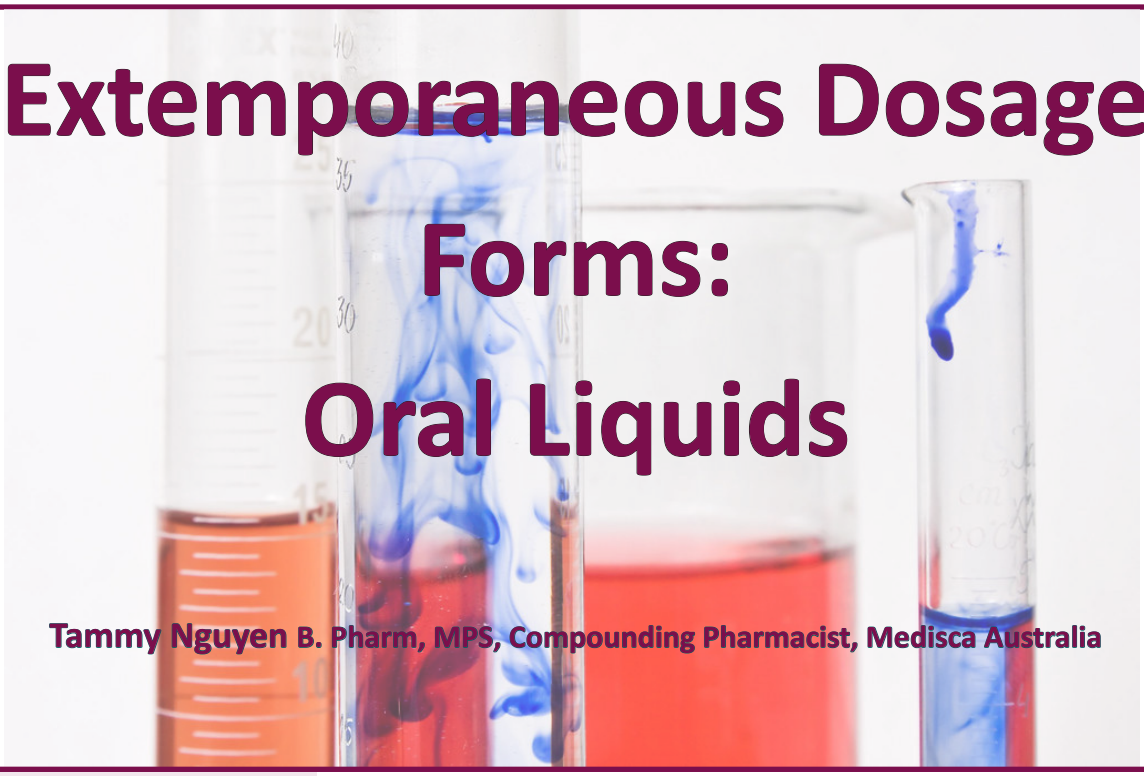
Extemporaneous Dosage Forms: Oral Liquids



Tammy Nguyen B. Pharm, MPS, Compounding Pharmacist, Medisca Australia

AFTER COMPLETING THIS ACTIVITY, PHARMACISTS SHOULD BE ABLE TO:

1. List populations for which the compounding of an oral liquid may be necessary
2. Outline necessary considerations that should be made by the pharmacist to ensure product stability
3. Describe methods used in the compounding of liquid preparations

The 2016 Standards addressed by this activity include: 1.3, 1.5, 3.1, 3.2, 3.4, 3.6

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the australian college of pharmacy

"Oral liquids provide flexibility in dosing and are beneficial when a patient requires dose titration,[1] however, many pharmaceutical drug products are not available as oral liquids[2]"

Oral liquid preparations are a versatile option for clinicians looking for an alternative to the more common oral solid dosage form. Compounding pharmacists may be required to prepare oral liquids if an oral solid dosage form is unsuitable for a specific patient or if the dosage required by the patient cannot be practically administered. This article discusses the various types of oral liquids and specific suitability and stability considerations related to them, including microbial and chemical. The compounding pharmacist may have additional considerations when dispensing oral liquids such as techniques used for extemporaneous preparations or when preparing medications for animals.

Liquid preparations are an ideal choice for a wide range of clinical settings, including, but not limited to:

- infants and children
- patients with enteral feeding tubes
- patients with dysphagia or aspiration
- veterinary patients

Oral liquids are separated into two main categories; solutions and suspensions[3]. Solutions are one of the oldest pharmaceutical dosage forms[3]. Solutions refer to liquids where all solid ingredients, including the active are fully solubilised in a solvent(s)[4]. The solvent may be aqueous or organic or a combination of both. Examples of oral solutions include syrups, elixirs, linctuses and aromatic waters.

Oral suspensions have insoluble components that are suspended in a dispersion medium with suspending agents[5]. Suspending agents are used to aid in the dispersion of powders evenly throughout the preparation to prevent the flocculation of

Table 1: Types of Solution[3]	
Type of Solution	**Definition**
Syrup	Aqueous preparation containing a high proportion of sucrose or another sweetener
Elixir	A hydroalcoholic liquid containing syrup
Linctus	A viscous liquid containing sucrose with a small intended volume of administration
Aromatic Waters	Saturated solutions of volatile liquids

particles in the preparations[5,6]. Flocculated particles clump together and if the particles are large enough, gravitational forces pull the particles down resulting in sedimentation[4]. Alternatively, if the particles clumped together are relatively small, they can float to the top of the suspension and result in creaming[4]. Suspensions, if poorly prepared can result in the inaccurate dosing to the patient.

Dysphagia

Solid oral dosage forms are frequently unsuitable for children under the age of six[7]. Additionally, between 25-45% of children in general, suffer from dysphagia (difficulty swallowing)[8]. Dysphagia is a condition also seen in elderly populations due to the incidence of age-related changes in salivary gland function[8]. The prevalence of dysphagia also increases in patients with cognitive dysfunction or neurodegenerative diseases, and in patients who have had a stroke[8].
Global trends indicate a continuous increase in life expectancy, and thus there is a worldwide expectation that the elderly will make up a greater proportion of the population[4], thereby potentially increasing the prevalence of dysphagia.

Available Dosage Forms

The WHO List of Essential Medicines for Children[9] and WHO List of Essential Medicines for Adults[10] lists 76 and 84 medications, respectively, available in an oral liquid or powder for oral liquid out of possible 433-listed medications. Tablet formulations tend to be more cost-effective for pharmaceutical companies to develop[11], and have the added benefits of being more economical to transport and store compared to their liquid counterparts[11].

Pharmaceutical companies may be challenged with greater regulatory requirements when conducting studies for children, resulting in the higher outlay in investment for a smaller return given the smaller market potential[11]. The lack of availability of manufactured formulations for paediatric populations has led to off-label or unlicensed use of adult medications. This practice itself poses a risk to paediatric patients as they are a distinct and heterogeneous population which exhibit different pharmacokinetic and pharmacodynamics when compared to adults[13]. All of these factors combined, indicate a continuous need for liquid oral preparations in the health care setting into the future.

TGA-registered (when treating humans) and APVMA-registered products (when treating animals) are the first choice of pharmacotherapy for clinicians, as they have undergone extensive scrutiny for safety, stability and efficacy prior to being becoming available on the Australian market. Part of the documentation submitted to regulatory authorities are the results of pharmacopeia tests, some of which will be discussed. Although extemporaneous preparations are not required to undergo such tests, pharmacists can utilise pharmacopeia tests in order to manage the risks to

Table 2 Advantages and Disadvantages of Solutions[4]	
Advantages	**Disadvantages**
Drug may be immediately absorbed	Drug stability may be reduced, due to events such as hydrolysis
Homogeneous, no need to shake the container	Unpalatable tastes are difficult to mask
	Some drugs are poorly soluble

Table 3 Advantages and Disadvantages of Suspensions[4]	
Advantages	**Disadvantages**
Drug may be more palatable when insoluble	Container requires shaking prior to administration
Drug may be more stable when insoluble	Reduced dose accuracy compared to solutions
Enable bulk administration of insoluble powders	Risk of flocculation resulting in creaming or caking

patients using extemporaneous preparations.

Modification of Manufactured Products in the Compounding of Extemporaneous Preparations

Pharmacists and clinicians are faced with two options when it comes to compounding a liquid preparation:

1. To crush a commercially available product and incorporate it into a liquid preparation (and consider whether or not this is an appropriate option) or
2. To use the raw Active Pharmaceutical Ingredients (APIs) to prepare compounded preparations[13].

The Australian Pharmaceutical Formulary 24 (APF 24) and Professional Practice Standards (PPS) recommend pharmacists exercise caution when modifying commercially available products to use in extemporaneous preparations[14,15]. Modification of the commercial product can pose a risk to the patient, as the excipients included in the commercial product may be incompatible with the liquid formulation[14,15] and are often of undisclosed concentrations. If the compounding pharmacist is required to use several units of the commercial product, the increased amount of excipient may cause instability and sedimentation.

Prior to using a commercial product in an extemporaneous formulation, it is important that pharmacists identify whether the formulation is intended to be immediate release or modified release[13]. Crushing the commercial solid dosage form products in a mortar and pestle will alter the intended pharmacokinetics of the drug[14]. The compounding pharmacist may also have to overcome the barrier of enteric or film coats in order to pulverise the product adequately. The *Do Not Rush to Crush Handbook* published by the Society of Hospital Pharmacists of Australia, is the primary resource for pharmacists in Australia in determining whether a commercial product can be modified for direct oral administration or for the administration of medication into enteral feeding tubes[16]. The resource also provides some guidance on the occupational risk to administrators posed due to cytotoxicity, teratogenicity or hazardousness[16]. The drug hazard classification is used to make recommendations on when products should not be crushed[16]. Chemicals that fall within this category require Work Health Safety considerations for compounding[15]. The facility needs to be appropriately equiped with powder containment hoods and Heating Ventilation Air Conditioning (HVAC) systems, in order to protect both the operator and the external environment. The compounding personnel are also required to have appropriate Personal Protective Equipment (PPE)[15]. Safety Data Sheets (SDS) provided by chemical suppliers, detail the hazard status of the chemical[15], and can be useful when determining if a product is safe to crush and compound into a liquid preparation.

Suitability and Stability

Pharmacists must perform a risk assessment before the compounding of any preparation. This risk assessment should encompass both the risk to the compounding personnel and to the patient[15]. The PPS provides the patient-centred care model in Standard 5 and a risk assessment tool in Appendix 7 to assist pharmacists with this process[15]. Formulation considerations include but are not limited to solubility, stability, palatability and suitability. The United States Pharmacopeia (USP)/National Formulary (NF) defines stability as the extent to which products retain the same properties and characters possessed at the time of its preparation[17] and categorises stability into five types: chemical, physical, microbiological, therapeutic and toxicological[17.] Suitability of the formulation is particularly important for paediatric patients, as excipients widely used for adults, may not be suitable for infants or children[18].

Additional formulation considerations will include whether the pharmacist chooses to compound the extemporaneous liquid using a proprietary oral liquid base

or prepare a base from raw ingredients. Formulations based on published literature may include both types of preparations. Manufactured proprietary bases will often take into consideration unsuitable excipients for paediatric patients, as they have been designed for use in both adults and children.

The USP/NF lists standard formulas for vehicles for oral solutions and vehicles for suspensions under the following listing Vehicle for Oral Solution NF, Vehicle for Oral Solution Sugar-Free and NF Vehicle for Oral Suspension NF[19-21]. These vehicles are prepared before the addition of the appropriate APIs, required for the formulation. As per the USP guidelines for beyond use dates, in the absence of further stability data, these vehicles can be kept for six months after the date of preparation [19-21]. In Australia, the APF 24 makes no such recommendations for the preparations of oral vehicles. In the absence of stability studies, the APF 24 allows a maximum expiry date of 28 days for all compound liquid preparations[14]. This can pose a practical challenge to pharmacists in Australia, as compounded oral vehicles must be prepared immediately prior to the addition of active ingredients for an expiry date of 28 days to be assigned. Consequently, both the time required to compound and the cost of the preparation, are increased.

Alternatively, there are several proprietary oral suspending vehicles available on the Australian market. Examples include Medisca's Oral MixTM, Professional Compounding Chemists of Australia's (PCCA) Suspendit® and Fagron's Syrspend®. These proprietary vehicles eliminate the need for compounding personnel to prepare an oral vehicle on each occasion. As these bases are manufactured under Code of Good Manufacturing Practice conditions, they have a longer shelf life than vehicles prepared in the compounding pharmacy. It is important for pharmacists to ensure the vehicle chosen is suitable for the API being prepared. The specification for USP/NF oral vehicles requires these vehicles to be slightly acidic (pH 4.0-5.0) in nature[19-21]. Compounding pharmacists need to assess using literature, the optimal pH for the stability of the API.

Acid-labile APIs require additional ingredients to adjust or buffer the pH of the formulation. Proton pump inhibitors such as omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole are acid-labile. Bulk-manufactured proprietary alkaline oral vehicles are designed to facilitate the preparation of acid-labile APIs.

Some proprietary vehicles have additional pharmacopeia testing such as the antimicrobial efficacy test (AET) or preservative efficacy test (PET), to provide pharmacists an additional level of quality assurance. Microbial load in oral liquid preparations, is a relevent consideration when dispensing medications to children, the elderly and immunocompromised patients. Microbial studies can be performed on both the starting oral vehicle or the finished preparation. Both the USP and the British Pharmacopeia (BP) outline validated methods for testing antimicrobial efficacy[23,24]. Successful passing, confirms that over time the microbial load of the preparation has not increased significantly beyond stated allowable limits. An AET or PET can only be performed if a preservative has been included in the formulation. Products labelled as "preservative free" may undergo other microbial studies such as USP <61> and USP <62>[24, 25]. These tests are used to identify and quantify microbes found in the product.[24, 25] A successful pass means that product still falls within an accepltable microbial load limit despite not containing a preservative[24,25] and is a method of assuring **microbial stability**.

Proprietary oral vehicles may undergo stability-indicating studies for specific concentrations or bracketed concentrations of particular APIs in identified compounded formulations. Stability-indicating studies is a method of assurance of **chemical stability**. Depending on the study results, these formulations may permit pharmacists to assign a longer expiry date to the oral liquid, beyond the 28 days stipulated by the APF 24[14]. Stability indicating studies should include information on the specific closure container system as well as the storage conditions for the shelf life of the compound[26]. To assign the extended expiry date, compounding pharmacists must not deviate from the formulation that was studied.

Stability-indicating studies must use a validated method. Validation is achieved by force degrading the active ingredient by exposing it to known degraders, such as high heat, high humidity, UV radiation, acid, base and peroxide[27]. Stability-indicating studies cost significant more

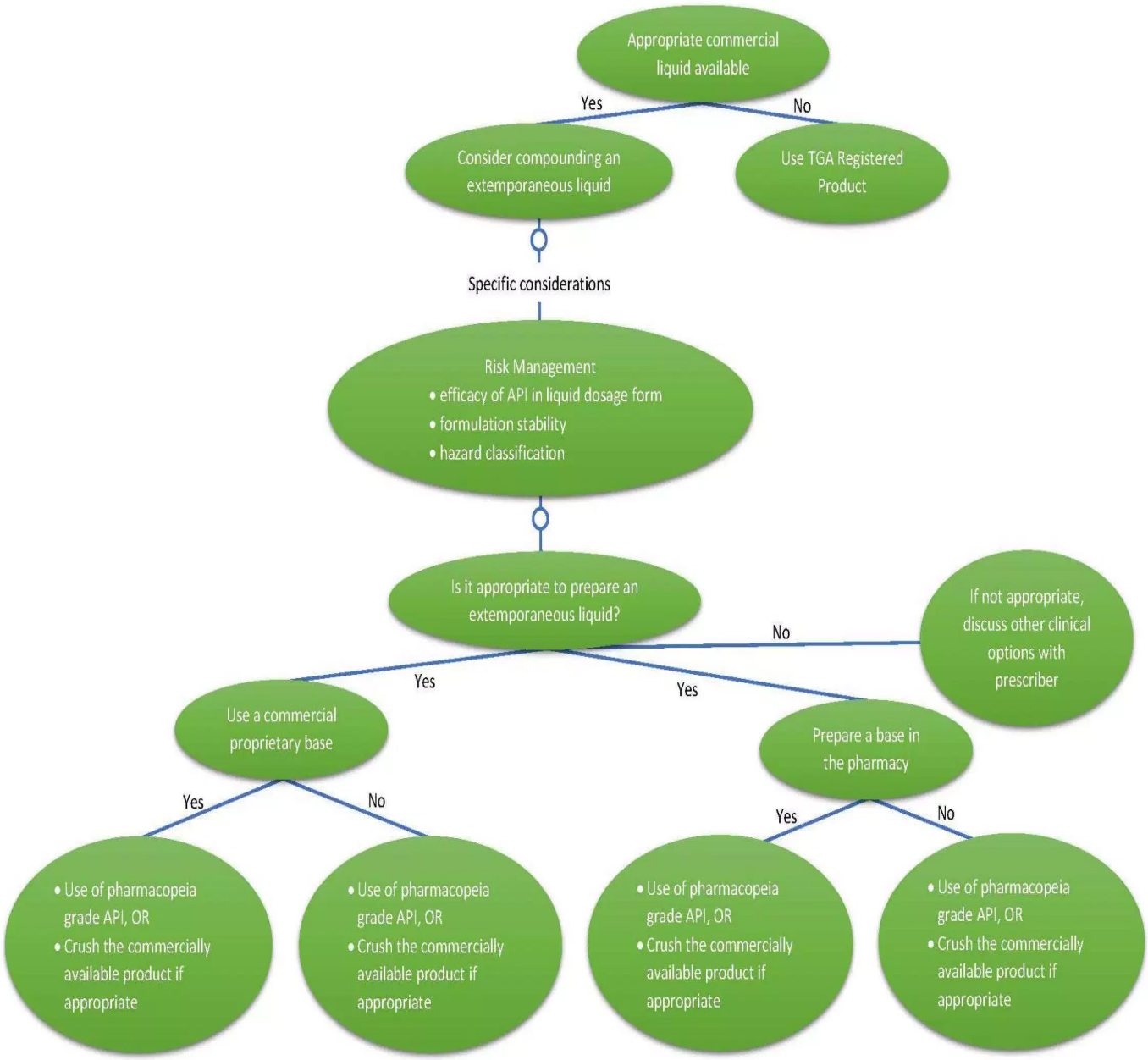

Figure 1: Decision tree for compounding liquids for children and adults

Table 4 Excipients, which pose toxicity and safety, risk to newborns and infants < 6 months[18]	
Excipient	**Common Functions**
Benzyl alcohol	Solvent, preservative
Ethanol	Solvent, preservative
Propylene glycol	Levigating agent, solvent, preservative
Polysorbate 20	Surfactant, emulsifier
Polysorbate 80	Surfactant, emulsifier

than potency assays, are often published in journals or white papers. Pharmacists should be aware that the pharmacopeia requirements for stability-indicating studies have changed over time. The method used should be thoroughly scrutinised, as current requirements are more stringent. The updated version of USP<795>, due to be implemented in the USA from the 1st of December 2019, requires stability indicating studies to perform and pass additionally:

1. an antimicrobial efficacy test on certain aqueous preparations
2. the container-closure needs to be studied[28].

A stability-indicating study is not necessarily the same as a strength or potency assay. Stability-indicating studies may indicate potency, but not necessarily vice versa[27]. A potency assay performed at different times, only determines the amount of the drug present over time[27]. Some potency tests do not distinguish how much of the drug is a degraded over time, as degradants may still appear on the potency assay due to a similarity in chemical structure[27]; whereas a stability-indicating assay always identifies the API concentration from its degradants. Degradants of analytes do not necessarily have the same therapeutic action as the original active ingredient. A degradant may be either completely inert, toxic or harmful to the patient, or exhibit an increased therapeutic activity to the original chemical.

Databases, which list the compatibilities of specific bases, are not the same as stability-indicating study results. Compatibility results only consider whether the APIs and base are **physically stable** rather than examining chemical stability.

We will now look at a common condition, which may present in the pharmacy and compare two methods of preparing an oral liquid to facilitate appropriate treatment for a child.

Case Study – Omeprazole Suspension

Omeprazole is a proton pump inhibitor indicated for children for the treatment of gastro-oesophageal reflux disease (GORD).[14] Omeprazole suppresses the secretion of gastric acid by inhibiting the (H+/K+ ATPase) enzyme system, also referred to as the 'proton pump' of the gastric parietal cell[29]. Other indications for omeprazole include management of peptic ulcer disease, H. Pylori eradication and Zollinger-Ellison syndrome.

Omeprazole is white to off-white powder slightly soluble in water and sparingly soluble in alcohol[29]. Omeprazole is optimally stable at pH 11 and begins to rapidly decompose at pH 7.8[30]. Omeprazole is known to be sensitive to heat, humidity, light and organic solvents.[32] The degradation of omeprazole can be significantly slowed when the active is protected from light[32].

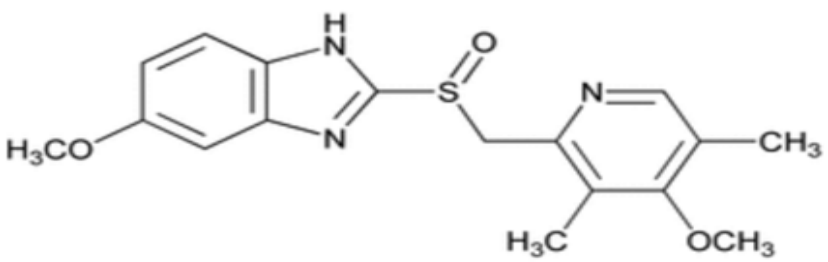

Figure 2 Structure of Omeprazole[33]

Dosage for omeprazole in children is dependent on weight, which makes an oral liquid an ideal choice of dosage form given the ease of dose adjustment.[14] Commercially-available capsule products and delayed release or enteric coated tablets are all designed to offer protection of the API from stomach acid. However these dosage forms are usually unsuitable when dispensing for children.

The APF 24 provides a formulation where the omeprazole is suspended in a buffered 8.4% sodium bicarbonate solution[14]. The APF24 formulation allows the pharmacist to prepare the liquid with either the raw API or the commercially available capsules. Compounding suppliers have also formulated bases buffered in an alkaline environment to reduce the degradation of omeprazole[31]. The formulation prepared with a proprietary base has a supporting stability indicating study to justify an extended expiry date. However, the formulation must be prepared with the raw API to assign this longer expiry date. Due to the degradation of omeprazole by light, an amber closure system is the final dispensing container of choice in both formulations[14,31].

Formula: Omeprazole 2mg/mL (100 mL)[14] - See table 5

Method of Preparation

1. Weigh out omeprazole and sodium bicarbonate
2. Dissolve sodium bicarbonate

in purified water.
3. Add compound hydroxybenzoate solution
4. Add omeprazole to form white dispersion
5. pH should be adjusted to be above 8 using sodium hydroxide solution 10%

Expiry Date: 28 days after preparation. Refrigerate at 2-8°C[14]

Storage: Glass Amber Bottle

Formula: Omeprazole 10mg/mL (100mL) Oral Liquid Suspension[30] -See table 6

Method of Preparation

1. Weigh out omeprazole and Oral Mix Dry Alka.
2. Combine and triturate the powders to form a fine homogeneous powder.
3. Incrementally add the purified water (60 mL) to the powder blend and disperse the powders.
4. Transfer to dispensing bottle and add additional purified water to the required batch size and shake vigorously.

Expiry Date: 70 days after preparation. Refrigerate at 2-8°C, USP <61> and USP <62> pass after 70 days[31].

Storage: Amber, UV resistant polypropylene bottle

Conclusion

Oral liquids are an important dosage form option when treating paediatric and geriatric patients. Although oral solid dosage forms are more prevalent, they are not appropriate for all patients, hence pharmacists may be required to prepare an oral liquid extemporaneously if there is no suitable registered product. Pharmacists must undertake risk assessments and use professional guidelines when formulating medications into oral liquids, to ensure the dosage form is appropriate for the patient and there is sufficient evidence of stability for the specific formulation.

Pharmacists may prepare an oral vehicle in their laboratory or use a proprietary base. Manufacturers of proprietary bases may have studies or data to support the evidence of chemical and microbial stability with specific APIs. These considerations may mitigate the risk to the patients using medications extemporaneously prepared and/or "off label".

Table 5: Formula: Omeprazole 2mg/mL (100 mL)[14]

Ingredient/Chemical	Quantity	Unit
Omeprazole*	0.200	g
Sodium bicarbonate	8.400	g
Compound hydroxybenzoate solution	1.0	mL
Purified Water, USP	q.s. to 100.0	mL

*omeprazole 20mg capsules may be used but may take longer to form a dispersion due to the enteric coated pellets (up to 2 hours)

Table 6: Formula: Omeprazole 10mg/mL (100mL) Oral Liquid Suspension[30]

Ingredient/Chemical	Quantity	Unit
Omeprazole USP	1.000	g
Oral Mix Dry Alka, SF (Cherry Flavoured)	6.750	g
Purified Water, USP	60.0	mL
Purified Water, USP	q.s. to 100.0	mL

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CPD MULTIPLE CHOICE QUESTIONS

1. What is the maximum expiry date applied to a compounded liquid in the absence of stability-indicating study as per Australian Pharmaceutical Formulary 24 (AFP 24)?
   A. 14 days
   B. 6 months
   C. 28 days
   D. 90 days

2. A potency assay test over time is enough to indicate stability
   A. True
   B. False

3. Which of the following can be appropriately crushed for the preparation of oral liquids.
   A. Slow release tablets
   B. Cytotoxic tablets
   C. Immediate-release tablets
   D. Enteric coated capsules

4. Populations in which oral liquids may be utilised for increased compliance include
   A. paediatrics
   B. geriatrics
   C. animals
   D. all of the above

5. Forced degradation involves exposing the active ingredient to known degraders, such as high heat, high humidity, UV radiation, acid, base and peroxide. This procedure is used in:
   A. an antimicrobial efficacy test
   B. a stability-indicating study
   C. a preservative efficacy test
   D. a microbial examination for non-sterile products

6. Consider the statements below regarding stability-indicating studies and choose the most correct answer:
   I. Stability-indicating studies are carried out for at least 6 months, whilst potency studies are carried out for any selected time period
   II. Stability-indicating studies always assay the API under forced degradation, whilst potency studies do not
   III. Stability-indicating studies include specific packaging and temperature conditions
   IV. Stability-indicating studies always separate the API from it's degradants, whereas potency studies do not

   A. I. is correct
   B. Only II and III are correct
   C. II, III and IV are correct
   D. All are correct

7. The Australian Pharmaceutical Formulary 24 (APF 24) and Professional Practice Standards (PPS) recommend pharmacists:
   A. modify commercially available products to use in extemporaneous preparations where possible.
   B. exercise caution when modifying commercially available products to use in extemporaneous preparations
   C. never use a commercially available product to compound into a liquid preperation
   D. modify commercially available products to use in extemporaneous preparations where possible, ensuring they disclose concentrations of all excipients.

QUESTIONS CONTINUED ON NEXT PAGE

CPD MULTIPLE CHOICE QUESTIONS

8. Compounded omeprazole suspensions should be stored in a clear glass bottle.
   A. True
   B. False

9. Choose the INCORRECT option.
   A. Proprietary oral suspending agents have a longer shelf life than vehicles prepared in the compounding pharmacy
   B. Compounding pharmacists do not need to consider the pH of the formulation they are compounding, as oral proprietary suspending vehicles adjust the pH themselves
   C. Some proprietary vehicles have additional pharmacopeia testing, which provides pharmacists with a higher level of quality assurance
   D. All of the above options are incorrect