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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

COMPOUNDING ORAL LIQUIDS

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INTRODUCTION

Pharmacists are often called upon to extemporaneously compound oral liquid dosage forms. Reasons for these requests may be based on the following.

1. Many drug products are not commercially available as oral liquids.
2. Infant, pediatric, geriatric and some psychiatric patients cannot swallow solid dosage forms.
3. Some products are therapeutically better in liquid form.
4. The bulk of some preparations make oral liquids more feasible.
5. Some patients are often administered oral liquids to prevent them from placing tablets/capsules under the tongue and not swallowing them at the time of administration, i.e., nursing home, incarcerated patients.
6. Patients on enteral feeding methods require a liquid dosage form.
7. They offer a wide diversity of dosage forms and dosage strengths.
8. Drugs are often more bioavailable from oral liquids than from solids.

Several technical difficulties must be confronted and overcome to prepare a successful oral liquid product: unstable drugs are even more unstable in solution; poorly soluble drugs must be solubilized or suspended; bad tasting drugs must be masked and a palatable product prepared. The formulation of a successful product depends upon a combination of scientific acuity and the pharmaceutical art. The preparation of an oral liquid dosage form involves consideration of physicochemical, pharmaceutical and patient factors.

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Dear Pharmacist

This issue is the first in a new series of *Secundum Artem*, a publication designed for pharmacists that compound prescriptions; nonsterile and sterile, traditional and high technology. It is often through the proper compounding of prescription medication that *individualization of patient therapy* can be achieved. The frequency of pharmaceutical compounding has increased and it appears that it may continue to increase in the future with the opportunities in biotechnology-derived drugs and in opportunities of decreasing the costs of health care.

As the compounding activities of pharmacists have expanded and become very diverse, there is a shortage of information available for the pharmacy student and the practitioner for training and continuing education in this field. This publication should help fill the gap in providing a source of information concerning techniques and procedures for extemporaneous compounding, both traditional and high technology.

We invite you to submit comments, questions, suggestions and ideas that you would be willing to share with your fellow health care professionals.

Remember, at Paddock Laboratories, you, the professional pharmacist, always come first.

Sincerely,

Bruce G. Paddock, R.Ph
President

Another practical consideration is the source of the active ingredient. Best results can be obtained by using the pure USP drug powder. The compounding pharmacist then is assured of the potency of the product being used. If the pure drug is not available, a second source involves prefabricated dosage forms, e.g. injectables, tablets, capsules. It is common practice to use dosage forms as a drug source but the presence of excipients must be considered in preparing the extemporaneous product.

Depending upon the physiochemical and stability characteristics of the active drug, a number of dosage forms can be prepared, i.e., syrups, elixirs, suspensions. Factors to be considered in oral liquid dosage formulation include the:

1. physical and chemical properties of ingredients,
2. order of mixing and adjuvants,
3. pharmaceutical techniques required,
4. incompatibilities in preparation and storage,
5. stability and potency of ingredients, and
6. proper labeling, including accessory labels.

Major physical and chemical considerations with which to be concerned include the drug concentration, solubility, pKa, taste, and stability. Vehicle considerations include pH, flavor, sweetener, color, preservative, viscosity, compatibility and, if indicated, suspending and emulsifying agents. The major points will be briefly discussed.

Drug concentration and solubility in various solvents will dictate the type of dosage form to prepare. For example, if the drug is water soluble, a syrup can be prepared; if soluble in water-alcohol-glycerin cosolvent systems, an elixir can be prepared; if insoluble, a suspension; if the drug is an oil, an emulsion can be prepared.

The *pH of the vehicle and pKa of the drug* partially determine the overall solubility of the drug. Slight adjustments in pH can greatly affect the solubility of the drug and should be controlled in the preparation of a solution. It may be necessary to buffer a solution to maintain its solubility characteristics.

Another area affected by pH is chemical stability. Reference sources such as (1) "Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists" 2nd Ed. (KA Connors, GL Amidon, VJ Stella), (2) Remington's Pharmaceutical Sciences (Ed. by AR Gennaro), (3) American Hospital Formulary Service Drug Information-92 (American Society of Hospital Pharmacists), (4) The Merck Index, (5) the series entitled "Analytical Profiles of Drug Substances" (Ed. by K. Florey) and numerous journals (American Journal of Hospital Pharmacy, U.S. Pharmacist, etc.) can be consulted to obtain information on the required pH for maximum stability for specific drugs. This can help establish guidelines for selection of the best vehicle.

If the active drug has a *disagreeable taste or odor*, it will be necessary to use a flavoring technique, to be discussed later, to make the product palatable to enhance patient compliance.

Other factors listed will be discussed throughout the paper as appropriate to specific applications.

Depending upon the overall characteristics of the active drug, it may be best to prepare, among other dosage forms, a syrup, elixir or a suspension. Numerous other formulations are possible, but these are the most common for extemporaneous preparation.

SYRUPS

Syrups are concentrated, aqueous preparations of a sugar or sugar-substitute with or without flavoring agents and medicinal substances. Syrups can serve as pleasant-tasting vehicles for active drugs.

Syrups are appropriate when the drug is water soluble. The usual pH requirement for many drugs is normally slightly to moderately acidic and flavored syrups can often effectively mask the taste of poorly-tasting drugs.

The viscosity of syrups will keep the flavor in the mouth longer but also may decrease the rate of dissolution of the active drug in the vehicle during preparation. It is easier to first dissolve the active ingredient in a small quantity of water and then "qs" to volume with the syrup.

The preservative properties of a syrup are partially dependent upon maintaining a high concentration of sucrose or sugar in the final product. If the sucrose concentration is decreased, it may be necessary to add another "preservative", i.e., alcohol, to the product. For example, how much 95% ethanol would be required to preserve the following prescription?

Rx	Active drug #1 (Powder)	120 mg
	Active drug #2 (Aq. Soln)	20 mL
	Water	10 mL
	Syrup, qs	120 mL

As this prescription is written, the sucrose concentration and preservative properties are going to be decreased because 30 mL of water and aqueous solution is diluting the syrup. One has a number of options, of which the addition of 95% alcohol is relatively simple. To calculate the quantity of alcohol required:[1]

1. Since approximately 90 mL of syrup is required, this will contain (85% X 90 mL) 76.5 G of sucrose.
2. One gram of sucrose preserves 0.53 mL of water, so 76.5 G of sucrose will preserve 40.5 mL of water.
3. One gram of sucrose occupies a volume of 0.647 mL, so 76.5 G will occupy 49.5 mL.
4. 40.5 + 49.5 = 90 mL of solution is preserved by the sucrose present.

5. 120 mL - 90 mL = 30 mL of solution is not preserved, i.e., 30 mL of "free water" or "unpreserved water".
6. To preserve the remaining solution using 18% alcohol, (18% X 30 mL) 5.4 mL of absolute alcohol, or (5.4/0.95) 5.7 mL of 95% alcohol would be required. This 5.7 mL volume will replace part of the 10 mL of water that is to be used.

This should produce a product that is adequately preserved. Other preservatives that can be used in oral liquids are listed in Table 1.[2] Syrups are often refrigerated to enhance their stability and palata-bility.

TABLE 1

Common preservatives for oral liquid products.

Preservative	Concentration (%)
Alcohol	15-20%
Benzoic Acid	0.1%
Methylparaben	≤ 0.2%
Propylparaben	≤ 0.2%
Sodium Benzoate	0.1%
Sorbic Acid	0.1%

Some syrup vehicles are listed in Table 2. As is evident from this table, most syrups have slightly acidic pH values.[3] The commercially prepared products, i.e., Ora-Sweet, Ora-Sweet SF and Syrpalta, have pH values of approximately 4.2, 4.2 and 4.5 respectfully. The pH of Cherry Syrup, Coca-Cola Syrup, Orange Syrup and Raspberry Syrup all are less than 4.0. Neutral syrup vehicles include Simple Syrup (Syrup USP) and Aromatic Eriodictyon Syrup.

TABLE 2

Syrup vehicles commonly used in extemporaneous compounding of oral dosage forms.

Syrup	pH	Alcohol Content (%)
Acacia Syrup	5.0	
Aromatic Eriodictyon Syrup	7.0-8.0	6-8
Cherry Syrup	3.5-4.0	1-2
Citric Acid Syrup (Lemon Syrup)		<1
Coca-Cola™ Syrup	1.6-1.7	0
Glycyrrhiza Syrup	6.0-6.5	5-6
Ora-Sweet™	4.0-4.5	0
Ora-Sweet SF™	4.0-4.4	0
Orange Syrup	2.5-3.0	2-5
Raspberry Syrup	3.0	1-2
Sasparilla Compound Syrup	5.0	
Syrpalta™	4.5	
Syrup, USP	6.5-7.0	
Tolu Syrup	5.5	
Wild Cherry Syrup	4.5	1-2

The commercially available products contain preservative systems, therefore additional preservatives would normally not be needed if the vehicle is not significantly diluted.

ELIXIRS

Elixirs are clear, sweetened, hydroalcoholic solutions that are usually flavored and are suitable for drugs that are insoluble in water alone but soluble in water-alcohol mixtures. They are usually less sweet and less viscous than syrups and are generally less effective in masking taste. Elixirs may also contain different solvents as cosolvent systems, e.g., water, alcohol, glycerin, sorbitol, propylene glycol and polyethylene glycol 400.

The advantages of these mixtures of water and alcohol is they dissolve both alcohol-soluble and water-soluble substances, depending on the percentage of each solvent present. Glycerin, also present in some elixirs, is comparable in solvent properties with alcohol but, due to its viscosity, solutes dissolve slowly. Propylene glycol is also miscible with water and alcohol and is frequently substituted for glycerin.

Elixirs are usually prepared by simple solution. When preparing elixirs, care must be taken to keep the alcohol concentration and pH within the range for maximum stability of both the drug and the dosage form. One must also consider whether the salt form of the drug (more water soluble) or the free acid or base (more alcohol soluble) form is to be used.

When preparing elixirs, generally the alcohol soluble components are dissolved in the alcohol and the water soluble components in the water. Then, the aqueous phase is generally added to the alcoholic solution to always maintain the highest alcohol concentration possible. If the situation is reversed, then the oils/drug may come out of solution as soon as the alcohol solution contacts the water.

If a clear product is not obtained and the cloudiness is due to aromatic oils (an excess of oils has been added), the technique of talc filtration may be used to obtain a brilliantly clear product. This involves adding, per 100 mL of solution, approximately 1-3 G of talc to the liquid, mixing and filtering, returning the first portions back through the filter until a clear product is obtained.

Cosolvent systems serve not only to dissolve the active drug but also the flavoring components, since they are often volatile oils. Artificial sweeteners, e.g., saccharin, may be required for sweetening since sucrose may not be sufficiently soluble in the alcoholic system.

Example elixir vehicles are listed in Table 3. The most commonly available elixir vehicle is aromatic elixir, with an alcohol content of approximately 22%. Some syrups now contain some alcohol so the distinction between syrups and elixirs is sometimes vague. The use of the two isoalcoholic elixirs (Low: 8-10% alcohol, High: 73-78% alcohol) can be adjusted to obtain a vehicle of the desired alcohol concentration.

TABLE 3

Elixirs that can be used in the extemporaneous preparation of oral liquids.

Elixir	pH	Alcohol Content (%)
Aromatic Elixir	5.5-6.0	21-23
Benzaldehyde Compound Elixir	6.0	3-5
IsoAlcoholic Elixir* (Low, High)	5.0	8-10%, 73-78%

*(These two elixirs can be mixed in various ratios to obtain the required alcohol concentration as discussed in Remington's Pharmaceutical Sciences.)

SUSPENSIONS

A suspension is a 2-phase system consisting of a finely divided solid dispersed in a solid, liquid or gas. Suspensions are prepared when the drug is not sufficiently soluble in ordinary solvents. A good suspension is dependent upon a uniform dispersion of the drug throughout the vehicle.

The first step is to obtain uniform, small particles of the drug through particle size reduction. Following this, the active insoluble material should be thoroughly wetted prior to mixing with the vehicle. Hydrophilic materials are best wetted with water miscible liquids and hydrophobic substances can be wetted with nonpolar liquids or by the use of a surfactant. A general guideline in the use of wetting agents is to use the minimal amount required to produce the desired product. After the preparation of a thick paste of the drug and wetting agent, the vehicle is added with constant stirring.

Example suspension, vehicles are listed in Table 4. If unavailable, a good suspension vehicle can be obtained by preparing a 0.5-5% methylcellulose (usually about 1-2%) or a 0.5-1.5% sodium carboxymethylcellulose dispersion. The viscosity required is related to the tendency of the active drug to settle, which in turn is related to the powder's density and particle size. After the suspending agent is prepared, it can be mixed 1:1 with a flavored syrup.

One characteristic of a good suspension is its resuspendability. The product can be observed over time to determine the settling/caking tendencies. Caution should be observed that the product not be made too thick, as difficulty may be encountered by the patient when pouring, especially if the product is refrigerated.

FLAVORING

One goal in the preparation of an oral liquid dosage form is to mask the taste of an objectionable tasting drug. The stronger the objectionable taste, the more difficult the task. The flavor experience is a combination of the sensations of taste, smell, touch (texture), sight

TABLE 4

Suspending agents and vehicles for extemporaneous preparation of suspensions.

Agent	Final Concentration (%)
Acacia, NF	2.0-5.0
Carbomer Resins, NF	0.5-5.0
Carboxymethylcellulose Sodium, USP	0.5-1.5
Colloidal Silicon Dioxide, NF	1.5-3.5
Methylcellulose, USP	0.5-5.0
Tragacanth, NF	0.5-2.0

Vehicle	pH	Alcohol Content (%)
Cologel™*	4.0	5
Ora-Plus™	4.0-4.5	0
Suspendol-S™	5.3-6.0	0

*No longer manufactured.

touch (texture), sight and sound.

The four primary tastes include sweet, sour, salty and bitter. Table 5 details some representative solutions that can be prepared to illustrate slight, moderate and strong levels of each

TABLE 5

Representative solutions that can be prepared to illustrate the four primary tastes.[4]

	Sweet (% Sucrose)	Sour (% Citric Acid)	Salty (% NaCl)	Bitter (% Caffeine)
Slight	5	.05	.4	.05
Moderate	10	.10	.7	.10
Strong	15	.20	1.0	.20

of the four primary tastes for comparison.[4] Table 6 provides some correlations between chemical properties of the active drug that can be used as guidelines in flavor selection.[5] This can serve as a reasonable starting point for flavor selection.

TABLE 6

Some correlations between chemical properties and taste and odor that can be used as guidelines in flavor selection.[5]

Taste	Chemical Property
Sour	H+
Salty	Simultaneous presence of anions and cations
Bitter	High molecular weight salts
Sweet	Polyhydroxyl compounds, Polyhydrogenated compounds, a-Amino acids
Sharp, biting	Unsaturation
Odor	
Fruity	Esters, lactones
Pleasant	Ketones
Camphoraceous	Tertiary carbon atom

The selection of an appropriate flavor for the patient will generally involve aspects of (1) immediate flavor identity, (2) rapid full flavor development, (3) acceptable mouthfeel, (4) short aftertaste, and (5) no undesirable sensations.[4] A general table for masking basic tastes is shown in Tables 7 and 8.[4,5,6]

TABLE 7

Representative flavors used to mask some basic tastes.[4-5]

Taste	Flavor
Sweet	Vanilla, Fruit, Grape, Bubblegum, Berry
Acid/Sour	Lemon, Lime, Orange, Cherry, Grapefruit, Raspberry
Salty	Nut, Butter, Butterscotch, Spice, Maple
Bitter	Licorice, Coffee, Chocolate, Mint, Grapefruit, Cherry, Peach, Raspberry, Orange, Lemon, Lime

The selection of a sweetening agent can have an impact on flavor development in the mouth. For example, saccharin may give a rapid bitter sensation prior to the sweet, flavor sensation that follows. Sucrose, on the other hand, yields a fast sweet sensation that enhances the development of a full-bodied flavor. In other words, sucrose, generally provides a better balance of flavor.

Other ingredients in the formula may also impact the flavor, e.g., preservatives. For example, methylparaben has a floral, gauze-pad-like aroma and propyl and butyl paraben, though they have very little aromatic effect, have a numbing mouth-feel.[4] Consequently, when using these preservatives, the lowest effective concentration is usually selected.

TABLE 8

Suggested flavors for selected classes of drugs.[6]

Drug Class	Flavors
Antibiotics	Cherry, maple, pineapple, orange, raspberry, banana-pineapple, banana-vanilla, coconut-custard, strawberry-vanilla, lemon-custard, cherry custard, fruit-cinnamon.
Antihistamines	Apricot, black currant, cherry, cinnamon, custard, grape, honey, lime, loganberry, peach-orange, peach-rum, raspberry, root beer, wild cherry.
Barbiturates	Banana-pineapple, banana-vanilla, black currant, cinnamon-peppermint, grenadine-strawberry, lime, orange, peach-orange, root beer
Decongestants & Expectorants	Anise, apricot, black-currant, butterscotch, cherry, coconut-custard, custard-mint-strawberry, grenadine-peach, strawberry, lemon, gooseberry, loganberry, maple, orange, orange-lemon, coriander, orange-peach, pineapple, raspberry, strawberry, tangerine
Electrolytes	Cherry, grape, lemon-lime, raspberry, wild cherry syrup
Geriatrics	Black currant, grenadine-strawberry, lime, root beer, wild strawberry.

Numerous approaches can be utilized to prepare palatable liquid preparations in addition to simply selecting a flavor. Flavoring techniques include (1) blending, (2) overshadowing, (3) physical, (4) chemical, and (5) physiological methods.[5]

Blending, the use of a flavoring substance that blends with the drug taste, is illustrated by using citrus fruit flavors with drugs with an acidic taste. Overshadowing is the use of a flavor with a stronger intensity and longer residence time in the mouth, i.e., using methyl salicylate and glycyrrhiza. Physical methods include (1) the formation of insoluble compounds (since the drug will not "taste" if it is not in solution) and preparing a suspension, (2) the emulsification of oils (placing the objectionable drug in the internal phase of an emulsion and flavoring/sweetening the external phase—which is the phase that will be tasted, (3) effervescence, which is good for salty tasting drugs, (4) high viscosity fluids, which involves the use of syrups which help to keep the flavor in the mouth longer, and (5) the coating of tablets. Physiological techniques involve the use of the anesthetic action of some agents, e.g., menthol and mint, and the cooling effect experienced by mannitol—due to its negative heat of solution.

If a coloring agent is used, it should be selected to match the flavor, i.e., green for mint, red for cherry. It is not necessary to always color a product. If coloring is used, better results are usually obtained by using minimal quantities of dyes to produce light-moderate density colors.

TECHNIQUES

Many techniques are utilized in the preparation of oral liquid dosage forms. The most common is simple solution, i.e., dissolving a drug in a solvent. A number of points to remember on solubility and dissolution are listed in Table 9. Most materials will dissolve by simple stirring; some may require heat or a high degree of agitation. Another, e.g., methylcellulose, is dispersed initially in about 1/3-1/2 of the total volume of hot water, followed by the addition of the remaining water as ice water or ice. When wetting the methylcellulose in hot water, it helps to finely sprinkle the powder on the surface of

the water so it can hydrate. If clumps form by adding the powder too rapidly, it is difficult to wet the inside particles due to the outer shell of the hydrated clump. Sometimes the hydration step can be assisted by using an intermediate liquid, such as alcohol or glycerin prior to adding water. This intermediate liquid serves to displace entrapped air in the powder and replaces it with a water-miscible liquid. When water is then added, it will more easily wet the powder.

TABLE 9

Points to remember on solubility techniques.

1. Small particles dissolve faster than large particles.
2. Stirring increases the dissolution rate of a drug.
3. The more soluble the drug, the faster its dissolution rate.
4. When working with a viscous liquid, the dissolution rate of a drug is decreased.
5. An increase in temperature generally leads to an increase in the solubility and dissolution rate of a drug.
6. The solubility of a nonelectrolyte drug may be increased or decreased by the addition of an electrolyte.
7. An alkaloidal base, or any nitrogenous base of relatively high molecular weight, is generally poorly soluble unless the pH of the medium is decreased (conversion to a salt).
8. The solubility of poorly soluble acidic substances is increased as the pH of the medium is increased (conversion to a salt).

The use of magnetic stirrers, blenders, electric mixers, etc., can assist the compounding pharmacist in saving time and obtaining uniform products. It is important, however, to minimize the amount of entrapped air in the product.

Numerous filtration devices are commercially available to assist the pharmacist in obtaining clear products. Some are disposable, some require an air or vacuum source, and some can simply be placed on the end of a syringe.

Small, inexpensive (< $50) pH meters are also available to check the final pH of a product. Electronic balances are available for obtaining very small quantities of solid drugs and micropipettes can be used for measuring volumes as low as a few microliters; this is sometimes necessary when using various flavoring oils.

Some miscellaneous points to remember when preparing oral liquids include:

1. Do not "qs" with a stirring rod in the graduate in which you are preparing a product.
2. Dissolve salts in a minimum quantity of water before adding a viscous vehicle.
3. Constantly stir a mixture when adding two liquids together.
4. When incorporating an insoluble material, levigate the powder with a small amount of the vehicle, or a liquid that is miscible with the vehicle.
5. Stir smoothly and don't shake the product as it may entrap air and cause foaming in the product.
6. Add high viscosity liquids to low viscosity liquids.
7. For preparing dilutions, to obtain small quantities of items, use a solvent, not just a liquid.
8. Always be aware of the pH and alcohol concentration of the products being prepared.
9. If filtering during a step in the preparation of a product, be aware of what is being retained on the filter.
10. When working with hydrocolloids, allow them to slowly hydrate first.

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