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Secundum Artem

Current & Practical Compounding Information for the Pharmacist.

Preparation of Oral Suspensions and Syrups: Basic Concepts

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INTRODUCTION

The common use of extemporaneously prepared oral suspensions in pharmacies has been, over the last several decades, displaced by the pre-manufactured dosage form such as the tablet and capsule. However, there will always be a demand for the suspension; the prescribing physician may desire a unique concentration not found in prepared dosage forms or the pharmacist may be confronted with a significant proportion of the population, especially very young children, who have difficulty in swallowing tablets or capsules. Many of the more recently developed drugs are basically hydrophobic in nature with low aqueous solubilities which do not lend themselves to solutions.

The discussion below considers the theoretical aspects of suspensions and attempts to reduce these aspects to practice.

DEFINITION

What makes a good suspension? Remington's Pharmaceutical Sciences discusses the attributes of an acceptable suspension. "There are certain criteria that a well-formulated suspension should meet. The dispersed particles should be of such a size that they do not settle rapidly in the container. However, in the event that sedimentation occurs, the sediment must not form a hard cake. Rather, it must be capable of re-dispersion with a minimum effort on the part of the patient. Additionally, the product should be easy to pour, pleasant to take, and resistant to microbial attack."

We might add to this list little or no potential for toxicity, pH buffered for better stability, no inhibition of absorption or pharmacological effects of drug, and chemical compatibility with the active drug.

The compounding pharmacist should consider the following concepts in order to obtain an "acceptable suspension."

Settling

At the risk of boring half of the readers, I would like to present an equation. The equation is Stokes' Law and it predicts the velocity of sedimentation of a uniform collection of spherical particles. The reader will already have an empirical feel for how a particle behaves in liquid: a light object floats, a dense object will sink; a larger particle will sink faster than a small one; a body will settle slower on a viscous liquid than in a thin liquid. Just how all these factors relate and how they in turn apply to making an acceptable suspension can be found by looking at Stokes' Law as a model.

We will neither attempt to mathematically solve any problems with Stokes' Law nor produce any final mathematical value. Rather, just note the equation predicts how a body falls (settles) in a liquid and what factors can affect the process. The equation is

$$v = \frac{(2r^2)\,(dP)\,(g)}{9u}$$ where v=(terminal) velocity

r=radius of the particle

dP=the difference in density of the solid, dispersed phase (p(s)) and the density of the liquid, dispersion medium (p(1)), i.e., dP= p(s)-p(1).

u=the viscosity of the liquid

g=a constant due to gravity

Because we are only interested in (v) in terms of relationships, and not in terms of absolutes, we won't worry about units.

Let's look at what a compounding pharmacist can (and cannot) control in this equation. A suspension is going to settle. When settling occurs rapidly, velocity (v) will be relatively large. Conversely, a slowly settling suspension will have a relatively small (v). In most cases, anything that reduces (v) helps to retain the suspended state.

However, there will always be a demand for the suspension; the prescribing physician may desire a unique concentration not found in prepared dosage forms.

Obviously, there is not too much that can be done about gravity (g). Likewise, even though the velocity is a squared function of the radius of the material (i.e., a particle with its radius doubled will quadruple is falling velocity), there is not too much a pharmacist can do to reduce particle sizes in the typical pharmacy. Now the good news. The settling rate (v) is directly proportional to dP, the difference in density between the solid and the liquid, and inversely proportional to viscosity of the suspending liquid. Both may be controlled by the compounding pharmacist.

While there is no need to know absolute values for either p(s), the density of the solid, or p(l), the density of the liquid, the difference (dP) between the two is important. The solid is more dense than the liquid or else it would not settle and the density of the solid you are working with is fixed as you must have a certain concentration of the compound in the final suspension. Therefore, to reduce the difference between the solid and the liquid, i.e., reduce dP, you must manipulate the density of the liquid to make the liquid more dense. The liquid is commonly made more dense by adding sucrose, sorbitol, glucose, glycerin or other soluble non-toxic materials.

Remington's lists three major problem areas associated with suspensions: (1) adequate dispersion of particles in the vehicle (2) settling of the dispersed particles and (3) caking of these particles in the sediment so as to resist re-dispersion.

Viscosity (u) is best controlled by adding thickening or "suspending" agents. These include sodium carboxymethylcellulose, carbomer, methylcellulose, xanthan gum, colloidal silicon dioxide, tragacanth, and acacia. Several of these are available to the compounding pharmacist.

Let's review the discussion to this point. By using Stokes' Law as a model we can modify the settling rate (v) by decreasing the difference between the density of the solid and liquid and/or increasing the viscosity (u) of the fluid. The former is accomplished by adding solubles to the liquid (which may also increase viscosity) while the latter is best completed by addition of thickening agents.

A common mistake in the compounding of suspensions is to use too much of the suspending liquid in the initial wetting step. High shear is critical to the initial wetting step.

PREPARATION OF SUSPENSIONS

With the aforementioned background in mind, a discussion of the actual preparation of a suspension is in order. Remington's lists three major problem areas associated with suspensions: (1) adequate dispersion of particles in the vehicle (2) settling of the dispersed particles and (3) caking of these particles in the sediment so as to resist re-dispersion. We have discussed item (2) already, so let's move on to items (1) and (3).

Wetting

Wetting is a frequently encountered difficulty. It is also of prime importance in preparing a successful suspension formulation.

Hydrophilic substances are most easily wetted by water or other polar liquids. Hydrophobic substances repel water but can generally be wetted with nonpolar liquids. Hydrophobic materials can also be wetted by use of a surfactant; the mechanism of which is thought to involve preferential adsorption of the hydrocarbon chain by the hydrophobic surface, with the polar aspect of the surfactant being directed toward the aqueous phase. Only the minimal amount of wetting agent compatible with producing an adequate dispersion should be used, as excessive amounts of surfactants may cause foaming or unacceptable taste.

In most pharmacies, the method of preparation for all suspensions is the mortar and pestle. A common mistake in the compounding of suspensions is to use too much of the suspending liquid in the initial wetting step. High shear is critical to the initial wetting step. This is most easily accomplished through a localized high viscosity system (i.e., a thick paste). After thoroughly wetting the solids with minimal wetting agent, the suspension can be diluted with further portions of the vehicle. Common wetting agents for hydrophobic materials are alcohol (ethanol), glycerin, or the contents of a docusate capsule. Remember, in your initial wetting step, keep it thick!

Caking

The third problem of suspension compounding is the development of deflocculated sediment which is not suspendable (i.e., "caking"). Major contributors to caking are the formation of crystal bridges and closed aggregate (coagule) formation. Foregoing a long, dry technical discussion, remember both situations may be mitigated by employing strategies that favor dispersion of the particles within the suspension.

One strategy you may recall is a "controlled flocculation". (If you are like most pharmacists, you remember the terms flocculation and deflocculation and that it was hard to remember which was which!) Basically, a flocculated suspension is the result of the formation of loose aggregates. Loose is the key word. Because the particles are aggregates, they are heavier than single particles, hence they settle faster (Stokes' Law!) but, because of surface charges, the flocs repel each other and intimate contact is avoided, eliminating caking conditions.

An industrial formulator will use electrolytes, polymers, and/or surfactants to control this flocculation process. The compounding pharmacist doesn't have this luxury of time to explore various options. His or her best choice is to use polymers or protective colloids, which thicken the liquids as well as coat the individual particles, providing a mechanical barrier which prevents coalescence of the particles. Often a combination of colloids gives favorable results.

Other Considerations

Apart from what has been discussed, the pharmacist must consider the system's ability to resist microbial attack. As you are aware, the consumer has developed a phobia about preservatives in the recent past. Judicious selection and use of preservatives may be required for both patient acceptance and a pharmaceutically acceptable product. If preservatives are a concern to the patient, it may be in the patient's best interest to consult with the physician to determine the

duration of therapy. You, as the dispensing pharmacist may elect to dispense the medicated suspension in quantities of only a few days. In this event a preservative may not be needed provided the medication is stored in the refrigerator.

The use of the common parabens decrease the susceptibility of microbial attack. Acceptable use levels are 0.025-0.20 percent for methylparaben and 0.01-0.02 percent for propylparaben. Both of these parabens dissolve slowly and may require use of boiling water to speed up the process. While they are effective over a wide pH range and provide good antimicrobial protection, they may impart a "medicine" taste and may cause an anaesthetic effect on the tongue.

Stability is still another consideration. Both physical and chemical stability will probably be aided by refrigeration. As many drug solubilities are temperature-dependent, wide temperature swings will optimize the chances of crystal growth ("caking"). Chemical degradation, for a variety of reasons, is favored by elevated temperatures. Without drug specific information available, a "keep refrigerated" sticker is in order. Likewise, a "shake-well" label may be indicated. In the event your suspension is difficult to resuspend, consider an oversized bottle, especially if you have a viscous product.

COMMON EXCIPIENTS

Suspending Agents
(The higher percentages may produce a gel-like structure)

1. Tragacanth	(0.5-2.0%)
2. Acacia	(0.5-2.0%)
3. Colloidal Silicon Dioxide	(1.5-3.5%)
4. Sodium Carboxymethycellulose	(0.5-1.5%)
5. Methylcellulose	(0.5-5.0%)
6. Carbomer Resins	(0.5-5.0%)

Common Vehicles

1. Simple Syrup	(50-100%)
2. Cherry Syrup	(50-100%)
3. Ora-Sweet (Paddock)	(20-100%)
4. Ora-Plus (Paddock)	(20-100%)
5. Cologel (Lilly)	(10-100%)
6. Vehicle-S (Paddock)	(50-100%)
7. Sorbitol	(5-10%)
8. Glycerin	(2-10%)

Common Preservatives

1. Methylparaben	(0.025-0.20)
2. Propylparaben	(0.01-0.02)
3. Sorbic Acid	(0.05-0.2)
4. Sodium Benzoate	(0.05-0.1)

QUESTIONS, ANSWERS, AND UP-TO-DATE INFORMATION ABOUT EXTEMPORANEOUS COMPOUNDING

Question
I am interested in attempting some compounded formulations, but where do I begin?

Answer
The first step is choosing a delivery dose. Is the volume delivered best suited for a teaspoon (5-ml) or a tablespoon (15-ml)? With that decision comes the next question, what is total volume? This is simply your single dose volume times the number of anticipated doses (plus 10-15% extra for compounding losses). Next is the choice of vehicle. You may elect to produce your own suspending agent or purchase a "ready-made" vehicle. This vehicle should be sweetened and flavored, ranges of use for syrups are listed above.

Chemical degradation, for a variety of reasons, is favored by elevated temperatures. Without drug specific information available, a "keep refrigerated" sticker is in order.

Powders can be hard to wet. The contents of a DSS capsule or a few drops of Tween 80 often greatly help the initial wetting step. Remember to keep the initial wetting mass thick! This keeps the shear value high. With mixing gradually add your vehicle.

The contents of a DSS capsule or a few drops of Tween 80 often greatly help the initial wetting step.

Specific questions can be addressed to Paddock Laboratories. We'll be glad to offer our suggestions.

Question
I have tried to use methylcellulose as a suspending agent, but I always seem to get a lumpy, unacceptable product.

Answer
To prepare a suspension with methylcellulose, slowly add the desired amount of methylcellulose to about one-third the required amount of (boiling) water and stir the mixture until the material is thoroughly wetted; if the methylcellulose is not thoroughly wetted, lumps will form which are very difficult to disperse. Add the remainder of the water, preferably in the form of ice, and dissolve the wetted material with constant stirring.

Question
I have made experimental batches of formulations and felt I had a nice product. Yet the patient has brought back the same product complaining about the solids being "stuck to the bottom". What happened?

Answer
If you have made a reasonable product, chances are the patient has done something to enhance caking. Most likely the product has been subject to temperature extremes, resulting in changes in solubilities of the ingredients. The best approach is to convey to the patient that the product is best stored at one temperature (probably the refrigerator).

An Alternative to Lengthy Compounding Procedures

Paddock Laboratories has developed two new products to alleviate most of the problems associated with the extemporaneous compounding of oral suspensions. These products may be used alone or combined to produce elegant, consistent, good-tasting products with the absolute minimum of preparation time.

ORA-PLUS is a suspending vehicle designed to meet the widest range of potential uses. Several different agents in optimal ratios are used to produce suspension with excellent synergistic properties. ORA-PLUS has significant thixotropic characteristics, it is capable of suspending significant amounts of material while maintaining acceptable pour properties.

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ORA-PLUS may be diluted to a significant degree provided an adequate dispersion has been initially formed. Because ORA-PLUS is unflavored and is essentially tasteless, and because it may be diluted with sweetening agents, alcohol, flavors, surfactants, or other ingredients common to suspensions, its use in your compounding responsibilities can be tailored by you to meet your requirements.

ORA-SWEET is a prepared syrup vehicle offered to the compounding pharmacist as an alternative to the preparation of simple syrup vehicles. As a prepared syrup vehicle, it provides benefits not found in the extemporaneous vehicle. ORA-SWEET contains pleasant citrus-berry flavoring to help mask bitter drugs as well as buffering agents to minimize common degradation pathways found at higher pH's. In addition, sorbitol and glycerin are included to reduce the "cap-lock" phenomena common to simple syrup formulas.

Although a wide range of suitable diluents may be used with ORA-PLUS, consistent results may be obtained with the use of ORA-SWEET syrup vehicle. Together, these agents supply the compounding pharmacist with the tools to formulate a uniform, pharmaceutically elegant product with minimal effort.

GENERAL USE OF ORA-PLUS AND ORA-SWEET

The most common method of producing a suspension using ORA-PLUS and ORA-SWEET is to combine them in approximately 50-50 ratios. This is done by four easy steps:

(1) Calculate the total amount of active ingredient needed. Calculate the total volume required for the entire prescription (add approximately 10% extra for compounding losses).
(2) Using ORA-PLUS, measure approximately half of the total volume required for the suspension into an appropriate measuring vehicle.
(3) If the active ingredient is in the form of a tablet, finely grind the tablet in a mortar and pestle. The finer the powder, the better the suspension.
(4) Using the measured ORA-PLUS, wet the powder mass with MINIMAL amounts of ORA-PLUS (or surfactant, if desired), so that a thick, viscous mass is formed. This mass should be smooth and thoroughly uniform (no lumps) The remaining ORA-PLUS is added by ever-increasing amounts, working in each addition until a good mix is formed. ORA-SWEET may then be added to complete the volume. The suspension (ORA-PLUS, active and ORA-SWEET) is then mixed and dispensed.

REPRESENTATIVE FORMULAS

METRONIDAZOLE 500mg/5ml x 10 doses

(1) The total volume required is 50ml. The necessary number of tablets (500mg) would be 10. With excess for compounding losses, figure 11 doses. This excess would be 11 tablets and 55ml in total.
(2) Measure about 27ml of ORA-PLUS into a graduate. Use this amount to gradually wet the finely rushed tablets. Accomplish this by wetting with 3-4ml and triturating until wetted; adding small amounts of ORA-PLUS as needed, forming a thick paste. Add increasingly larger amounts of ORA-PLUS until it is all incorporated into the suspension.
(3) Complete to volume with ORA-PLUS. This may be accomplished by measuring the ORA-PLUS—active drug mixture into a graduate and completing to volume with ORA-SWEET. This mixture is then mixed briefly in the mortar and pestle and dispensed. As metronidazole is light sensitive, dispense in an amber bottle with appropriate labeling.

NYSTATIN 500,000 UNITS PER DOSE
T.I.D. DOSING FOR ONE WEEK.

(1) The total volume required (at 500,000 units per tablespoonful) would be 15ml x 3 treatments x 7 days = 315ml. Make 345ml for excess (23 total doses rather than 21). 500,000 units x 23 doses equal 11.5 million units. Calculate the total milligrams of nystatin needed.
(2) Considering the volume, add the powder to an appropriate mortar. Measure out approximately 150-157ml of ORA-PLUS into a graduate. Wet the powder and gradually add the ORA-PLUS as above in the METRONIDAZOLE example.
(3) Because sugars should be avoided in patients with Candida infections, complete to volume with water rather than ORA-SWEET or other syrup base. Protect from light, label appropriately and use very conservative dating due to the loss of potency of nystatin in aqueous environments.