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Basics of Compounding with Dilutions and Concentrates

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Abstract **Pharmacists use various sources for obtaining the active pharmaceutical ingredient for compounding medications. In many cases, it is the pure drug (*United States Pharmacopeia, National Formulary,* or similar grade); in some cases, it can be a commercial dosage form; and, in some cases, it may be a dilution or concentrate. If the drug is not present at full strength, then adjustments may be necessary to obtain the required quantity of drug. Also, in many cases, it is necessary to use a dilution or a concentrate of a drug due to safety and quality reasons. Presented within this article are new sources of active pharmaceutical ingredients that are now available to aid pharmacists in meeting future *United States Pharmacopeia* <800> standards. It is critical that the pharmacist be aware of the strength of the drug and any other excipients that may be available.**

Pharmacists involved in compounding must consider a number of factors when determining the actual quantity of an active ingredient to use for a compounded prescription. Many drug substances and excipients are available as dilutions (triturations) and concentrates and do not consist of 100% drug or chemical. Since the bulk substance, or active pharmaceutical ingredient (API) or excipient is not 100% in all cases, then it is important to know the strength of the item so that appropriate allowances can be made to obtain the correct amount.

Terminology used to describe the new sources of APIs is not well-defined. The following definitions are available and commonly used.

TRITURATION	A dilution of a potent solid substance to a specific concentration by mixing it thoroughly with a suitable diluent.
DILUTION	• A diluted solution or mixture. • A diluted substance.
CONCENTRATES	A liquid preparation of increased strength and reduced volume, which is usually diluted prior to administration or use. • Something concentrated. • To make less dilute. • Concentrates can also be non-liquid preparations.
STOCK PREPARATIONS	Concentrated products of active pharmaceutical ingredients or excipients and are used as a convenience to compound preparations of lesser concentration.

As is evident, clear, defined descriptions of these as they may be applicable to compounding of various dosage forms is missing.

Substances are available as dilutions (also called triturations) and concentrates for a number of reasons.

REASON 1: The quantities required for dosing or compounding are so small they cannot be accurately weighed, so dilutions or triturations are prepared, assayed, and utilized.

REASON 2: Some items (e.g., nitroglycerin) are explosive and must be diluted in order to be safely handled.

REASON 3: Many substances (e.g., acids, bases) are commercially available in percentage strengths that vary from one acid to another and depend on the solubility and stability of the solute in water and on the manufacturing process. The diluted acids are aqueous solutions usually 10% w/v but diluted acetic acid is 6% w/v. The concentrations of the official undiluted acids are expressed as percentages weight in weight (w/w) but the strengths of official diluted acids are expressed as percentages weight in volume. Therefore, it is necessary to consider the specific gravities of the concentrated acids when calculating the volume required to prepare a given quantity of diluted acid.

Table 1 lists a number of official and nonofficial solids and liquids available as dilutions or concentrates.

A recent development leading to the increased use of concentrates is the requirements for handling hazardous drugs. Powders pose a significantly greater problem as compared to handling liquids or even diluted powders. Potent powders diluted significantly with inert powders make them safer and more accurate in compounding. Examples include dilutions of levothyroxine and liothyronine. Liquid concentrates are much safer and easier to handle during compounding than potent hazardous drugs. Semisolid concentrates are easier to handle and concentrates of estradiol, estrone, estriol, progesterone, and testosterone are commercially available. Liquid and semisolid concentrates are not generally airborne and pose less danger to personnel handling them.

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Actually, the use of concentrates and even dilutions is not new. It is routine to utilize manufactured dosage forms as the drug source, including tablets, capsules, parenterals, etc. When this is done, it is important to be aware of the total composition of the dosage form (e.g., excipients) and whether or not the excipients contained may impact the final compounded preparation. It is also critical to confirm that any vehicle used for preparing a dilution or concentrate is compatible with the API.

Dilutions and Concentrates

SOLID DILUTIONS: STABLE

Dilutions were at one time official and consisted of diluting one part by weight of the drug with nine parts of finely powdered lactose; they were 10% mixtures of the drug. The purpose of these dilutions was for a means of conveniently obtaining small quantities of a drug for compounding purposes. Today, the strengths vary but the concept is the same, as the following examples show.

T3 AND T4 SOLID DILUTIONS (PROFESSIONAL COMPOUNDING CENTERS OF AMERICA)

Liothyronine Sodium USP (T3) and Levothyroxine Sodium USP (T4) are used primarily for thyroid disorders and are dispensed in a highly diluted form. However, both T3 and T4 historically were not typically available pre-diluted. This requires pharmacies to dilute T3 and T4 themselves—a procedure that takes time, skill,

and patience. The physical characteristics of the two drugs are as follows:

- Levothyroxine sodium occurs as a light yellow to buff-colored, odorless, tasteless, hygroscopic powder that is only very slightly soluble in water and slightly soluble in alcohol.
- Liothyroinine sodium occurs as a light tan, odorless, crystalline powder that is slightly soluble in alcohol and very slightly soluble in water.

Professional Compounding Centers of America (PCCA) have available 1:1000 dilutions of both T3 and T4. This saves the pharmacy time and money, and increases quality by eliminating the need to make a dilution in-house or to grind tablets. The pharmacy operation is enhanced while building trust with practitioners and customers—with accuracy and quality meticulously assured, as follows:

- Each gram of PCCA's T3 and T4 contains 1 mg of Liothyronine Sodium USP (1 mg/g) and 1 mg of Levothyroxine Sodium USP (1 mg/g), respectively.
- This is a tremendous time saver for complex formulations such as capsules.
- Every batch is tested to ensure accurate potency and content uniformity.
- The dilutions are available in a variety of package sizes for less-frequent T3 and T4 compounding.

EXAMPLE

Prepare 100 capsules of levothyroxine sodium 100 µg. How much of theT-4 levothyroxine sodium 1:1000 (1 mg/g) will be required for the prescriptions.

100 capsules × 100 µg = 10,000 µg or 10 mg of levothyroxine sodium is required.

The dilution contains 1 mg/g, so

1 mg/1 g = 10 mg/X g

X = 10 g of the dilution will provide 10 mg of levothyroxine sodium.

So, 10 g of the 1:1000 dilution will be required for the prescription.

SOLID DILUTIONS: UNSTABLE–NITROGLYCERIN

Diluted nitroglycerin contains the cautionary labeling: [Caution: Taking into consideration the concentration and amount of nitroglycerin ($C_3H_5N_3O_9$) in Diluted Nitroglycerin, exercise appropriate precautions when handling this material. Nitroglycerin is a powerful explosive and can be detonated by percussion or excessive heat. Do not isolate nitroglycerin ($C_3H_5N_3O_9$).]

Isosorbide dinitrate and Isosorbide mononitrate have similar warnings.

Undiluted nitroglycerin occurs as a white to pale yellow, thick, flammable, explosive liquid that is soluble in alcohol and slightly soluble in water. Diluted nitroglycerin with lactose is a white, odorless powder; when diluted with propylene glycol or alcohol, nitroglycerin is a clear, colorless, or pale yellow liquid. Dilutions are safer to handle as shown in this example of nitroglycerin.

EXAMPLE

To obtain 40 mg of nitroglycerin to prepare 100 nitroglycerin 0.4-mg dosage units would be:

*A 10% nitroglycerin trituration contains 1 g of nitroglycerin per 10 g of mixture.

*40 mg = 0.040 g

1 g/10 g = 0.04 g/X g

X g = 0.4 g or 400 mg of the dilution would be required.

LIQUID: AQUEOUS CONCENTRATES

Many aqueous concentrates are available and are convenient to use; a notable example in compounding is benzalkonium chloride solutions.

Benzalkonium chloride occurs as white or yellowish-white, thick gel, or gelatinous pieces. It is very soluble in water and in alcohol. Benzalkonium chloride solution occurs as a clear liquid that is colorless or slightly yellow unless a color has been added. It is commonly available as 17% and 50% concentrates.

EXAMPLE

How many milliliters of a benzalkonium chloride 17% solution would be required to prepare 4,000 mL of a 1:10,000 solution?

1/10,000 = X / 4,000

10,000 X = 4,000

X = 0.4 g of benzalkonium chloride substance is required.

17 g/100 mL = 0.4 g/X

17 X = 40

X = 2.35 mL of the benzalkonium chloride 17% solution is required.

Methods of calculations using dilutions/triturations can include ratio and proportion, allegation alternate and allegation medial. One can consult pharmacy calculation texts for these procedures.

ACIDS AND BASES

It is important to check the label of each lot of concentrated acid or base when utilizing for a prescription or procedure, as they can sometimes vary. The following relationship can be used:

(Strength of diluted acid X 1000)/
(Strength of undiluted acid X sp gr of undiluted acid)

EXAMPLE

To make 1000 mL of Diluted HCL USP, using HCL assayed at 37.5% HCL with a sp gr of 1.18, the amount required is:

(10 X 1000)/(37.5 X 1.18) = 226 mL is required

Dilutions can be prepared by allegation, ratio, proportion, or other calculation methods. As previously mentioned, these methods are detailed in pharmacy calculations textbooks.

TABLE 1. EXAMPLE SUBSTANCES (OFFICIAL AND NONOFFICIAL) AVAILABLE AS CONCENTRATES/DILUTIONS/TRITURATIONS.

ITEM	PERCENT STRENGTH	COMMENT
Acetic Acid NF	36.0% to 37.0% w/w	
Acetic Acid, Diluted NF	5.7% to 6.3% w/v	
Alcohol USP	94.9% to 96.0% v/v; 92.3% to 93.8% w/w	Sp Gr 0.812 – 0.816
Alcohol, Diluted NF	48.4% to 49.5% v/v	Sp Gr 0.935 – 0.937
Aluminum Sulfate USP	54.0% to 59.0%	
Amifostine USP	78.0% to 82.0%	
Aminophylline USP	84.0% to 87.4%	
Ammonia Solution Strong NF	27% to 31% w/w	
Ammonium Lactate 70% Solution	70%	
Ammonium Lauryl Sulfate 28%	28%	
Benzalkonium Chloride Solution NF	Varies; 17% and 50% available. Check label.	
Benzoyl Peroxide USP	65.0% to 82.0%; Usually 70%	Note: Store in original container – Explosive
Beta Carotene Beadlets	10%	
Boron Citrate 5% Powder	5%	
Curcumin Powder 95%	95%	
Formaldehyde Solution USP	NLT 34.5% w/w	
Glutaraldehyde 25% Aqueous Solution		
Glycolic Acid 70%		
Hydrochloric Acid NF	36.5% to 38.0% w/w	
Hydrochloric Acid, Diluted NF	9.5% to 10.5 % w/v	
Hydrofluoric Acid 49%		
Hydrogen Peroxide Concentrate USP	29.0% to 32.0% w/w	Strong oxidant
Hydrogen Peroxide Topical Solution USP	2.5% to 3.5% w/v	
Hypophosphorous Acid NF	30.0% to 32.0%	
Isopropyl Rubbing Alcohol USP	68.0% to 72.0%	Sp Gr 0.872 – 0.883
Isosorbide Concentrate USP	70.0% to 80.0% w/w	
Isosorbide Dinitrate, Diluted USP	Varies-usually about 25% w/w	
Isosorbide Mononitrate, Diluted USP	See label	Explosive
Lactic Acid USP	88.0% to 92.0% w/w	
Lutein 5% Beadlets		
Maltitol Solution NF	NLT 50.0%	
Misoprostol 1% HPMC Dispersion		
Nitroglycerin, Diluted USP	10% usually w/w	
Pamabrom USP	72.2% to 76.6%	
Phenol, Liquified USP	90% w/w	
Phytic Acid 50% in Water		
Phosphatidylserine 40%		
Phosphoric Acid NF	85.0% to 88.0% w/w	
Phosphoric Acid, Diluted NF	9.5% to 10.5 % w/v	
Sodium Hypochlorite Solution USP	4.0% to 6.0% w/w	
Sodium Lactate Solution USP	NLT 50.0% w/w	
Sorbitol Solution	NLT 64.0%	
Zinc Pyrithione 48% (min) Aqueous Dispersion		

NF = *National Formulary;* NLT = not less than; USP = *United States Pharmacopeia*

SAMPLE OF ALPHA TOCOPHEROL

LIQUID: OIL CONCENTRATES OF LIQUIDS

Vitamin A is available as the palmitate in oil (50% and 75%) and as the acetate (1,000,000 IU/g, 2,500,000 IU/g, and 2,800,000 IU/g. Vitamin A in liquid form occurs as a light-yellow to red oil that may solidify upon refrigeration. In solid form, it has the appearance of any diluent that has been added. In liquid form it is soluble in absolute alcohol and in vegetable oils but insoluble in water and in glycerin. In solid form, it may be dispersible in water.

Vitamin E is available as 400 U/mL. Vitamin E occurs as the alpha tocopherols and alpha tocopheryl acetates as clear yellow, or greenish yellow, viscous oils. Alpha tocopherol acid succinate occurs as a white powder that is soluble alcohol and in vegetable oils. Other forms of Vitamin E are insoluble in water, soluble in alcohol, and miscible with vegetable oils.

SEMISOLID CONCENTRATES OF SOLIDS: CREAM BASED (HUMCO)

There are five sex hormones used in compounding that are considered hazardous drugs (HD) produced in Humco's HRT Heavy compounding base. The four female sex hormones are three estrogens: Estrone (E1), Estradiol (E2), and Estriol (E3), as well as the progestogen, Progesterone (P4). The androgen is Testosterone (T). These hormones are used therapeutically in different concentrations—either alone or in various combinations—and they are applied to the skin to enter the systemic circulation via the transdermal route.

The hormones and their characteristics are as follows:

ESTRADIOL occurs as a white or creamy white, small crystals or crystalline powder that is soluble in alcohol, sparingly soluble in vegetable oils, and practically insoluble in water.

ESTRIOL occurs as a white to practically white, odorless, crystalline powder that is soluble in vegetable oils and insoluble in water.

ESTRONE occurs as small, white crystals or white to creamy white crystalline powder that is soluble in vegetable oils and practically insoluble in water.

PROGESTERONE occurs as a white or creamy white, odorless, crystalline powder that is sparingly soluble in vegetable oils and practically insoluble in water.

TESTOSTERONE occurs as white or slightly creamy white crystals or crystalline powder. It is soluble in vegetable oils and practically insoluble in water.

FIGURE 1. FORMULATIONS USING CONCENTRATES. STOCK HORMONE CREAMS

HORMONE	% CONCENTRATION		MG/G CONCENTRATION	
Progesterone	400	%	400	mg/g
E3	10	%	100	mg/g
E2	10	%	100	mg/g
E1	1	%	10	mg/g
Testosterone	20	%	200	mg/g

FIGURE 2. TYPICAL RATIOS OF PRESCRIBED HORMONES.

HORMONE		TYPICAL RATIOS			
Estriol	E3	80	70	50	80
Estradiol	E2	10	20	50	20
Estrone	E1	10	10	0	0

Rx #1: Bi-Est 1.5 mg/g (50/50) Progesterone 200 mg/g Cream, Dispense 100 g
Rx #2: Bi-Est 2.5 mg/g (80/20) Progesterone 25 mg/g Cream, Dispense 100 g
Rx #3: Tri-Est 3 mg/g (70/20/10) Progesterone 100 mg/g Testosterone 5 mg/g Cream, Dispense 100 g

HUMCO™

INSTRUCTIONS: Fill in all of the appropriate blue fields. Strength-Desired fields may be left blank if the API is not required in the formulation. The green fields will automatically calculate the amount of Humco Concentrates that are required for compounding. For further information please contact Humco Compounding Resource Center, **CRC@Humco.com**

Triest 5mg/mL Test 5mg/mL DHEA 5mg/mL Prog 100mg/mL

Final Weight (gm): 60

	Strength Desired (mg/gm)	Ratio Desired (Decimal)	Humco Concentrates	Amount of Concentrate to Add (gm)
Estrogen/Biest/Triest				
	5			
Estriol (E3)		0.7	Estriol 10%	2.1
Estradiol (E2)		0.2	Estradiol 10%	0.6
Estrone (E1)		0.1	Estrone 1%	3
Testosterone				
	10		Testosterone 20%	3
DHEA				
	5		DHEA Powder 100%	0.3
Progesterone				
	100		Progesterone 40%	15
			Humco HRT Heavy	36
			Final Weight (gm)	60

*Note: If "RATIO OUT OF BALANCE" is displayed, there is an issue with the ratio of E3, E2, and E1. The values must add up to 1.0 (100%)

FIGURE 3. WORKSHEET FOR TRIEST, TESTOSTERONE, DEHYDROEPIANDROSTERONE, AND PROGESTERONE FORMULATIONS.

Humco manufactures these five hormones as concentrates (See Figure 1). These five hormones are considered to be hazardous drugs; they may be harmful if the dust is inhaled. In order to prevent formation of dust from the hormones, the hormone concentrates have been manufactured to contain a certain amount of each hormone already incorporated into HRT Heavy. The HRT Heavy base is specifically designed for male and female hormone restoration formulations and has an ample API carrying capacity.

HRT Heavy is a pharmaceutically elegant oil-in-water emulsion cream which spreads on the skin easily and does not leave a sticky residue. These concentrates will have a shelf life of no less than two years. Figure 2 shows varying ratios that estrogens are commonly prescribed.

Using Calculation Aids with Concentrates

Humco's Hormone Quantity Calculator spreadsheet can calculate any ratio the prescriber may want, as shown in Figure 3. Figure 4 shows an example of three commonly prescribed hormone therapies. You can input these or any combination of these hormones into the calculator to obtain the quantity of each hormone from the concentrate and the amount of hormone base that must be added to the concentrates.

Conclusion

Dilutions and concentrates are a way of life in pharmaceutical compounding and offer means of convenience and increased accuracy, quality, and safety for personnel. It is incumbent on compounding pharmacists to be aware of the strength of the drug substances used and whether or not they are available as aliquots, dilutions, and concentrates. If they are available, appropriate calculations are in order to ensure quality compounding.

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FIGURE 4. THREE EXAMPLE HORMONE THERAPIES.

RX #1			MG/G	PARTS
Progesterone			200	50
Bi-Est 50/50	1.5 mg/g	E3	0.75	7.5
		E2	0.75	7.5
Total Hormones (from base)				65
Inert HRT Base (q.s.)				35
Total RX Weight (g)				100
RX #2			**MG/G**	**PARTS**
Progesterone			25	16
Bi-Est 80/20	2.5 mg/g	E3	2	20
		E2	0.5	5
Total Hormones (from base)				41
Inert HRT Base (q.s.)				59
Total RX Weight (g)				100
RX #3			**MG/G**	**PARTS**
Progesterone			100	25
Tri-Est 70/20/10	3 mg/g	E3	2.1	21
		E2	0.6	6
		E1	0.3	30
Testosterone			5	2.5
Total Hormones (from base)				84.5
Inert HRT Base (q.s.)				15.5
Total RX Weight (g)				100

HRT = hormone replacement therapy