sodium chloride makes 1 fl oz. of a 0.9% solution.

This was given by Mellen & Seltzer, also called tonicic equivalent.

* The sodium chloride equivalent of a drug is the amount of sodium chloride that is equivalent to (i.e. has same osmotic effect as 1 g or other weight unit of the drug.

It is represented by "E". E_{value} can be calculated for number of drugs.

It can be calculated from Liso or freezing point depression value.

For solution containing 1 g of drug in 1000 ml or (1L) of solution the molar concentration is

$$c = 1\ g/Mwx_1$$

$$\Delta T_f = Liso\ 1\ g/Mwx_1$$

Now E is the weight of NaCl with "same freezing point depression" of 1 g of the drug and for NaCl solution containing E grams of drug per 1000 ml.

$$\Delta T_f = 3.4E/58.45 \text{ (Liso of NaCl = 3.4)}$$

$$Liso\ 1\ g/Mwx_1 = \frac{3.4E}{58.45}$$

$$E = \frac{17 \times Liso}{Mw}$$

Example 2.3:

Calculate the number of gram of sodium chloride, which should be added to 120 ml of 0.5% solution of pilocarpine hydrochloride to make it isotonic.

Solution:

Weight of pilocarpine hydrochloride contained in the prescription = 120 × 0.5% = 0.6 g Sodium chloride equivalent of pilocarpine hydrochloride = 0.22.

Hence, the amount of sodium chloride represented by pilocarpine hydrochloride contained in the prescription = 0.6 x 0.22 = 0.132 g.

120 mL of 0.9% sodium chloride would contain 120 × 0.9 = 1.08 g of sodium chloride.

This is the amount of sodium chloride required to make 120 ml of isotonic solution in absence of pilocarpine hydrochloride.

Hence, the number of g of sodium chloride required = 1.08 g – 0.132 g = 0.948 g

Example 2.4:

Calculate the number of gram of sodium chloride needed to render 30 ml of physostigmine salicylate solution isotonic.

Solution:

Weight of physostigmine salicylate contained in the prescription = 30 × 0.5 = 0.15 g.

Sodium chloride equivalent of Physostigmine salicylate = 0.14

Hence, Physostigmine salicylate present in the prescription is equivalent to:

$$0.15 \times 0.14 = 0.0210 \text{ of sodium chloride.}$$

30 ml of a solution containing 0.9% sodium chloride will contain 30 × 0.9% = 0.27 g of sodium chloride if sodium chloride alone is present in the prescription.

Number of gram of additional sodium chloride needed = 0.27 g – 0.0210 g = 0.2490 g

Example 2.5:

Calculate the amount of sulphate as barium sulphate from sodium sulphate.

Solution:

Solution of sodium sulphate (Na_2SO_4) is treated with solution of barium chloride ($BaCl_2$) to get precipitates of barium sulphate ($BaSO_4$). The precipitates are then washed, dried and ignited to get free from impurities and then weighed.

$$Na_2SO_4 + BaCl_2 \rightarrow BaSO_4 + 2N$$

Molecular weight of $BaSO_4$ = 233.42 g

Molecular weight of SO_4^- = 96.06 g

Suppose obtained weight of BaSO4 precipitates = X g

233.42 gm of $BaSO_4$ = 96.06 gm of SO_4^- ions

$$BaSO_4 = \frac{96.06}{233.42}$$

= 0.411 g of SO_4^- ions

Suppose 25 ml solution is consumed, then

25 ml solution contains = 0.411 g of SO_4^- ions

1000 ml solution conatins = (0.411 x 1000)/25 = 16.44 g of SO_4^- ions

Example 2.6:

Calculate the amount of zinc oxide from zinc sulphate.

Solution:

A solution of zinc sulphate is boiled to convert it into zinc carbonate by adding solution of sodium carbonate. Sodium carbonate is added to precipitate zinc completely as zinc carbonate. Precipitates of zinc carbonate is boiled for few minutes to convert it into zinc oxide and collected in a tarred Gooch crucible. Precipitates are washed with hot water until it gets free from alkali and then dried, ignited and weighed to a constant weight.

$$ZnSO_4 + Na_2CO_3 \rightarrow ZnCO_3 + Na_2SO_4$$

$$ZnCO_3 \rightarrow ZnO + CO_2$$

$$ZnSO_4 = ZnCO_3 = ZnO$$

$$ZnSO_4 = ZnO$$

Molecular Weight of $ZnSO_4$ = 168 gm

Molecular Weight of ZnO = 81.38 gm

81.38 gm of ZnO = 168 gm of $ZnSO_4$

1 gm of ZnO = ?

$$= \frac{168 \cdot 1}{81.38}$$

= 1.984 gm

Example 2.7:

Calculate the amount of Boric acid from Borax.

Solution:

Borax is an alkaline substance, and reacts with conc. HCl to form Boric acid. Boric acid is freely soluble in boiling water and precipitated out in cold water. To get high grade of Boric acid, Borax is treated with conc. HCl as it is volatile in nature and would not left any residual traces on crystal surface of Boric acid.

Weigh and dissolve 5 gm of Borax in 15 ml of distilled water. Add 7 ml of conc. HCl, mix thoroughly with glass rod and mark the original volume with glass rod. Evaporate the solution till the volume reduces to half of the original volume. Allow to cool at room temperature. Keep it aside for few minutes and add ice water. Filter the residue under suction and dry it in air. Weigh the compound preparation.

$$Na_2B_4O_7 \cdot 10H_2O \rightarrow 4H_3BO_3 + 5H_2O + 2NaCl$$

Molecular weight of Borax = 381.37 gm, Molecular weight of Boric acid = 61.83 gm

Practical yield: X gm

381.37 gm of Borax = 4 × 61.83 gm of Boric acid

X gm of Borax = ?

= (4 x 61.83) /381.37

= 0.674 g of Boric acid

4. Percentage Solutions:

The concentration of a solution is often expressed as the percentage of solute in the total amount of solution. For the extremely dilute solutions the concentration unit parts per million (ppm) is often used. Since, the amounts of solute and solution present can be stated in terms of either weight or volume.

A percentage solution is an weight or volume of something per 100 ml or 100 g of a solution. Percentage means rate per hundred.

50% means 50 parts in 100 of same kind = 50/100 = 0.5

There are three types of percentage solution:

1. Percentage weight by volume (w/v).
2. Percentage volume by volume (v/v).
3. Percentage weight by weight (w/w).

Percent weight in volume w/v: number of gram of a constituent in 100 ml of solution or liquid preparation.

Percent volume in volume v/v: express number of ml of a constituent in 100 ml of a solution or preparation.

Percent weight in weight w/w: express number of gram of a constituent in 100 gram of a solution or preparation.

(a) Percentage Weight by Volume w/v:

$$\text{Concentration (expressed in \%)} = \frac{\text{Quantity or volume of solute}}{\text{Quantity or volume of preparation}}$$

Example 2.8:

How many grams of dextrose are required to prepare 4000 ml of 5% solution?

Solution:

Let the quantity of solute be X

Using the formula

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$5\% = \frac{X}{4000}$$

Therefore $$X = \frac{4000 \times 5}{100}$$

$$= 200 \text{ gram of dextrose}$$

Example 2.9:

What is the percentage (w/v) of solution of urea if 80 ml contain 12 g?

Solution:

Let the percentage of urea be X.

Using the formula,

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$X\% = \frac{12}{80}$$

Or $$\frac{X}{100} = \frac{12}{80}$$

Or $$X = \frac{12 \times 100}{80}$$

$$= 15\%$$

Example 2.10:

How many ml of 3% solution can be made from 27 g of ephedrine sulphate?

Solution:

$$\text{Volume of preparation} = X$$

$$\text{Concentration} = \frac{\text{Quantity of solute}}{\text{Quantity of solution}}$$

$$3\% = \frac{27}{X}$$

Or, $$\frac{3}{100} = \frac{27}{X}$$

Therefore, $$X = \frac{27 \times 100}{3} = 900 \text{ ml}$$

(b) Percentage Volume by Volume v/v:

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$\text{Specific gravity} = \frac{\text{Given weight}}{\text{Volume required}}$$

Example 2.11:

How many ml of liquefied phenol should be used in compounding the following prescription?

Liquid Phenol - 2.5%

Calamine lotion – 240 ml

Solution:

Using the formula,

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$2.5\% = \frac{X}{240}$$

$$X = \frac{2.5 \times 240}{100} = 60 \text{ ml}$$

Example 2.12:

For preparing 250 ml of lotion, 4 ml liquid phenol is used. What was the (v/v)% of liquefied phenol in solution?

Solution:

Using the formula,

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$X\ \% = \frac{4}{250}$$

$$\frac{X}{100} = \frac{4}{250}$$

Or, $$X = \frac{4 \times 100}{250}$$

$$= 1.6\%$$

Example 2.13:

What is the % strength (v/v) of a solution of 800 g of a liquid with a specific gravity of 0.8 in enough water to prepare 4000 ml.

Solution:

$$\text{Specific gravity} = \frac{\text{Weight given}}{\text{Volume required}}$$

$$\text{Volume required} = \frac{\text{Weight given}}{\text{Specific gravity}} = \frac{800}{0.8} = 1000$$

$$\text{Concentration} = \frac{\text{Volume of solute}}{\text{Volume of preparation}}$$

$$= \frac{1000}{4000}$$

$$\frac{X}{100} = \frac{1000}{4000}$$

$$X = 25\%\ v/v$$

(c) Percentage Weight/Weight (w/w):

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

Example 2.14:

How many grams of phenol should be used to prepare 240 g of 5% (w/w) solution in water?

Solution:

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

$$5\ \% = \frac{X}{240}$$

$$X = \frac{5 \times 240}{100} = 12\ g$$

Example 2.15:

How many grams of a drug substance are required to make 120 ml of a 20% w/w solution having specific gravity of 1.15.

Solution:

$$\text{Volume of solution} = 120 \text{ ml}$$

$$\text{Weight} = ?$$

$$\text{Volume} = \frac{\text{Weight}}{\text{Specific gravity}}$$

$$\text{Weight} = 120 \times 1.15 = 138 \text{ g}$$

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of preparation}}$$

$$20\% = \frac{X}{138}$$

$$X = \frac{20 \times 138}{100} = 27.6 \text{ g}$$

Example 2.16:

How many grams of a drug substance should be dissolved in 240 ml of water to make a 4% (w/w) solution.

Solution:

$$100\% - 4\% = 96\% \text{ (by weight) of water}$$

240 ml of water weighs 240 g

$$\text{Using formula Concentration} = \frac{X}{240}$$

$$\frac{4}{96} = \frac{X}{240}$$

$$X = 10 \text{ g}$$

Example 2.17:

How should you prepare 100 ml of a 2% (w/w) solution of a drug substance in a solvent having specific gravity of 1.25 ml.

Solution:

100 ml of water weighs 100 g

$$\text{Specific gravity} = \frac{\text{Weight}}{\text{Volume}}$$

$$1.25 = \frac{X}{100}$$

$$X = 125 \text{ g is weight of 100 ml solvent}$$

$$\text{Concentration} = \frac{\text{Weight of solute}}{\text{Weight of solution}}$$

$$2\%\ (w/w) = \frac{X}{125}$$

$$\frac{2}{98} = \frac{X}{125}$$

$$X = \frac{2 \times 125}{98} = 2.55\ g$$

Dissolve 2.55 g of drug in 125 g of solvent.

Alcohol Dilutions:

Dilute alcohols are made from 95% alcohol which contains 95 parts by volume of ethyl alcohol and 5 parts by volume of water.

Following changes occur when alcohol gets mixed with water.

(a) There is sudden rise in temperature.

(b) There is contraction in volume.

Appearance of turbidity in the solution because solubility of air is more in alcohol than in water. When alcohol is diluted with water, minute bubbles of air get evolved from the alcohol and make the solution turbid.

So when the alcohol is diluted with water, it is necessary to cool the mixture to about 20°C and then final volume is made up.

The formula used is:

Quantity of stronger solution to be used X concentration of alcohol used

= Quantity required to prepare X Concentration of alcohol required.

Example 2.18:

If 500 ml of a 15% solution are diluted to 1500 ml, what will be the percent strength?

Solution:

Using the above formula

$$500\ ml \times 15\% = 1500\ ml \times X\%$$

$$7500 = 1500X$$

$$\frac{7500}{1500} = \frac{1500X}{1500}$$

$$X = 5\%$$

Example 2.19:

If 2000 gm of ointment contain 75 gm of hydrocortisone, what is the percentage strength (w/w) of the ointment?

Solution:

$$\frac{75\ gm\ (Active\ ingredient)}{2000\ gm\ (Total\ amount)} = \frac{1}{X\%}$$

Divide to solve for X.

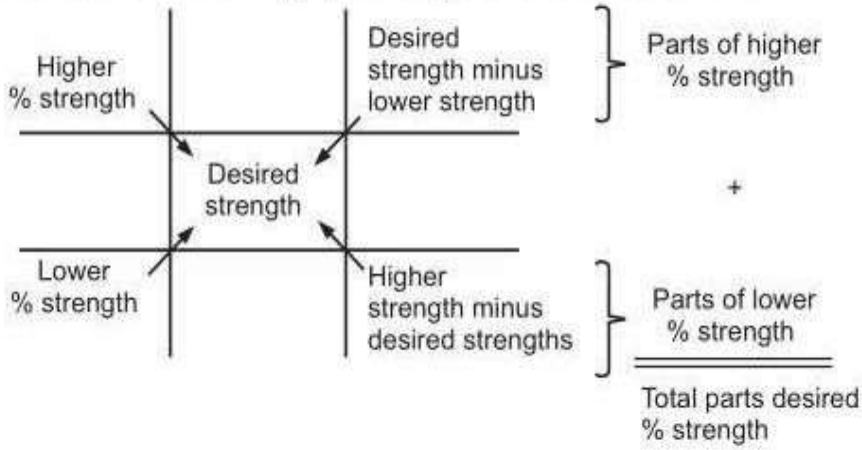
$$\frac{2000}{75} = X$$

$$X = 0.0375$$

$$X = 3.75\ \%$$

Alligation Method:

When the calculation involves mixing of two similar preparations of different strength, in order to prepare intermediate strength, the alligation method is used.



Example 2.20:

What would be the percentage strength of alcohol obtained by mixing 200 ml of 12%, 150 ml of 10%, 100 ml of 5%. (Based on Alligation method).

Solution:

$$200\ ml \times 12\% = 2400$$

$$150\ ml \times 10\% = 1500$$

$$100\ ml \times 5\% = 500$$

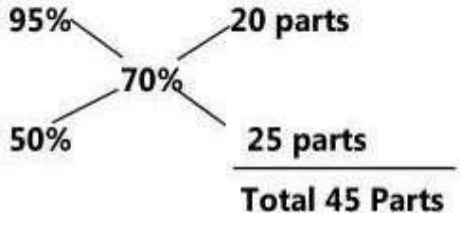
$$450\ ml\ of\ X\% = 4400$$

Or $$X = 9.78\%$$

Example 2.21:

How much 95% alcohol and how much 50% alcohol will be needed to attain 450 ml of 70% alcohol? (Based on Alligation Alternate)

Solution:



Volume of 95% alcohol required is $20 \times \frac{450}{45}$ = 200 ml.

Volume of 50% alcohol required is $25 \times \frac{450}{45}$ = 250 ml.

2.3 PROOF SPIRIT

Proof spirit: Proof spirit is defined as a mixture of absolute alcohol and water which has 57.1% v/v ethyl alcohol. The strength of alcoholic preparations are indicated by degrees 'over proof' and 'under proof' for excise purpose. Proof spirit is that mixture of alcohol and water which at 51° F weighs $12/13^{th}$ of an equal volume of water. In India 57.1 volume of ethyl alcohol is considered to be equal to 100 volumes of proof spirit. This means that alcoholic solutions containing 57.1%v/v alcohol is a proof spirit which is said to be 100 proof. So any strength above proof strength is expressed as over proof (O.P.) and any strength below proof strength is expressed as under proof (U.P.)

Formula for calculation of over proof and under proof:

(i) 57.1% v/v alcohol = 100 volume of proof spirit.
Therefore, 1% v/v alcohol = 100/57.1 = 1.753 volume of proof spirit.

(ii) So multiply the given percentage strength of alcohol by 1.753 and deduct from the product.

(iii) If the result is positive it is known as over proof.

(iv) If the result is negative, it is known as under proof.

Conversion of percentage strength in to proof strength: Multiply percentage strength v/v with 100/57.1 i.e. 1.753 and substract the resulting product from 100.

Example 2.22:

Find out the proof strength of alcohol which is 90%v/v and 30%v/v.

Solution:

90% v/v = 90 × 1.753 = 157.77

Thus, proof strength = 157.77 – 100 = 57.77° O/P (Over proof)

30% v/v = 30 × 1.753 = 52.59.

Thus, proof strength = 52.59 – 100 = – 47.41 i.e. 47.41° U/P (Under proof)

Conversion of proof strength in to percentage strength: Add 100 to over proof and substract 100 for under proof spirit, and divide the resulting product by 1.753.

Example 2.23:

Find out the percentage strength corresponding to 40° O/P and 25° U/P.

Solution:

$$40° \text{ O/P} = \frac{100 + 40}{1.753} = 79.86\% \text{ v/v.}$$

$$25° \text{ U/P} = \frac{100 - 25}{1.753} = 42.79\% \text{ v/v.}$$

2.4 POWDER

A powder is a homogeneous mixture of more or less finely divided particle or material in dry form. It is a solid dosage form of medicament which are meant for internal and external uses. They are present in crystalline and amorphous form.

Advantages

- They impart flexibility with regard to a wide selection of drugs.
- They are stable when compared to other dosage forms.
- They show rapid therapeutic effect.
- Ease in administration to all categories of patients.
- They are economical because they do not require special technique or machinery.
- Chances of incompatibility are less.

Disadvantages

- Drugs having bitter, nauseous and unpleasant taste cannot be dispensed in powdered form.
- Deliquescent and hygroscopic drugs cannot be dispensed in powdered form.
- Drugs which get affected by atmospheric conditions are not suitable for dispensing in powder form.

General Method of Preparation

- The crystalline substances are powdered separately and then weigh the required quantity of each ingredient.
- Mix all ingredients in ascending order of their weight. Mix thoroughly to obtain homogeneous mixture.
- Weigh required number of powders and wrap in the papers.
- The hygroscopic and deliquescent and volatile substance requires to be double wrapped.
- The inner wrapper should be wax paper so as to prevent volatilization.

Types of powders

1. Divided Powders
   (a) Simple Powder
   (b) Compound powder
2. Bulk Powder
   (a) Dusting Powder
   (b) Effervescent Powder
   (c) Dentifrices
   (d) Insufflations
   (e) Douche Powder
   (f) Snuffs

1. **Divided Powder:** These are unit dose powders normally packed properly.

(a) **Simple powder:** Contains only one ingredient either in crystalline or in amorphous form. Then finely divided powder is weighed wrapped as individual dose.

(b) **Compound powder:** Contains two or more than two substances which are mixed together and then divided into individual doses.

2. **Bulk powders:** Powder supplied in bulk quantities are applied by the patient according to his need. They are preferably provided in sifter type container.

2.4.1 Dusting Powder

A powder is used on skin to relieve irritation or absorb moisture and to keep skin soft and comfortable. Dusting powders are used externally for local application not intended for systemic action. They are applied to various part of body as lubricants, protectants, absorbents, antiseptics, astringent and antiperspirant.

Dusting powders always should be dispensed in a very fine state of subdivision to enhance effectiveness and minimize irritation.

When necessary they may be passed through 80, 100, number sieves.

Characteristics of dusting powder

(i) Dusting powder should be homogeneous in nature.
(ii) It should have non-irritable property.
(iii) It should be Free flowing.
(iv) Powder should have good spreadibility.
(v) Dusting powder should have good adsorption and absorption property.
(vi) Dusting powder usually contains substances as zinc oxide, starch, magnesium, carbonate, light magnesium oxide, boric acid, talc, kaolin, etc.
(vii) Dusting powder should not be applied to broken skin.

Formula:

R_X

Zinc oxide	-	20 gm
Salicylic acid	-	5 gm
Starch	-	25 gm
Talc	-	50 gm

Labelling: FOR EXTERNAL USE ONLY.

2.4.2 Effervescent Powder

They are specially prepared solid dosage form of medicament meant for internal use. They contain medicament (API) mixed with citric acid, tartaric acid and sodium bicarbonate. Saccharine may be added as sweetening agent. Before administration the desired quantity is dissolved in water, the acid and bicarbonate react together producing effervescence (releasing CO_2). This mixture should be taken while effervescing.

Preparation

1. Fusion method 2. Wet method

(a) Fusion method: In this method, all the ingredients are placed in a porcelain dish and kept in water bath, they releases water and this moisture supports to produce a hard mass. This mass is passed through 20 number sieve. Granules obtained are dried (60°C in oven). Then the granules are collected and sieved again. Leading to fine granules.

(b) Wet method: Ingredients are wet with alcohol (non-aqueous solvent) and follow the same procedure.

Formula

R_x

Sodium Bicarbonate	-	35 gm
Citric acid	-	25 gm
Tartaric acid	-	15 gm
Anhydrous sodium carbonate	-	25 gm

Storage: It should be packed in wax paper and doubly wrapped.

Fig. 2.1

Hygroscopic powder: A hygroscopic substance absorbs water from the atmosphere. It may absorb enough to clump together, but a deliquescent substance absorbs so much water from the atmosphere that it actually forms a liquid.

Deliquescence, the process by which a substance absorbs moisture from the atmosphere until it dissolves in the absorbed water and forms a solution. Deliquescence occurs when the vapour pressure of the solution that is formed is less than the partial pressure of water vapour in the air.

Problem Encountered in Powder Formulation

1. Hygroscopic and Deliquescent Powder

Problem 1: Absorption of moisture from air leading to partial or complete liquefaction.

Solution:

(A) Applied in a granular form to decrease the exposed surface to air.

(B) Packed in aluminium foil or in plastic film packets.

(C) Addition of light magnesium oxide to reduce the tendency to damp.

(D) Addition of adsorbent materials such as starch.

Examples:

- Halide salts (Example: Sodium Iodide).
- Certain alkaloids (physostigmine HCl).

2. Efflorescent Powders

When some substances are exposed to air, they lose water to the atmosphere, thereby reducing in weight. Solids that behave in this way are those with water of crystallization. The molecules of water of crystallization are partially or completely lost to the atmosphere, thereby making them to lose their crystalline forms.

Example: $Na_2SO_4 \cdot 10H_2O$ loses all its water of crystallization when exposed to air; $Na_2CO_3 \cdot 10H_2O$ loses 9 of its molecules of water of crystallization; and $FeSO_4 \cdot 7H_2O$ loses all its molecules of water of crystallization.

Some crystalline substances liberate water of crystallization wholly or partly on exposure to humid atmosphere or during trituration and thus become wet or liquefy. Example of such substances include caffeine, citric acid, ferrous sulphate etc. This difficulty may be overcome by using either corresponding anhydrous salt or an inert substance may be mixed with efflorescent substance before incorporating with other ingredients.

Problem 2: Crystalline substances which during storage loose their water of crystallization and change to powder (to be efflorescent). The liberated water convert the powder to a paste or to a liquid.

Solution:

Using the anhydrous form, and treating it in a manner similar to hygroscopic powders.

Examples: Alum- atropine sulfate-citric acid-codeine phosphate.

Eutectic Mixtures

A eutectic mixture is defined as a mixture of two or more components which usually do not interact to form a new chemical compound but, which at certain ratios, inhibit the crystallization process of one another resulting in a system having a lower melting point than either of the components. Eutectic mixtures, can be formed between Active Pharmaceutical Ingredients (APIs), between APIs and excipient or between excipient; thereby providing a vast scope for its applications in pharmaceutical industry. Eutectic mixture formation is usually governed by the following factors:

(a) The components must be miscible in liquid state and mostly immiscible in solid state.

(b) Intimate contact between eutectic forming materials is necessary for contact induced melting point depression.

(c) The components should have chemical groups that can interact to form physical bonds such has intermolecular hydrogen bonding etc.

(d) The molecules which are in accordance to modified Vant Hoff's equation can form eutectic mixtures.

Certain substances such as menthol, thymol, camphor, phenol, salol etc. when mixed in a particular proportion tend to liquefy due to reduction in their respective melting points.

Such mixture are known as eutectic mixtures. Greek meaning of eutectic is easy melting.

The phenomenon of eutectic formation has also been used in pharmaceutical practice to improve the dissolution behaviour of certain drugs.

For example: Aspirin-acetaminophen (37% and 63% respectively), Urea – acetaminophen (46% and 54% respectively) dissolve more rapidly than the drug alone or their simple mixtures.

Problem 3: Mixture of substances that liquefy when mixed, rubbed or triturated together. The melting points of many eutectic mixtures are below room temperature.

Solution:

(A) Using inert adsorbent such as starch, talc, lactose to prevent dampness of the powder.

(B) Dispensing the components of the eutectic mixture separately.

Examples: Menthol, thymol, phenol, salol, camphor etc.

Applications of Eutectic Mixtures in Pharmaceutical Industry

During pre formulation stage, compatibility studies between Active Pharmaceutical ingredients and excipient plays a crucial role in excipient selection. Testing for eutectic mixture formation can help in anticipation of probable physical incompatibility between drug and excipient molecules. Eutectic mixtures are commonly used in drug designing and delivery processes for various routes of administration. During manufacturing of pharmaceutical dosage form, it is extremely necessary to anticipate the formation of eutectics and avoid manufacturing problems if any. For example, during tablet compaction the heat produced in the punch and die cavities may lead to fusion or melting of tablet powder compacts leading to manufacturing defects. Thus, knowledge of eutectic points of powder components may help to avoid these problems. During pharmaceutical analysis, understanding of eutectic mixtures can help in the identification of compounds having similar melting points. Compounds having similar melting points, as a rule will have different eutectic point with a common other component. This knowledge could be used to identify compounds like Ergotamine, Allobarbital etc. The listed drugs can be distinguished by their tendency to form eutectic mixtures with Benzanilide.

Geometric Dilution

Geometric dilution is a pharmaceutical process that thoroughly mixes a small amount of a drug with an appropriate amount of a diluent, an inert substance that thins or binds the drug. It ensures equal distribution of the drug throughout the resulting compound, according to the UNC Eshelman School of Pharmacy.

The method used depends on the types of substances used, such as a fluid or powder, and the form, such as an ointment or tablet, of the compound. Two commonly used geometric dilution methods include trituration, which can be used to combine powders or mix a powder into an ointment, and the liquid aliquot method, which involves combining fluids to create a solution, as explained by the UNC Eshelman School of Pharmacy.

Trituration, which involves reducing a substance to particle size, requires the use of a mortar and pestle to grind together equal parts of substances in small-batch quantities, adding the same amount of each substance and repeating the process until the entire amount of both substances has been mixed together. The liquid aliquot method involves dissolving a quantity of the drug in a small quantity of an appropriate solvent, often water or alcohol, to reach a desired volume, according to the UNC Eshelman School of Pharmacy. The aliquot, which is the desired amount of the concentrated drug solution, is then added to a larger amount of solution to make up the total volume of the prescription.

Methods of Geometric Dilution

Geometric dilution is the process of diluting something based on its measured size. Most often, scientists and doctors employ this method when combining fine powders of unequal amounts to ensure equal distribution. Bakers sometimes use geometric dilution to equally combine the dry ingredients in a mixture. The process involves slowly combining the products in a small portion at a time.

(a) Two Powders (Standard)

The two-powder method requires a mortar and pestle. Take the powder of the smaller amount and place it in the pestle. Then add the other powder but only of equal amount to the lesser powder, leaving the rest outside the mixture. Fully triturate, or finely grind, the powder with the mortar so that it is completely mixed. Add an amount of the remaining powder equal to that in the pestle. Repeat the triturating process. Continue until all of the powder has been combined. In baking, the addition method is the same but you do not grind the powders; just mix them.

(b) Powder in Ointment

The same method used for two powders can be utilized when mixing a powder into an ointment. During the initial step you mix in the same amount of ointment as there is of the powder. Use the mortar to fully grind the powder into the ointment, ensuring uniformity. Add ointment of equal amount to the mixed ointment until you have fully combined the ointment with powder.

(c) Liquid Aliquot Method

The liquid aliquot method is similar to trituration but works with fluids instead. The theory is that the liquids need to be combined equally, but you might need to mix more together than you actually need. You calculate the total volume of the drug you wish to give and your end amount of fluid. Then give the measurement of how the drug is available you mix it with the appropriate amount of solution. You then draw up in a syringe the amount of mixed fluid you need to give to the patient.

(d) Radar Geometric Dilution

An entirely different type of geometric dilution is that of radar or radio waves. This process requires you use geometry to cross cut the radar waves making them less effective. Developed as a way to interfere with foreign signals, this form of dilution tends to be used most by the military. The dilution angles can be calculated to protect your radar from being discovered or to "jam" the enemy's radar. Jamming the other radar can help to keep you safe or eliminate communications aiding in a sneak attack.

2.4.3 Dentifrices (Tooth Powder)

- Dentifrices are bulk powders used to clean teeth.
- They contain a soap or detergent (for cleaning action), mild abrasive and an anti-cryogenic agent.
- Mild abrasion can be provided by using finely precipitated Calcium Carbonate, Sodium Chloride, Magnesium Chloride etc.
- A strong abrasive substance should not be used as it may cause damage to the tooth.
- They are applied with the help of tooth brush for cleaning the surface of teeth.

Formula

R_x

For 100 gm tooth powder

Hard soap, fine powder - 5 gm

Precipitated calcium carbonate - 94 gm

Saccharine sodium - 2 gm

Peppermint oil - 4 gm

Fig. 2.2

2.4.4 Insufflations

- These are finely divided powders introduced into body cavities such as the ear, nose, throat, tooth sockets and vagina.
- An insufflators is employed to administer these products.
- It sprays the powder into a stream of finely divided particles all over the site of application.
- Pressure aerosols also have been employed as a means of administering insufflations, especially for potent drugs.

Fig. 2.3

2.4.5 Snuffs

These are finely divided solid dosage form of medicament which are inhaled into nostrils for its antiseptic, bronchodilator and decongestion actions. Traditionally, it is sniffed or inhaled lightly after a pinch of snuff is either placed onto the back surface of the hand, held pinched between thumb and index finger, or held by a specially made "snuffing" device. Snuff comes in a range of texture and moistness, from very fine to coarse, and from toast (very dry) to very moist.

2.5 LIQUID DOSAGE FORM

The use of liquid pharmaceuticals has been justified on the basis of ease of administration and rapid and efficient absorption of drug.

Dosage forms meant either for internal, external or parenteral use may be sub-classified into monophasic or biphasic liquid dosage forms. The monophasic liquid dosage forms consists of either true or colloidal solutions or solubilised system. All these consists of only a single phase and may have either aqueous or non-aqueous solvents as the base. Biphasic dosage forms are represented by emulsions and suspensions and consist of two immiscible phases, the continuous phase and the dispersed phase. The continuous phase in both is a liquid, the dispersed phase in emulsions is also a liquid while in case of suspensions, the dispersed phase consists of a finely divided solid. The classification of liquid dosage form is given in Fig 2.4. and the comparison of characteristics of various liquid dosage forms are shown in Table 2.1.

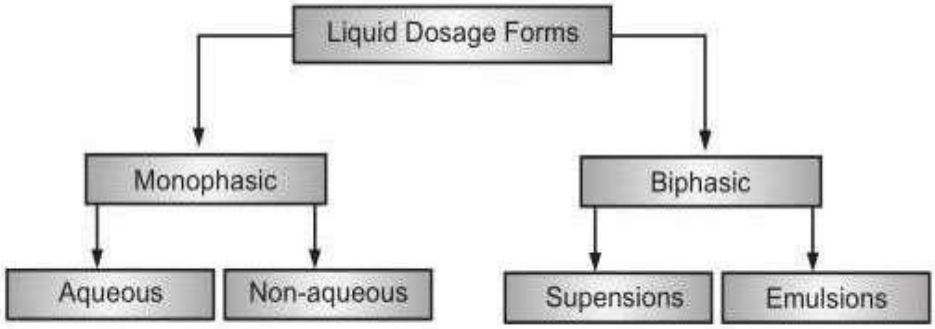


Fig. 2.4: Classification of Liquid Dosage Forms

Table 2.1: Comparison of characteristics of various liquid dosage forms

Characteristic	Solutions	Suspensions	Emulsions
	Monophasic system in which solute is dispersed molecularly in a suitable solvent	Biphasic system composed of finely divided insoluble solid suspended in a liquid medium	Biphasic system in which one liquid is dispersed throughout another liquid in form of minute droplets
Thermodynamic Stability	Thermodynamically stable on storage	Unstable, undergo caking on storage	Unstable, undergo creaming on storage
Homogeneity	Homogenous system No dose variation	Heterogenous system Dose variation	Heterogenous system Dose variation
Hydrolytic Stability	Most susceptible to hydrolysis	Less	Least
Appearance	Clear dispersions	Cloudy	Greasy/Smooth
Pharmacokinetics	Rapid onset of action	Slowest onset of action	Slower onset of action
Viscosity	Low viscosity	High viscosity	Highest viscosity

2.5.1 Advantages of Liquid Dosage Forms

The presentation of drugs as liquid dosage form offers the following advantages:

(i) The drug is more readily available for absorption from liquid dosage forms as compared to solid dosage form. By providing the drug in solution, the dissolution phase of the absorption process can be surpassed, providing faster therapeutic response.

(ii) The doses of drugs can be easily adjusted according to the need of the patient. If the dose of active ingredient is to be altered, a simple adjustment to the quantity of solution to be taken is all that is required.

(iii) Liquids are easier to swallow than tablets or capsules and are therefore especially suitable for children, elderly, intensive care and psychiatric patients.

(iv) Gastric irritation due to certain drugs like potassium chloride and when administered as a solid dosage form is avoided or reduced on administration as a liquid dosage form because of the immediate dilution by gastric content.

(v) Drugs with large doses can be easily administered as liquid dosage form.

(vi) Distribution of drug in liquid dosage forms is better than solid dosage forms.

(vii) Liquid dosage forms are more economical to produce than solid dosage forms.

(viii) Liquid dosage forms can be designed to administer via number of routes. Parenteral preparations, douches for vaginal use, cutaneous (for use on skin) preparations and ophthalmic preparations can all be liquids.

Disadvantages of Liquid Dosage Forms

There are also some disadvantages associated with the use of liquid preparations:

(i) Drugs are usually less stable in liquid dosage forms as compared to solid dosage forms like tablets and capsules, particularly if they are susceptible to hydrolysis.

(ii) Liquids, especially aqueous preparations, are susceptible to microbial contamination.

(iii) Masking the unpleasant taste of a drug in solution is more difficult than when the drug is in a solid dosage form.

(iv) Liquid preparations are usually bulky and therefore inconvenient to store and carry. Liquid dosage forms are always much larger and more bulky than solid formulations. Coupled with this is the fact that pharmaceutical liquids are packed in glass bottles, which are prone to breakage.

(v) Administration of the correct dose is less precise since it depends on the ability of the patient to measure the correct dose using a suitable measuring device such as a spoon or a dropper.

(vi) Measuring device is to be supplied to the patients for accurate dose administration. This will have cost implications and in addition the counselling is required for its use.

(vii) Suspensions and emulsions have the added drawback that they must be thoroughly shaken to allow accurate dosing.

2.5.2 Excipients used in Formulation of Liquid Dosage Forms

Sweetening agent: Sweeteners are indispensable components of many liquid oral dosage forms, especially those containing bitter or other unacceptable tastes. In fact, sweetening agents may comprise large portions of solid content in most liquid oral dosage forms. Sweeteners are often classified as either nutritive (caloric) or non-nutritive (non-caloric). Non-caloric sweetening agents are preferred for diabetic patients, as ingestion does cause increase in systemic glucose concentrations. Some of the most commonly used sweeteners include sucrose, sorbitol, mannitol, liquid glucose, honey molasses, saccharin, aspartame, sucralose, and acesulphame-K. The types and concentrations of sweeteners for

common prescription liquid medications are reported by Hill, Flaitz, and Frost. Sucrose is the most widely used sweetener, with a long history of use. It is a white crystalline powder, soluble in water and alcohol. It inhibits the growth of microorganisms in solution at sucrose concentrations above 65 wt% by reducing the water-activity coefficient. Official simple syrup is an 85%w/v solution of sucrose in water. During the preparation of sucrose solution, care should be taken to avoid charring and caramelization caused by heat. Sucrose is chemically and physically stable in the pH range of 4.0–8.0. It is frequently used in conjunction with sorbitol, glycerin, and other polyols, which reduces its tendency to crystallize.

One of the manifestations of the sucrose crystallization is "cap-locking," which occurs when sucrose crystallizes on the threads of the bottle cap and interferes with opening. Liquid glucose is an extremely viscid substance that imparts both body and sweetness to liquid formulations. It is obtained by the incomplete hydrolysis of starch and consists chiefly of dextrose, dextrins, maltose, and water. It imparts a characteristic odour and flavour to the formulation in similar fashion to honey and molasses, but to a lesser degree. Although liquid glucose is not a pure chemical entity, its method of manufacture can be well controlled, and batch to batch variability is usually not significantly problematic. The same is not true of honey and molasses, in which quality depends on uncontrollable natural factors.

Saccharin (Sweet' N Low) is a non-nutritive synthetic sweetening agent. It has approximately 500 times the sweetening power of sucrose, depending in extent on the strength of the solution. The relative sweetening power is greatest in dilute solution. Saccharin is a sucrose substitute for diabetics, the obese, and others who do not wish to ingest sucrose. It is commonly found in its sodium salt form, which is more palatable than saccharin and comparatively free of unpleasant after taste. Sodium cyclamate is another synthetic sweetening agent that is approximately 30 times as sweet as sugar. However, its use as an artificial sweetener is banned in the U.S.A. because of the possible toxicity of its metabolite cyclohexylamine. Aspartame, is 200 times sweeter than sucrose and, unlike saccharin, has no aftertaste. Its aqueous solubility is adequate for formulation purposes. It is stable in the solid form, but its stability in solution depends on temperature and pH. It hydrolyzes to aspartylphenylalanine and diketopiperazine, with a loss in sweetness by aspartame synergistic with saccharin, sucrose, glucose, and cyclamate. In addition, its taste can be improved by adding sodium bicarbonate, gluconate salts, and lactose.

Newer non-caloric sweetening agents have come to market in the last decade. Sucralose (Splenda) is approximately 600 times sweeter than sucrose and differs from sucrose by the substitution of three chlorines for hydroxyl groups. Sucralose is heat stable and stable over a wide pH range affording its utility in formulations prepared at high temperatures. Acesulphame-K is approximately 200 times sweeter than sucrose and is commonly used concomitantly with aspartame to synergistically enhance overall sweetening. This sweetener is also heat stable. Furthermore, Monoammonium glycyrrhizinate has even been used in liquid oral preparations.

Viscosity controlling agents

It is sometimes desirable to increase the viscosity of a liquid, either to serve as an adjunct for palatability or to improve pourability. This can be achieved by increasing the sugar concentration or by incorporating viscosity controlling agents such as polyvinylpyrrolidone or various cellulosic derivatives (e.g., methylcellulose or sodium carboxymethylcellulose). These compounds form solutions in water that are stable over a wide pH range. Methylcellulose and carboxymethylcellulose are available in a number of different viscosity grades. Carboxymethylcellulose may be used in solutions containing high concentrations of alcohol (up to 50%) without precipitating. It is precipitated, however, as an insoluble salt of a number of multivalent metal ions such as AT^{++} , Fe^{+++} and Ca^{++}. Methylcellulose polymers do not form insoluble salts with metal ions, but can be salted out of solution when the concentration of electrolytes or other dissolved materials exceed certain limits. These limits may vary from about 2 to 40%, depending on the electrolyte and the type of methylcellulose involved.

Viscosity inducing polymers should be used with a degree of caution. They are known to form molecular complexes with a variety of organic and inorganic compounds, and in so doing, influence the activity of these compounds. It is conceivable that highly viscid systems that resist dilution by gastrointestinal fluids might impede drug release and absorption.

Buffers

During storage of liquid preparations, degradation of the product, interactions with container components or dissolution of gases and vapors causes change in their pH level, which can be prevented by addition of buffer. A suitable buffer system should have adequate buffer capacity to maintain the pH level of the product. Commonly used buffer systems are phosphates, acetates, citrates, and glutamates. Although buffers ensure pH stability, the buffer system can affect other properties such as solubility and stability. The ionic strength contributions of the buffer systems can affect stability. Buffers can also act adversely as general acid or general base catalysts and cause degradation of the drug substance. Therefore, before selecting any buffer system, the effect of buffer species should be studied.

Antioxidants

Various drugs in solution are subject to oxidative degradation. Oxidation is defined as a loss of electrons from a compound leading to change in the oxidation state of the molecule. Such reactions are mediated by free radicals or molecular oxygen, and are often catalyzed by metal ions. Moreover, oxidation often involves the addition of oxygen (or other electronegative atoms like halogens) or the removal of hydrogen. Drugs possessing favorable oxidation potential are especially vulnerable to degradation. Agents with an oxidation potential lower than that of the drug in question are called **antioxidants**. Additionally, certain properties of the selected primary packaging (such as polymer degradation, oxygen transmission rates, impurities, etc.) can readily lead to oxidation of drug molecules in solution and hence may require the addition of antioxidants to maintain

product stability. They are added to solutions alone or in combination with a chelating agent or other antioxidants and function by being preferentially oxidized and gradually consumed or by blocking an oxidative chain reaction where they are not consumed.

Salts of sulfites are the most common antioxidants in aqueous solutions and their antioxidant activity depends on their final concentration and the final pH level of the formulation. Generally, sodium metabisulfite is used at low pH, sodium bisulfite at near neutral pH, and sodium sulfite is used at basic pH. A combination is often used since single antioxidant may provide incomplete protection. Certain compounds (e.g., citric and ascorbic acids) have been found to act as synergists, increasing the effectiveness of antioxidants, particularly those that block oxidative reactions. Often, chelating agents such as edetic acid derivatives such as ethylene diamine tetra acetate (EDTA) are used in formulations containing trace amounts of heavy metals that would otherwise catalyze oxidative reactions. Moreover, synthetic phenolic compounds, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA) serve as hydrogen atom donors and can successfully prevent oxidation of oils and fats in oral liquid formulations.

Flavours

Flavouring can be divided into two major categories: selection and evaluation. Much has been written on both phases of pharmaceutical flavoring, but selection remains a totally empiric activity.

The four basic taste sensations are salty, bitter, sweet, and sour. Some generalizations concerning the selection of flavours to mask specific types of taste have been suggested by Janovsky and by Wesley. (Table 2.2)

Table 2.2: Flavour Selection

Taste Sensation	Recommended Flavour
Salt	Butterscotch, maple, apricot, peach, vanilla, wintergreen mint.
Bitter	Wild cherry, walnut, chocolate, mint combinations, passion fruit, mint spice, anise.
Sweet	Fruit and berry, vanilla.
Sour	Citrus flavors, liqorice, root beer, raspberry.

A combination of flavoring agents is usually required to mask these taste sensations effectively. Menthol, chloroform, and various salts frequently are used as flavour adjuncts. Menthol and chloroform are sometimes referred to as de-sensitizing agents. They impart a flavour and odour of their own to the product and have a mild anesthetic effect on the sensory receptor organs associated with taste. Monosodium glutamate has been widely used in the food industry, and to a lesser extent, in pharmaceuticals, for its reported ability to enhance natural flavors. A carefully selected panel reported this substance to be effective in reducing the metallic taste of iron containing liquids, as well as the bitterness and after

taste of a variety of other pharmaceutical preparations. It cannot be used in pediatric products.

Chemburkar and Joslin have reported that the partitioning of parabens into flavouring oils from aqueous systems depends on the concentration of the flavouring oil, the nature and concentration of the additives, and pH.

Wesley's Pharmaceutical Flavor Guide contains suggestions for flavoring over 51 types of pharmaceutical preparations. It and many similar reports provide some guidance for the formulation chemist, but the final selection must result from a trial and error approach. Inherent in this approach is what is referred to as taste fatigue. Repeated samplings of strong tasting substances soon result in decreased flavour acuity, and therefore, impaired ability to evaluate flavour properly. Preliminary flavoring should be carried out on diluted samples. This is done by preparing flavoured vehicles and adding increments of the medicament or other formulation components responsible for the taste problem. The concentration at which the taste of the medicament is perceptible is referred to as the *minimum threshold level*. The vehicles that are most effective in masking low levels of drug are candidates for full-strength flavour evaluation.

Flavour evaluation techniques have progressed to a much greater extent than flavour selection. Taste panels can be useful in selecting one of several candidate formulations. This subject, as well as other flavour considerations, has been surveyed in an excellent book assembled by Arthur D. Little, Inc.

Preservative

In recent years, adequate preservation of liquid products has increased in importance. Reports of clinical complications arising from microbial contamination of oral and topical products have originated in several European countries and the United States. Numerous product recalls and tightened regulatory and compendia limits have re-emphasized the need for die formulator to carefully and thoroughly consider all aspects of the preservative system chosen for a particular formula. In addition to presenting a health hazard to the user, microbial growth can cause marked effects on product stability.

Numerous sources of contamination exist. Including among these are raw materials, processing containers and equipment, the manufacturing environment, operators, packaging materials, and the user.

Manufacturing techniques to minimize microbial contamination are presented under the heading "Manufacturing Considerations." The remainder of this section deals with preservative systems for liquid products.

An ideal preservative can be qualitatively defined as one that meets the following three criteria:

1. It must be effective against a broad spectrum of microorganisms.
2. It must be physically, chemically and microbiologically stable for the lifetime of the product.
3. It must be non-toxic, non-sensitizing, adequately soluble, compatible with other formulation components, and acceptable with respect to taste and odour at the concentrations used.

No single preservative exists that satisfies all of these requirements for all formulations. The selection of a preservative system must be made on an individual basis, using published information and "in house" microbiologic studies for guidance. Frequently, a combination of two or more preservatives are needed to achieve the desired antimicrobial effect.

The antimicrobial agents that have been used as preservatives can be classified into four major groupings: acidic, neutral, mercurial, and quaternary ammonium compounds. Table 2.3 lists some representative members of these groupings and the concentration ranges at which they have been used.

Table 2.3: Some Pharmaceutically Useful Preservatives

Class	Usual Concentration (%)
Acidic	
Phenol	0.2-0.5
Chlorocresol	0.05-0.1
O-phenyl phenol	0.005-0.01
Alkyl esters of parahydroxybenzoic acid	0.001-0.2
Benzoic acid and its salts	0.1-0.3
Boric acid and its salts	0.5-1.0
Sorbic acid and its salts	0.05-0.2
Neutral	
Chlorobutanol	0.5
Benzyl alcohol	1.0
o-phenylethyl alcohol	0.2-1.0
Mercurial	
Thiomersal	0.001-0.1
Phenylmercuric acetate and nitrate	0.002-0.005
Nitromersol	0.001-0.1
Quaternary Ammonium Compounds	
Benzalkonium chloride	0.004-0.02
Cetylpyridinium chloride	0.01-0.02

The phenols are probably the oldest and best known pharmaceutical preservatives, but are little used in oral pharmaceuticals, owing to their characteristic odour and instability when exposed to oxygen. The more useful members of the series, for this application, are

the parahydroxy-benzoic acid esters, and the salts of benzoic and sorbic acid. They are adequately soluble in aqueous systems and have been demonstrated to possess both antifungal and antibacterial properties.

Frequently, a combination of two or more esters of parahydroxybenzoic acid are used to achieve the desired antimicrobial effect. Methyl and propyl parahydroxybenzoic acid, for example, are often used together in a ratio of 10 to 1, respectively. The use of more than one ester makes possible a higher total preservative concentration, owing to the independent solubilities of each, and according to some researchers, serves to potentiate the antimicrobial effect. The solubilities of a series of parabens have been studied at four temperatures. The solubilities are expressed in terms of ideal, actual, and excess free energies.

The remaining three classes of preservatives have been widely used in ophthalmic, nasal, and parenteral products, but have been little used in oral liquids. The neutral preservatives are all volatile alcohols, and their volatility introduces odour problems as well as concern for preservative loss on aging. The mercurials and quaternary ammonium compounds are excellent preservatives. They are, however, subject to a variety of incompatibilities, with mercurials being readily reduced to free mercury and the quaternary compounds being inactivated by a variety of anionic substances. The incompatibilities common to these and other preservatives are discussed by Lachman.

Syrups containing approximately 85% sugar resist bacterial growth by virtue of their exosmotic effect on microorganisms. Syrups that contain less than 85% sucrose, but a sufficient concentration of polyol (such as sorbitol, glycerin, propylene glycol, or polyethylene glycol) to have an exosmotic effect on microorganisms, similarly resist bacterial growth. It is possible, however, for surface dilution to take place in a closed container as a result of solvent evaporation followed by condensation, with the condensate flowing back onto the liquid surface. The resulting diluted surface layer makes an excellent medium for bacterial and fungal growth. These products, therefore, should be designed so that even after dilution, they do not support microbial growth. This can be done either by incorporating a sufficient concentration of preservative, so that a diluted sample of the product resists microorganism growth, or by including approximately 5 to 10% ethanol in the formulation. The vapour pressure of ethanol is greater than that of water and normally vaporizes to the surface of the liquid and the cap area, preventing, or at least minimizing, the potential for microorganism growth as a result of surface dilution.

An effectively designed preservative system must retain its antimicrobial activity for the shelf-life of the product. To ensure compliance with this precept, the preservative characteristics of the product in its final form (including formulation and package) must be studied as a function of age. The best method of demonstrating preservative characteristics is by microbiologic evaluation.

To determine whether a specific organism is hazardous, one must consider the nature of the product and its dose, the state of health of the user, and clinical reports on the frequency and severity of infections caused by the microorganism.

The FDA distinguishes between organisms that are "always objectionable" and "usually objectionable." The former designation is based on only two factors: pathogenicity of the organism and site of use. The latter designation is based on an additional determinant, the state of health of the user. The official compendia are continually reevaluating their standards based on the latest FDA data and guidelines.

Specific organisms generally recognized as undesirable in oral liquids include *Salmonella* species, *Escherichia coli*, *Enterobacter* species, *Pseudomonas* species (commonly *P. aeruginosa*), proteolytic species of *Clostridium* and *Candida albicans*. Some liquid pharmaceuticals (i.e., ophthalmic solutions) must be processed aseptically and rendered sterile.

Chemical analysis for the antimicrobial constituent frequently provides a helpful guide but can be misleading. Molecular interactions involving preservatives and commonly used pharmaceutical adjuvants, such as surfactants and cellulose derivatives, have been observed. For example, it has been shown that Tween 80 interacts to a significant extent with the methyl and propyl esters of parahydroxybenzoic acid, and that the preservative surfactant complex is essentially devoid of antibacterial activity. Chemical analysis for the parahydroxybenzoate esters would not differentiate between the unbound substance (microbiologically active) and the bound substance (microbiologically inactive).

2.6 SOLUBILITY

Solubility is defined as amount of solute that can be dispersed molecularly in the given amount of solvent under standard conditions of temperature, pressure and pH. The following questions related to solubility must be resolved before formulating solution dosage form:

(a) Will the drug(s) dissolve in the vehicle?
(b) How much drug will dissolve?
(c) How long will dissolution take?
(d) What is optimum pH for dissolution?

To determine the solubility of solute in solvent following points are to be considered:

(a) Temperature must be controlled.
(b) The solute and the solvent should be pure.
(c) A saturated solution of the solute should be prepared before withdrawing the sample for analysis.
(d) A proper method of separation of saturated solution from the undissolved solute.
(e) Dissolved solute should be determined adequately by the suitable method of analysis.

Method of determination: An excess powder is added in the solvent to achieve the saturated solubility and constant stirring is given for long duration at required temperature till the equilibrium is achieved. There should be few amount of undissolved solute should be present in order to ensure that the solvent is saturated. The aliquot of the saturated solution is taken separated from the undissolved solute by specific method. Generally speaking,

filtration is the common method employed for most of the studied. Further the quantity of the drug dissolved or the solubility of the solute in the solvent is determined by the analyzing the sample by suitable method.

Table 2.4

Terms	Expression of solubility Part by volume of solvent required to dissolve 1 part by weight of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or insoluble	Greater than 10,000

During compounding of a solution the solids will need to go through a dissolution phase, so it is worth remembering that rate of dissolution generally increases with:

(1) Effective stirring (2) Lower viscosity

(3) Increasing temperature (4) Decreasing particle size

2.7 TECHNIQUES OF SOLUBILIZATION

In liquid pharmaceuticals solutions sometime the active drug is poorly soluble or insoluble in desired solvent and could not able to achieve the required concentration of formulation. In such cases, it is required to increase the solubility of that material in the solvent by a suitable technique. Solubilization is the technique by which the desired solubility of a poorly water-soluble substance is achieved. Since, water is the most commonly used solvent in pharmaceutical liquids, the following techniques have been aimed at increasing the solubility of a drug substance in water.

Pharmaceutical Approach

1. pH Adjustments

Most of the drugs are either weak acids or weak bases. The aqueous solubility of a weak acid or a weak base is greatly influenced by the pH of the solution. Hence, the solubility of drug that is either a weak base or a weak acid may be altered by adjusting the pH of the solution. The solubility of a weak base can be increased by lowering the pH of its solution whereas the solubility of a weak acid can be improved by increasing the pH. pH adjustment for improving the solubility can be achieved in two ways:

(a) Salt formation.

(b) Addition of buffers to the formulation.

However, pH adjustments should be done judiciously since other factors such as stability, bioavailability, etc. can also be affected by a change in pH.

e.g. Gatifloxacin is insoluble in water at higher pH but the same drug get solubized at the lower pH and attends maximum solubility below the pH of 5. Hence the parenteral preparation of Gatifloxacin is formulated at the pH of 3.5 to 5.5.

e.g. The solubility of various chemotherapeutic agents such as Methotrexate, Fluorouracil, Cytrabine etc. also gets affected by the alteration in pH changes.

2. Cosolvency

Cosolvency is the technique of increasing the solubility of poorly soluble drugs in a liquid by addition of a solvent miscible with the liquid in which the drug is also highly soluble. Cosolvents such as ethanol, glycerol, propylene glycol or sorbitol decreases the interfacial tension or alter the dielectric constant of the medium and increases the solubility of weak electrolytes and non-polar molecules in water. Example: Formulation of Diazepam injection using propylene glycol as cosolvent.

3. Complexation

In certain cases, it may be possible to increase the solubility of a poorly soluble drug by allowing it to interact with a soluble material to form a soluble intermolecular complex. It is however essential that the complex formed is easily reversible so that the free drug is released readily during or before contact with biological fluids. A number of compounds, such as nicotinamide and Beta-cyclodextrin, have been investigated as possible agents to increase the solubility of water insoluble drugs.

e.g. Interaction of Iodine with Povidone to form water soluble complex and preparation of Itraconazole injection by forming inclusion complex of itraconazole with hydroxy propyl beta cyclodextrin.

4. Surface active agent

A surface active agent is a substance which reduces the interfacial tension between the solute and the solvent to form thermodynamically stable homogeneous system. The mechanism involved in this solubilization technique involves micelle formation and due to formation of stable system it is widely used in pharmaceutical formulations. When a surfactant having a hydrophilic and a lipophilic portion is added to a liquid, it first accumulates at the air/solvent interface; further addition leads to its dispersion throughout the liquid bulk. At a certain concentration known as the Critical Micelle Concentration (CMC), the dispersed surfactant molecules tend to aggregate into groups of 100 to 150 molecules known as micelle.

In aqueous medium, the surfactant molecule orient in such a manner that their hydrophilic portion faces the water while the lipophilic portion resides in the micelle interior. An insoluble compound added to the surfactant liquid either enters the micelle interior, gets adsorbed onto the micelle surface, or sits at some intermediate point depending on its polarity, thus effecting solubilization.

Surface active agents should be non-toxic and stable, possess good solubilizing power, and be compatible with other formulation ingredients. If they are intended for oral use, they should also have an agreeable taste and odour. Surfactants that are used as solubilising

agents generally have HLB values in excess of 13. Examples include polysorbate-80, polyoxyl 40 stearate, sodium lauryl sulphate and PEG-40-Castor oil (Cremophor).

e.g.: Fat soluble vitamins A, D, E and K, antibiotics like griseofulvin and chloramphenicol and analgesics such as aspirin and phenacetin have been solubilized by using surface active agents.

5. Hydrotropism

Hydrotropism is the term used to describe the increase in aqueous solubility of a drug by the use of large concentrations (20% to 50%) of certain additives. The exact mechanism for hydrotropism is not clear although complexation, solubilization or cosolvency have been suggested as the probable mechanisms. Hydrotropism is rarely applied to pharmaceutical formulations, as the increase in aqueous solubility is generally inadequate.

e.g.: Increase in solubility of caffeine and theophylline by addition of sodium benzoate and sodium salicylate respectively.

6. Micronization

Surface area and particle size are inversely related to each other. Smaller the drug particle, larger the surface area and greater is the solubility. A decrease in particle size achieved through micronization, will result in higher solubilization of drug.

e.g.: Micronization of poorly aqueous soluble, but non-hydrophobic drugs such as griseofulvin and chloramphenicol results in enhanced solubility.

7. Solid Solutions

Solid solutions are prepared by melting of physical mixture of solute, a poorly water soluble drug and solid solvent, a highly water soluble compound or polymer followed by rapid solidification. Solid solutions are also called as molecular dispersions or mixed crystals. When such binary system comprising of drug dispersed in a solid solvent is exposed to water, the soluble carrier dissolves rapidly leaving the poorly water soluble drug in a state of microcrystalline form with increased surface area resulting in enhanced solubility.

e.g.: Griseofulvin from succinic acid solid solution dissolves 6 to 7 times faster than pure griseofulvin and Digitoxin-PEG 6000 solid solution showed enhanced solubility.

Chemical Modification

Solubility of a substance can be improved by chemically modifying the substance. For example, aqueous solubility can be improved by increasing the number of polar groups in a molecule. This is often achieved by salt formation; for instance, alkaloids are poorly soluble in water whereas alkaloidal salts are freely soluble in it. Alternatively, a molecule may be modified to produce a new chemical entity or prodrug. The aqueous solubility of chloramphenicol sodium succinate, for example, is about 400 times greater than that of chloramphenicol. Prodrugs, however, must revert to parent molecule after administration.

Stability

In addition to the solubility of the medicament, other considerations regarding physical, chemical and microbiological stability of the preparation will need to be taken into consideration.