Basics of Compounding: Vehicles for Compounded Oral Liquid Medications: A Review

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Abstract
Compounded oral liquid medications play an important role in addressing the unmet needs of special patient populations, including pediatric, geriatric, and tube fed patients. The use of manufactured vehicles can streamline the compounding activities for pharmacists. In recent years, there is an increase in the availability of manufactured vehicles with various promotional features. This article uses the general formulation principles as a guide to compare and contrast the manufactured vehicles regarding their physicochemical properties, presence of preservatives and dyes, organoleptic properties, and ease of use. A summary table is provided as a reference tool to assist pharmacists in selecting the optimal vehicles for their patient care.

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BASICS OF COMPOUNDING

Vehicles for Compounded Oral Liquid Medications: A Review

Abstract

Compounded oral liquid medications play an important role in addressing the unmet needs of special patient populations, including pediatric, geriatric, and tube-fed patients. The use of manufactured vehicles can streamline the compounding activities for pharmacists. In recent years, there is an increase in the availability of manufactured vehicles with various promotional features. This article uses the general formulation principles as a guide to compare and contrast the manufactured vehicles regarding their physicochemical properties, presence of preservatives and dyes, organoleptic properties, and ease of use. A summary table is provided as a reference tool to assist pharmacists in selecting the optimal vehicles for their patient care.
Unmedicated oral vehicles are used to prepare oral liquid medications. Compounding of oral liquid formulations expands treatment options for patients who have difficulty swallowing tablets or capsules, as extemporaneous preparation can provide dosage forms that are not commercially available. Specific populations who may benefit from the compounding of these dosage forms include pediatric patients, geriatric patients, and patients with enteral feeding tubes. Multiple oral vehicles are available, and these products differ in their physicochemical and organoleptic properties. These vehicles can be used to prepare a variety of oral liquid dosage forms including solutions, suspensions, and emulsions. This article provides a review of commercially available oral vehicles as well as a discussion of vehicle properties to consider when selecting a vehicle for a specific drug, route, and patient. This information may serve as a reference for compounding pharmacists as well as for persons involved in formulating oral-liquid dosage forms for commercial applications.

**Discussion**

We have reviewed 26 oral liquid vehicles, considering various aspects such as:

- Appearance
- Osmolality
- pH
- Presence of preservatives and dyes
- Viscosity
- Suspending agent used
- Taste

This information is summarized in Table 1 as a reference tool for compounding pharmacists. Additionally, we have examined published literature and reference books to provide context for this data.

**Physicochemical Properties**

Oral dosage forms should be palatable and well tolerated, provide accurate and consistent dosing, and maintain physical integrity throughout their shelf life. Physicochemical properties to consider when preparing oral liquid formulations include viscosity, suspending agent, pH, and osmolality.

**Viscosity and Suspending Agent**

Oral liquid dosage forms include solutions, suspensions, and emulsions. In solutions, ingredients are solubilized in the solvent. Types of oral solutions include syrups, elixirs, spirits, and tinctures. Multiple syrups are commercially available as oral liquid vehicles. These do not contain suspending agents, and viscosity is essential primarily for pharmaceutical elegance and ease of use.

Suspensions are dispersed systems which have physical-stability challenges. An ideal suspension settles slowly and readily re-disperses upon agitation. During storage, suspensions may undergo sedimentation and aggregation (including cake formation) leading to physical instability and variability in dosing. Inconsistent dosing can have severe consequences for patients including drug toxicity and, conversely, undertreatment. Increased viscosity of suspensions can slow the rate of particle settling and improve the stability of the dispersion.

Suspensions are formulated with suspending agents that maintain the physical stability of the dispersion throughout the shelf life. Most of these suspending agents are pseudoplastic or shear-thinning systems, which leads to lowering of viscosity with respect to increased shear stress (i.e., shaking of the bottle or triturating of the ingredients to compound the suspension). Along with the pseudoplastic rheology, these systems are also thixotropic, a property which allows the system to regain its viscosity once the shear stress has been removed from the system. The thixotropic behavior of such commercial oral vehicles enhances the stability and shelf life of the compounded oral dispersions.

Like suspensions, emulsions are dispersed systems. Specifically, emulsions are dispersions of small globules of a substance in a vehicle in which it is immiscible. Because emulsions contain at least two phases, often an aqueous and an oleaginous phase, they provide a liquid dosage form more suitable for drugs that are unstable in aqueous formulations. Physical stability challenges for emulsions include creaming (weak associations between droplets of the internal phase) and cracking (irreversible coalescence of droplets of the internal phase). Viscosity regulators and thickening agents may be added to emulsions to slow the rate of particle settling and improve the stability of the dispersion.

An example of an oral liquid vehicle available as an emulsification system is Fagron’s Unispend Anhydrous. This vehicle, available both sweetened and unsweetened, is formulated with triglycerides and provides an anhydrous system which is favorable for water unstable additives.

As evident from Table 1, common suspending agents/viscosity enhancers include sodium carboxymethylcellulose, xanthan gum, and carrageenan. Each of these agents possesses their own incompatibility issues that a compounding pharmacist must consider while using the commercial oral vehicles that contain them. A detailed description of incompatibility concerns for each of these agents is available in the **Handbook of Pharmaceutical Excipients**. This study provides a brief overview of some of these major incompatibilities with respect to each of these agents. Sodium carboxymethylcellulose solutions are most stable at pH 5 to 10, however, those solutions can tolerate a broader range of pH 2 to 10 for final preparations. These solutions are also incompatible with quaternary nitrogen-containing compounds, iron salts, and metals such as aluminum, mercury, and zinc. Similarly, due to the anionic chemical structure of xanthan gum, it is incompatible with large cationic drugs, surfactants, polymers, and preservatives. Xanthan gum is also incompatible with oxidizing agents, some tablet film-coatings, dried aluminum hydroxide gel, and some active ingredients such as...
amitriptyline, tamoxifen, and verapamil. Lastly, carrageenan-containing solutions remain stable at pH 9 and can lead to its depolymerization if the pH of the solution is rendered acidic. Also, carrageenan may interact with cationic active pharmaceutical ingredients and is generally limited in its use in such cases.

A recent study by Visser et al. compares the rheological and sedimentation behavior of some of the commercially available oral vehicles. The study describes the preparation of an oral suspension of paracetamol to evaluate the efficacy of the following oral vehicles:

- Base for Suspension
- Ora-Blend
- Ora-Blend SF
- Simple Syrup
- SuspendIt
- Syr-Spend SF PH4

The study concludes that SyrSpend SF PH4 and SuspendIt resulted in the best-compounded preparations due to their pronounced pseudoplastic rheological profile. Both the vehicles provided adequate sedimentation rates, even pourability, and good resuspendability. These results are promising. However, the study can further be expanded to include other commercially available vehicles.

**pH**

Because many drugs are weak electrolytes (weak acids or weak bases), the pH of the formulation affects drug ionization, solubility, and physicochemical stability. Vehicles and formulations may be prepared with buffers to prevent sudden changes in pH. When selecting a vehicle for the oral liquid formulation, consideration should be given to any data regarding the effect of pH on the solubility and stability of the drug being prepared in the formulation. Most of the oral liquid vehicles described in this review have an acidic pH. For drugs that are unstable in acidic pH, alkaline vehicles are available. An example of such a product is Fagron’s SyrSpend SF Alka, which has a pH of >7.

**OSMOLALITY**

Oral vehicles with high osmolality have the potential to cause gastrointestinal (GI) upset and diarrhea. Some special patient populations are particularly prone to osmotic diarrhea. They include pediatric patients, geriatric patients, and patients with GI comorbidities such as irritable bowel syndrome. For instance, hypertonic solutions of >400 mOsm/kg were reported to injure GI tracts of neonates. Unfortunately, the osmolality data are not available for all vehicles from the manufacturers, and estimation is difficult for vehicles with proprietary formulas. The following discussion is based on the vehicles with reported values (Table 1) and general scientific knowledge of oral liquid formulations and excipients.

The osmolality of the normal GI fluids is between 100 mOsm/kg to 400 mOsm/kg. Several sugar-based syrup vehicles contain high concentrations of sucrose which result in extremely high osmolality. For example, the osmolality is 4109 mOsm/kg for Ora-Sweet (Perrigo) and 2381 mOsm/kg for Oral Syrup (Medisca). The same issue exists for some sugar-free vehicles, depending on the sweeteners used. Generally, the natural polyol sweeteners (e.g., sorbitol) have much lower sweetness than the artificial sweeteners (e.g., sucralose) and thus require much higher concentrations in the formulation. For example, sorbitol is used in a number of commercial vehicles, and it is only about 50% to 70% as sweet as sucrose. Hence, a vehicle sweetened mainly by sorbitol still requires a high concentration of sorbitol, which again leads to hyperosmolality. Furthermore, sorbitol is only partially absorbed in the GI tract. The non-absorbed sorbitol is fermented by the colonic flora with gaseous byproducts, which exacerbate the GI disturbances. As a safe practice, the compounding pharmacist should make sure that the sorbitol consumption from the prescribed dosage is below 20 g/day for adults. On the other hand, the non-sweetened suspension vehicles tend to have low osmolality, which are suitable choices for patients who cannot tolerate hypertonic liquids. Two good vehicle examples are Ora-Plus from Perrigo and Oral Suspend from Medisca at 157 mOsm/kg and 48 mOsm/kg, respectively. Finally, one notable product worth highlighting is SyrSpend SF from Fagron. It is the only all-in-one vehicle (sweetened, flavored, structured) with a low osmolality of <50 mOsm/kg. In addition, there are two similar SyrSpend SF powder products which are preservative-free but require reconstitution before use.

The concern of GI distress is heightened when the oral liquids are administered via enteral feeding tubes. Depending on the tubing types, the liquid medications are delivered directly to various GI regions without dilution. As expected, the adverse effects are most pronounced when the liquids are administered too rapidly into the stomach or delivered directly to the intestine. Since palatability is not a requirement for medications administered via enteral feeding tube, it is recommended to choose non-sweetened, non-flavored, and low-osmolality vehicles. If the viscosity of these vehicles presents a challenge for some narrow tubes, they should be diluted with purified water rather than another vehicle with high osmolality.

**Preservatives and Dyes**

Preservatives are often included in the formulations of oral liquid vehicles to provide microbial stability. Aqueous formulations are prone to microbial growth, and preservatives protect against bacterial, yeast, and mold infection. In addition to protecting the end user from pathogens, preservatives also provide a multiple year shelf life for products. Parabens are the most commonly-used class of preservatives which offer protection against a wide range of pathogens, even at low concentrations. Both methylparabens and propylparabens have low aqueous solubilities (1 g/400 mL of water and 1 g/2,500 mL of water, respectively) and are often solubilized with the aid of small amounts of a co-solvent such as alcohol or propylene glycol. Methylparaben is often used as a preferred preservative, as it can effectively preserve oral vehicles for a broader pH range of 4 to 8. Often, methylparaben is paired with propylparaben.
<table>
<thead>
<tr>
<th>TABLE 1. SUMMARY OF VEHICLES FOR COMPOUNDED ORAL LIQUID MEDICATIONS.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MANUFACTURER</strong></td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Ona-Sweet®</td>
</tr>
<tr>
<td>Ona-Powder</td>
</tr>
<tr>
<td>Ona-Blend®</td>
</tr>
<tr>
<td>Oral Mix®</td>
</tr>
<tr>
<td>Oral Syrup®</td>
</tr>
<tr>
<td>Oral Liquid®</td>
</tr>
</tbody>
</table>

**Notes:**
- **Dye:** Red dye #40, Dye-free
- **Appearance:** Clear liquid with a slight tint, Translucent, milky white, Opague, pinkish liquid
- **Preservative:** Methylparaben and potassium sorbate
- **Taste:** Sweet citrus-flavor, Bland, unsweetened
- **Osmolarity (mOsm./kg):** ~ 409, ~ 1979, ~ 157, ~ 1665
- **Viscosity (cP):** 4.0 to 4.5, 1300 to 7000, 1500 to 7000, 1000 to 7000

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<table>
<thead>
<tr>
<th>VEHICLE</th>
<th>MANUFACTURER NDC OR PRODUCT NUMBER</th>
<th>SUSPENDING AGENT</th>
<th>SWEETENER</th>
<th>PH</th>
<th>VISCOSITY (cPs)</th>
<th>OSMOLALITY (mOsm/kg)</th>
<th>TASTE</th>
<th>PRESERVATIVE</th>
<th>APPEARANCE</th>
<th>DYE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavor Plus</td>
<td>Humco 00395-0091-16</td>
<td>Microcrystalline cellulose, Carboxymethyl cellulose, Xanthan gum, Carrageenan</td>
<td>None</td>
<td>3.5 to 4.0</td>
<td>NA</td>
<td>NA</td>
<td>Unflavored</td>
<td>Methylparaben, Citric Acid, Sodium Phosphate, Potassium Sorbate</td>
<td>Viscous white opaque liquid</td>
<td>Dye-free</td>
</tr>
<tr>
<td>Flavor Sweet SF</td>
<td>Humco 00395-0094-16</td>
<td>Xanthan gum</td>
<td>Sodium saccharin, Sorbitol, Glycerin</td>
<td>4.5 to 5.0</td>
<td>NA</td>
<td>NA</td>
<td>Cherry flavor</td>
<td>Propylparaben, Methylparaben, Potassium Sorbate, Citric Acid, Sodium Citrate</td>
<td>Pale pink clear liquid</td>
<td>Red#3 FD&amp;C #40</td>
</tr>
<tr>
<td>Versa Free</td>
<td>Humco 00395-0125-16</td>
<td>Xanthan gum</td>
<td>Sorbitol, Sorbitame, Glycerin</td>
<td>4.3 to 5.0</td>
<td>750 to 1250</td>
<td>NA</td>
<td>Flavor-free</td>
<td>Sodium Benzoate, Potassium Sorbate, Citric Acid, Sodium Citrate (Paraben-free)</td>
<td>Clear colorless liquid</td>
<td>Dye-free</td>
</tr>
<tr>
<td>Versa Plus</td>
<td>Humco 00395-0126-16</td>
<td>Microcrystalline cellulose, Carboxymethyl cellulose, Xanthan gum, Carrageenan</td>
<td>None</td>
<td>3.5 to 4.5</td>
<td>500 to 1600</td>
<td>NA</td>
<td>Flavor-free</td>
<td>Sodium Phosphate, Citric Acid, Potassium Sorbate, (Paraben-free)</td>
<td>White liquid</td>
<td>Dye-free</td>
</tr>
<tr>
<td>Simple Syrup</td>
<td>Humco 0395-2661-16</td>
<td>NA</td>
<td>Sucrose</td>
<td>2.5 to 3.5</td>
<td>NA</td>
<td>NA</td>
<td>Unflavored</td>
<td>Methylparaben, Citric Acid</td>
<td>Clear colorless liquid</td>
<td>Dye-free</td>
</tr>
<tr>
<td>Cherry Syrup</td>
<td>Humco 00395-2662-16</td>
<td>NA</td>
<td>Sucrose</td>
<td>2.5 to 3.5</td>
<td>NA</td>
<td>NA</td>
<td>Cherry flavor</td>
<td>Sodium Benzoate</td>
<td>Red viscous liquid</td>
<td>FD&amp;C #40</td>
</tr>
<tr>
<td>Suspendit</td>
<td>PCCA 30-4825</td>
<td>NA</td>
<td>Natural sweetener derived from Monk fruit, Sucrose</td>
<td>NA</td>
<td>Thixotropic</td>
<td>NA</td>
<td>Vanilla</td>
<td>Paraben-free, Sodium benzoate</td>
<td>Viscous white opaque liquid</td>
<td>Dye-free</td>
</tr>
<tr>
<td>SyrSpend SF</td>
<td>Fagron 51552-1079-05</td>
<td>Modified starch</td>
<td>Sucralose</td>
<td>4 to 5</td>
<td>500 to 900</td>
<td>&lt;50</td>
<td>Unflavored (also available as cherry, grape)</td>
<td>Sodium benzoate</td>
<td>Hazy, white, translucent syrup</td>
<td>Dye-free</td>
</tr>
</tbody>
</table>
ben to achieve a synergistic effect and allow the use of low concentrations. Due in part to consumer perceptions, many preservative-free or paraben-free products are currently being marketed. However, available evidence does not support a need to avoid parabens, and the safety and efficacy of parabens have repeatedly been reported. Many prestigious health organizations worldwide, including the U.S. Food and Drug Administration, continue to support the use of parabens. As evident from Table 1, other commonly used preservatives for oral vehicles include sodium benzoate and potassium sorbate. Sodium benzoate can be effectively used to preserve oral liquids with a pH <5. Several of the commercial oral vehicles, including syrups, satisfy this qualification and are effectively preserved with this water-soluble preservative. Sodium benzoate’s pH-dependent efficacy should be considered with respect to the pH of the resulting compounded preparations using such oral vehicles. Similarly, potassium sorbate can be effectively used as a preservative for oral vehicles and formulations with a pH <6. Unlike the parabens, potassium sorbate is very soluble in aqueous systems (1 g/ 4.5 mL of water) and does not require any co-solvents. Additionally, Bruns et al also compares the stability of these common preservatives and concludes that potassium sorbate is the safest alternative for pediatric patients with respect to its efficacy for compounded oral preparations with a pH of 3.5 to 5.5.

Dyes provide pharmaceutical elegance to liquid dosage forms. Multiple oral liquid vehicles contain dyes, often Red #3 and FD&C #40. For patients who are allergic or sensitive to dyes, many dye-free vehicles also are available. Because neonates have relatively limited metabolic activity, both preservative- and dye-free oral liquid vehicles are preferred for this population. Compounded oral preparations for this population are generally prepared in limited quantities, stored in refrigerators, and consumed immediately or within short durations from preparation to avoid the use of preservatives.

### Organoleptic Properties

Organoleptic properties pertinent to oral liquid vehicles include taste, sweetness, and appearance. Patient adherence to therapy may...
be enhanced when the dosage form is palatable and pharmaceutically elegant. Some oral vehicles are flavored, while others are unflavored, allowing the compounding pharmacist to add flavors that match patient preference. Syrups have a high degree of sweetness, which may be appealing to particular patient populations such as pediatric patients. Some vehicles contain sugar-free sweeteners (including sugar alcohols) with the advantage of the lower glycemic load for diabetic patients. As discussed previously under the topic of osmolality, sugar alcohols such as sorbitol can cause osmotic diarrhea, as can sugars.

Practitioners should consider the effect of sweeteners, potentially avoiding those that cause diarrhea in certain patients, while recognizing that laxative effects may actually be beneficial for patients who are chronically constipated. The physical appearance of commercially available oral vehicles varies, ranging from clear to hazy and colorless to tinted (typically pink or red if colored). Multiple commercially available oral vehicles are also capable of taste-masking, which further enhances the palatability of compounded formulations, particularly when additives have an unpleasant taste. In patients who are receiving medications through an enteral feeding tube, organoleptic properties are less important as the patient will not experience taste and sweetness due to the route of drug delivery. However, physicochemical properties remain crucial as feeding tubes present unique drug-delivery challenges. When administration through an enteral tube is intended, the dosage form must neither be too viscous nor contain sizeable particulate matter which could occlude the tube.

Ease of Use

For ease of use, oral vehicles ideally permit pouring, measuring, withdrawal into an oral syringe, and instillation through an enteral feeding tube. Viscosity should be maintained within a range high enough to maintain physical stability but low enough to permit these procedures. To further facilitate ease of use, the product should re-disperse readily upon simple agitation.® Prolonged or vigorous agitation may be time consuming or complicated for providers and patients alike. Additionally, patients, pharmacists, and caregivers may have different interpretations of the directions "Shake well before using."® Dosage forms prepared with oral liquid vehicles should be able to provide uniform contents after simple manual agitation.

Additionally, most of these oral vehicles are available in conveniently packaged one-pint containers (473 mL), with a 24- to 36-month shelf life. This allows the pharmacist to easily stock and store these buffered, sweetened, flavored, and preserved oral vehicles in their inventory. Further, current published literature provides a plethora of information regarding the formulation and stability of several active pharmaceutical ingredients in these commercial vehicles. This strengthens the database for utilizing these vehicles to provide improved patient care. Due to the stability and versatile applications of these vehicles for compounded oral-liquid dosage forms, several pharmacies have phased out from preparing their in-house United States Pharmacopeia-compliant oral vehicles. The resulting increase in demand and competition by several manufacturers for these vehicles thereby feeds the cost-to-benefit ratio of purchasing these vehicles.
Cost Comparison

Standardized, current pricing information was not readily available for all the products. However, the average wholesale price (AWP) reported in Red Book ranged from approximately $16 to $63 (USD) per 473 mL.18 The actual cost of obtaining the vehicles can vary significantly from the AWP, depending on multiple factors such as bulk purchasing discounts and contract pricing between the manufacturer and buyer. For some of these products, multiple package sizes are available, which could impact pricing.

Limitations

This review is intended to describe common oral vehicles that may be seen in practice, and, as such, there may be additional oral vehicles on the market which have not been included. While multiple flavors and package sizes are available for some of the products described in this review, these parameters were simplified for the sake of summarization. In the case of multiple available package sizes, a representative package size is described in the Tables. The representative package size was selected as the closest size to 473 mL to facilitate comparison between products.

We identified four additional oral liquid vehicles, manufactured by Professional Compounding Centers of America (PCCA), which were not included in Table 1. These formulations are proprietary and, as such, we were not able to obtain data regarding specific ingredients and physicochemical properties. These products are PCCA-Plus Oral Suspending Vehicle, Syrup Vehicle, Sweet-SF Sugar-free Syrup Vehicle, and Acacia Syrup. The compounding pharmacist may be able to obtain guidance regarding these products from the manufacturer. An additional limitation is the fact that product availability and formulations may change over time. This article does not replace the responsibility of the compounding pharmacist to check technical data sheets and ingredient lists for the oral vehicles that they use to prepare dosage forms.

Conclusion

In conclusion, multiple un-medicated oral vehicles are available for use in preparing oral formulations. By comparing physicochemical and organoleptic properties, the compounding pharmacist can select the oral vehicle best suited for the drug, route, and patient.

References


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