21ST EDITION

Remington

The Science and Practice of Pharmacy

LIPPINCOTT WILLIAMS & WILKINS
A Wolters Kluwer Company

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Lippincott Williams & Wilkins

351 West Camden Street
Baltimore, Maryland 21201-2436 USA

530 Walnut Street
Philadelphia, PA 19106

Printed in the United States of America

Entered according to Act of Congress, in the year 1885 by Joseph P Remington, in the Office of the Librarian of Congress, at Washington DC

Library of Congress Catalog Card Information is available
ISBN 0-7817-4673-6

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pretations of the different type percentages involving solutions and mixtures.

The USP states

> Percentage concentrations of solutions are expressed as follows:
>
> *Percent weight in weight—(w/w)* expresses the number of g of a constituent in 100 g of product.
>
> *Percent weight in volume—(w/v)* expresses the number of g of a constituent in 100 mL of product, and is used regardless of whether water or another liquid is the solvent.
>
> *Percent volume in volume—(v/v)* expresses the number of mL of a constituent in 100 mL of product.

The term *percent* used without qualification means, for mixtures of solids, percent weight in weight; for solutions or suspensions of solids in liquids, percent weight in volume; for solutions of liquids in liquids, percent volume in volume; and for solutions of gases in liquids, percent weight in volume. For example, a one percent solution is prepared by dissolving one g of a solid or one mL of a liquid in sufficient of the solvent to make 100 mL of the solution.

Ratio Strength

Ratio strength is another manner of expressing concentration. Such phrases as "1 in 10" are understood to mean that one part of a substance is to be diluted with a diluent to make 10 parts of the finished product. For example, a 1:10 solution means 1 mL of a liquid or one g of a solid dissolved in sufficient solvent to make 10 mL of solution. Ratio strength can be converted to percent by:

$$\frac{1 \text{ g substance}}{10 \text{ mL solution}} \times 100 \text{ mL solution} = 10 \text{ g substance}$$

$$\frac{10 \text{ g substance}}{100 \text{ mL solution}} = 10\%$$

The expression "parts per thousand" (eg, 1:5000) always means parts weight in volume when dealing with solutions of solids in liquids and is similar to the above expression. A 1:5000 solution means 1 g of solute in sufficient solvent to make 5000 mL of solution. This can be converted to percent by

$$\frac{1 \text{ g substance}}{5000 \text{ mL solution}} \times 100 \text{ mL solution} = 0.02 \text{ g substance}$$

$$\frac{0.02 \text{ g substance}}{100 \text{ mL solution}} = 0.02\%$$

The expression "trituration" has two different meanings in pharmacy. One refers to the process of particle-size reduction, commonly by grinding or rubbing in a mortar with the aid of a pestle. The other meaning refers to a dilution of a potent powdered drug with a suitable powdered diluent in a definite proportion by weight. It is the second meaning that is used in this chapter.

When pharmacists refer to a "1 in 10 trituration" they mean a mixture of solids composed of 1 g of drug plus sufficient diluent (another solid) to make 10 g of mixture or *dilution*. In this case the "1 in 10 trituration" is actually a solid dilution of a drug with an inert solid. The strength of a trituration may also be stated as percent *w/w*. Thus, the term trituration has come to mean a solid dilution of a potent drug with a chemically and physiologically inert solid.

The meanings implied by the USP statements in the section

Weight-in-Volume Percentages

This is the type of percent problem most often encountered on prescriptions. The volume occupied by the solute and the volume of the solvent are *not* known because sufficient solvent is added to make a given or known final volume.

EXAMPLES

1. Prepare 1 f℥ of a 10% solution.
   Since this is a solution of a solid in a liquid, this is a *w/v* solution.

$$\frac{10 \text{ g drug}}{100 \text{ mL soln}} \times \frac{29.6 \text{ mL}}{1 \text{ f℥}} \times 1 \text{ f℥} = 2.96 \text{ g drug}$$

   2.96 g is dissolved in sufficient purified water to make 29.6 mL of solution.
2. How much of a drug is required to compound 4 f℥ of a 3% solution in alcohol?

$$\frac{3 \text{ g drug}}{100 \text{ mL soln}} \times \frac{29.6 \text{ mL}}{1 \text{ f℥}} \times 4 \text{ f℥} = 3.55 \text{ g drug}$$

3. How much 0.9% solution of sodium chloride can be made from ½ ℥ of NaCl?

$$\frac{100 \text{ mL soln}}{0.9 \text{ g NaCl}} \times \frac{31.1 \text{ g}}{1 \text{ ℥}} \times 0.5 \text{ ℥} = 1730 \text{ mL soln}$$

4. How many grams of a drug are required to make 120 mL of a 25% solution?

$$\frac{25 \text{ g drug}}{100 \text{ mL soln}} \times 120 \text{ mL} = 30 \text{ g drug}$$

5. How would you prepare 480 mL of a 1 in 750 solution of an antiseptic?
   Remember: percent *w/v* is indicated.
   1 in 750 means 1 g of the antiseptic dissolved in sufficient solvent to make 750 mL solution.

$$\frac{1 \text{ g drug}}{750 \text{ mL soln}} \times 480 \text{ mL} = 0.64 \text{ g drug}$$

   Dissolve 0.64 g of antiseptic in sufficient solvent to make 480 mL solution.
6. How much of a substance is needed to prepare 1 L of a 1:10,000 solution?
   The ratio 1:10,000 means 1 g of a substance in 10,000 mL of solution.

$$\frac{1 \text{ g substance}}{10{,}000 \text{ mL soln}} \times \frac{1000 \text{ mL}}{1 \text{ L}} \times 1 \text{ L} = 0.1 \text{ g substance}$$

7. How would you prepare 120 mL of 0.25% solution of neomycin sulfate? The source of neomycin sulfate is a solution which contains 1 g neomycin sulfate/10 mL.

$$\frac{10 \text{ mL stock soln}}{1 \text{ g drug}} \times \frac{0.25 \text{ g drug}}{100 \text{ mL soln}} \times 120 \text{ mL soln} =$$

$$= 3 \text{ mL stock soln}$$

   Add sufficient purified water to 3 mL of stock solution to make 120 mL.

Problems

1. How would you make 3 f℥ of a 12.5% solution?
2. How many liters of a 4% solution can be made from 4℥ of a solid?
3. How many liters of an 8% solution can be made from 500 g of a solid?

dipole moment or polarizability. In charge-transfer complexing, substituent effects that increase electron density in the donor or decrease it in the acceptor (Structures **5**, **6**, and **7** are examples of the latter type) may be expected to increase complex stability. Such effects have been observed.[30,31]

If the hydrophobic interaction makes an important contribution to complex stability, the incorporation of organic solvents will reduce the stability. According to the cavity theory of the hydrophobic effect, complex stability is related to the change in surface area upon complex formation, so it may be anticipated that, for such systems, complex stability is related to the size of the interactants. Such a dependence has been seen, but it is complicated by the presence of additional effects.[32] Another prediction of the cavity model is that, for a given complex, stability should be determined primarily by the solvent surface tension, and there is some experimental support for this prediction.[17,21,33]

COMPLEXES IN PHARMACY

APPLICATION TO DRUG DELIVERY—Some of the properties of a drug are so pertinent to dosage forms and drug delivery that it is reasonable to identify them as pharmaceutical or biopharmaceutical properties. Complex formation may affect these properties, sometimes to advantage and sometimes adversely. Many of these properties, with corresponding examples of drug complexes, are given in Table 14-9.[34]

A dosage form might be prepared either with the separate components S (the substrate or drug) and L (the ligand or complexing agent), or with the preformed solid complex.

In a solution dosage form the method of preparation makes no difference, because the complexation equilibrium immediately establishes the equilibrium composition. It must be remembered that the fraction of drug in the complexed form is given by Equation 11, so that the free-ligand concentration is a critical variable, and excess ligand may have to be added in order to "drive the equilibrium" in favor of the bound (complexed) form.

In a solid dosage form it may be preferable to incorporate the solid complex rather than a physical mixture of the drug and complexing agent. For many systems it has been shown that the complex provides faster dissolution and greater bioavailability than does the physical mixture. The processing characteristics (physical state, stability, flowability, etc) of the complex also may be better than those of the free drug.

Not all complexation is intentional or desirable, and some dosage-form *incompatibilities* may be the result of unwanted complexation reactions. For example, some widely used polyethers (Tweens, Carbowaxes, or PEGs) can form precipitates with H-bond donors such as phenols and carboxylic acids.

A substance used widely in liquid dosage forms as a complexer of metal ions is EDTA (ethylenediaminetetraacetic acid).

Table 14-9. Pharmaceutical Properties Affected by Complexation

PROPERTY	EXAMPLE[a,b]
Physical state	Nitroglycerin-cyclodextrin
Volatility	Iodine-PVP
Solid-state stability	Vitamin A-cyclodextrin
Chemical stability	Benzocaine-caffeine
Solubility	Aspirin-caffeine
Dissolution rate	Phenobarbital-cyclodextrin
Partition coefficient	Benzoic acid-caffeine
Permeability	Prednisone-dialkylamides
Absorption rate	Salicylamide-caffeine
Bioavailability	Digoxin-cyclodextrin
Biological activity	Indomethacin-cyclodextrin

[a] Listed in order of drug-complexing agent.

The purpose of this application of complexation is to improve drug stability by inhibiting reactions (usually oxidations) that are catalyzed by metal ions, the complexed form of the metal ion being catalytically inactive. Citric acid (in the form of the citrate anion) also is used for this purpose.[35]

The cyclodextrins have been shown to have effects on all of the properties listed in Table 14-9, and many pharmaceutical applications have been proposed.[19,20,36,37]

COMPLEXES IN PHARMACEUTICAL ANALYSIS—The formation of metal-ion coordination complexes provides the basis of many analytical methods for the determination of metals. Titration of divalent and trivalent metal ions with a solution of EDTA is a standard procedure called complexometric or chelatometric titration.[38] The theoretical titration curve is calculated readily, and it can be shown that the very large endpoint "break" is the result of the 1:1 stoichiometry between the metal ion and the multidentate EDTA tetraanion. The endpoint can be detected visually with metallochromic indicators or, potentiometrically, with ion-selective membrane electrodes.

Very low concentrations of metal ions can be determined spectrometrically by complexation with a ligand that produces a spectral change. If the complex absorbs in the visible region of the spectrum, this is called colorimetric analysis. Thousands of such methods have been developed.[39] Two examples are the determination of Fe(III) by complexation with 1,10-phenanthroline (see Table 14-1), and of Hg(II) by complexation with dithizone (diphenylthiocarbazone), $S{=}C(NHNHC_6H_5)_2$. Gravimetric analysis of metal ions can be accomplished via their precipitation as insoluble coordination complexes. For example, Ni(II) forms an insoluble square planar bis(dimethylglyoxime) complex, and many metal ions yield insoluble complexes with 8-hydroxyquinoline (see Table 14-1 for the structures of these ligands).

In some instances the analytical situation can be reversed to make the metal ion serve as the analytical reagent and the organic ligand as the sample. The *ferric hydroxamate* method for the detection and determination of carboxylic acid derivatives is a good example, in which a carboxylic acid derivative such as an ester, amide, or anhydride is reacted with hydroxylamine to form the corresponding hydroxamic acid.

An excess of Fe(III) is added, and this forms a red-violet coordination complex with the hydroxamic acid; the concentration of the complex is determined spectrometrically.

Colorimetric analyses also can be based on molecular complex formation. Recall that charge-transfer complexation often is accompanied by the development of an intense charge-transfer absorption band, and this can be put to analytical use. For example, tertiary amines can be determined spectrometrically by complexation with tetracyanoethylene (Structure **5**).

Many complex formation reactions are used in conjunction with, or as the basis for, a separation, either by liquid–liquid extraction or chromatography. A classical method for amines, the *acid-dye method*, is based upon complex formation between an amine and a dye molecule. The complex is extracted from the aqueous phase in which it is formed into an organic solvent, where the dye concentration is measured spectrometrically.

The success of the method is based on the condition that only the complexed form of the dye is extractable, so each molecule of amine results in the complexation of one molecule of dye, and this is extracted into the organic phase, where its concentration is an indirect measure of the amount of amine. In order to ensure the nonextractability of the excess (uncomplexed) dye, a dye is used that is a neutral weak acid, and the aqueous pH is controlled at a level above the pK_a of the dye, thus converting it to its anionic form.[40] The principle can be reversed to determine acidic compounds with basic dyes.[41] In a similar way metal ions may be extracted into organic solvents