

## Liquid Dosage Forms Extemporaneously Prepared from Commercially Available Products – Considering New Evidence on Stability

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**ABSTRACT** - Although the world's population is ageing and as a result of this an increasing number of patients are experiencing difficulty in swallowing, there remains a lack of commercially available oral liquids for both these older and paediatric patients. This presents a problem to health care professionals, especially the pharmacist in practice, who is often required to provide a solution for these patients by preparing oral liquids extemporaneously from commercially available products. Preparation of these oral liquids is challenging, both due to the lack of pharmacopoeial and stability-indicating formulae and the fact that their stability is not only determined by the active pharmaceutical ingredient, but also the ability of excipients from the commercial product to interact with each other and the active pharmaceutical ingredient. This increases the complexity of the stability considerations to be taken into account within these oral liquids, highlighting the number of parameters to be considered in the extemporaneous preparation of oral liquids.

This paper presents new evidence on the stability of 42 oral liquids prepared from commercially available products, reported on in the literature since the previous review published in 2006. However, unlike the previous review where the stability concerns in 7.2% of the extemporaneously prepared oral liquids were mainly due to interaction between the active pharmaceutical ingredients and the excipients in the commercial product, most of these stability considerations have been recognised and this has resulted in the authors proposing solutions to these problems prior to the extemporaneous preparation of the oral liquid.

As such this paper also focuses on the increased level of research that has been undertaken to solve previous issues related to stability, especially in terms of the use of commercial products, which is common practice in the extemporaneous preparation of oral liquids.

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### INTRODUCTION

The lack of commercially available oral liquid dosage forms is an ongoing problem for health care providers in many practice settings. Pharmacists are often challenged to provide extemporaneous oral liquids. While these are most commonly provided for paediatric patients where non-standard doses are more easily and accurately measured by using a liquid formulation, adults unable to swallow tablets or capsules and patients receiving medicines via nasogastric or gastrostomy tubes will also benefit from these preparations (1). The world's population is ageing and many people suffer from dysphagia either as a consequence of disease or as part of the ageing process. Elderly patients are more prone to diseases linked to dysphagia, such as Parkinson's disease and Alzheimer's and other dementias, stroke and cancer (2-4). Extemporaneous oral liquids are also needed

where, for example, a commercially available oral liquid is discontinued or temporarily unavailable, such as Tamiflu® (oseltamivir) Oral Suspension (5,6).

A number of parameters need to be considered in the formulation of a stable oral liquid. These include chemical, physical, microbiological, therapeutic and toxicological stability evaluations not only taking account of the active pharmaceutical ingredient (API), but also the excipients and packaging of the drug product. The extemporaneous preparation of oral liquids can be complex due to the addition of excipients to improve patient adherence and / or the stability of the final product. Further, due to convenience and availability of ingredients, it is

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common practice for oral liquids to be prepared from commercially available solid dosage forms such as a tablet or capsules. Therefore additional potential interactions may occur between the drug and the excipients in the solid dosage in the prepared oral liquid.

In addition to chemical stability, physical stability, microbial stability and palatability, excipient suitability (e.g. sugar free for diabetic patients) and interactions with packaging materials need to be considered in the preparation of a suitable extemporaneous oral liquid. These considerations are detailed in the discussion.

This review provides new evidence, since the previous review in 2006 (7), of stability data for extemporaneous oral liquids prepared from commercially available dosage forms including tablets, capsules and intravenous preparations. Further, the review outlines important stability considerations and the risk associated with modifying commercial products and provides guidelines to assist the pharmacist in preparing safe, effective and high quality oral liquids.

## METHODS

A review protocol was developed with data identified from MEDLINE, EMBASE, Informit, Google Scholar, reference texts related to the field and reference lists of articles and abstracts from conference proceedings. Searches were current as of April 2013.

Only those liquid dosage forms prepared from commercially available dosage forms were considered, as this is most commonly encountered in practice, where access to raw material as the is not often convenient or even possible. As in the first review (7), only those preparations that included a chemical stability assessment via a stability-indicating high performance liquid chromatography (HPLC) method were included and the oral liquids were considered chemically stable if they retained  $\geq 90\%$  of the initial drug concentration. The reasons for this are detailed in the previous review (7). Those oral liquids that have been previously reported on in the first review have not been included in this paper.

## RESULTS

This review includes 42 examples (Table 1) of oral liquids in practice, prepared by modification of commercial medications, including the methods, excipients, packaging and reasons for their extemporaneous preparation. The outcome of the chemical and physical stability studies

conducted is also presented. The highlighted (shaded) areas in Table 1 indicate those preparations that have been further detailed in the discussion.

## DISCUSSION

Of the 42 liquid dosage forms reviewed in the literature, all cases of instability were managed through the addition of specific excipients, illustrating that there is minimum risk associated with these dosage forms and that pharmacists taking cognisance of various factors such as drug stability, mechanisms and routes of degradation, and potential interactions with excipients in the tablets and/or capsules utilised in the formulation are further able to minimise the risk involved. The individual dosage forms displaying stability concerns are discussed below.

### **Omeprazole and lansoprazole oral liquid dosage forms**

Stability concerns with lansoprazole (20) are related to a slightly acidic pH of the final formula due to Ora-Blend being buffered to a slightly acidic pH of  $\sim 4.2$ . However, this instability has been largely addressed by the addition of  $\text{NaHCO}_3$ . Further, omeprazole is now commercially available as a powder for oral suspension (ZEGERID® Powder for Oral Suspension) which contains  $\text{NaHCO}_3$ , xylitol, sucrose, sucralose, xanthan gum, and flavourings.

### **Mercaptopurine oral liquid dosage forms**

A study reported on the stability of mercaptopurine, a drug susceptible to oxidation, resulting in the formation of acidic degradants (23). A buffer was therefore investigated to address the increased acidity due to the formation of these degradants. However the buffer resulted in a decreased stability of mercaptopurine, due to the increased pH. This stability issue was addressed by the addition of the antioxidant ascorbic acid which increased the shelf-life from 5 to 11 weeks.

The authors recommended further studies on the microbial safety of these vehicles, since they did not contain preservatives; however this can be addressed by using commercially available vehicles such as Ora-Blend which are adequately preserved.

### **Temozolomide oral liquid dosage forms**

Temozolomide is a prodrug, which after hydrolysis in an alkaline environment is converted to the active alkylating agent. Solid-

state temozolomide is thus also susceptible to hydrolytic degradation under accelerated temperature and humidity conditions (40 °C and 75% relative humidity), with a change in colour of the white powder first to pink and then brown, an indication that this chemical degradation has occurred. Temozolomide does however also exhibit polymorphism, with powder X-ray crystal structures confirming the identity of three crystalline polymorphs and a monohydrate. Although the powder X-ray diffraction pattern of the commercially available temozolomide is consistent with Form 1, which is non hygroscopic the discolouration of certain brands of tablets on storage raises the question as to which crystal form is present in these tablets (47). Temozolomide oral liquid extemporaneously prepared from commercially available capsules in both (1:1) Ora-Plus: Ora-Sweet and Ora-Plus: Ora-Sweet SF was stored at room temperature (23 °C) and at 4 °C (36), with stability confirmed for 1 week in Ora-Plus: Ora-Sweet (1:1) and 2 weeks in Ora-Plus: Ora-Sweet SF at room temperature (23 °C) and 60 days at 4°C. Because of the potential for polymorphism and the detection of crystals in the suspensions within a few days of storage at both temperatures, the excipient povidone K-30 was added to minimise this crystal growth, which if it does occur may result in inaccurate dosing.

The inclusion of povidone K-30 to prevent crystal formation and optimising the pH at 4 (citric acid) to reduce hydrolytic degradation produced a pharmaceutically acceptable suspension when stored under refrigeration.

#### **Clopidogrel oral liquid dosage forms**

Skillman *et al* (14) evaluated the stability of clopidogrel 5 mg/mL suspension prepared in Ora-Plus and Ora-Sweet and concluded that over 90 % of the initial clopidogrel concentration was retained after 60 days at room temperature or under refrigeration. However, the method used to measure clopidogrel concentration was not chirally selective and failed to consider the potential for isomeric inversion of the active S-clopidogrel to the inactive R-clopidogrel. A later study (14) highlighted the importance of the conversion of the active S form to the inactive R enantiomer. This study determined that 1.5 % and 3 % of S-clopidogrel was converted to the R enantiomer after storage for 49 days at 4 °C and 25 °C respectively. These authors then used this data to estimate the shelf-life assuming 90 % of the original content and recommended an expiry

of 1 month under refrigeration and 2 weeks at room temperature (25 °C).

#### **Packaging used in extemporaneous oral liquid preparations**

Ensom *et al* (19) reported on the stability of lansoprazole (3mg/mL) in extemporaneously compounded suspensions (see Table 2). The findings reported here are in contrast with those of a previous study (48) detailed in the first review (7), in which a lansoprazole suspension (3 mg/mL) was stable for only 8 hours when prepared from capsule contents mixed in 100 mL of 8.4% NaHCO<sub>3</sub> and stored at room temperature (22°C) in amber-coloured, plastic oral syringes. Although the refrigerated (4°C) samples in that study were reported to be stable for only 14 days, the refrigerated samples in the current study were stable for 91 days. It has been suggested by the authors that the different storage containers, namely plastic syringes and glass bottles, may account for the difference in stability of lansoprazole suspensions, and that a substance present in the plastic syringes but not in the glass might have reduced the stability of lansoprazole. In addition it was also suggested that the amber syringes stored at room temperature would not have protected the lansoprazole from UV light to the same extent as the suspension stored in the refrigerator, where it is naturally dark (19).

#### **Storage conditions for oral liquids**

It is important to note that refrigerated solutions do not always show increased stability and can have increased problems of caking as demonstrated by the study by Aliabadi *et al* (23) with a refrigerated suspension of mercaptopurine. This emphasises the importance of stability studies for specific drugs and the benefits of using a vehicle containing appropriate suspending agents.

#### **Considerations in the extemporaneous preparation of oral liquids**

When considering the suitability of an extemporaneous oral liquid, a number of factors, in addition to chemical stability need to be considered (Table 2). This includes physical stability, microbial stability, palatability, excipient suitability (e.g. sugar free for diabetic patients), interactions with packaging materials, accurate compounding procedures including calculations and cost.

**Table 2.** Considerations for the preparation of a stable, effective, quality oral liquid

Consideration		Potential excipients required
Chemical stability	Including the stability of the API and the effect of tablet excipients in solution; pH stability and the need for buffers.	Antioxidants EDTA Buffers
Physical stability	Caking, crystal growth, resuspension and the ability to administer an accurate dose.	Suspending agents Antifoaming agents
Microbial stability and shelf-life	Adequate preservation.	Preservatives
Palatability	Sufficient masking of bitter drugs.	Sweeteners Flavours Colours
Excipient suitability	Alcohol free for paediatric patients; sugar free for diabetic patients.	Alcohol free vehicles Artificial sweeteners
Packaging	Light protection; child safety; interactions with packaging materials (glass or plastic).	
Bioavailability	Absorption and therapeutic efficacy of a drug in a suspension compounded from crushed tablets is unlikely to differ appreciably from those of the original dosage form.	
Cost	Availability of starting materials; staff preparation time.	
Compounding considerations	Accurate measurement; appropriate equipment and facilities; exposure of sensitive ingredients (to light) during compounding; water source (no ions).	
Shelf-life	Assigning an appropriate beyond use date/ shelf life.	
Dose calculations	For example, not accounting for the weight of tablet excipients when calculating the weight of the API.	

From the Table 2 it can be seen that the design of an oral liquid from first principles is a lengthy process and would require careful consideration of a number of factors:

- (i) **chemical stability** includes considering the potential degradation of the API by pathways such as oxidation, hydrolysis, photolysis or thermolysis, and any potential interactions between the API, the excipients in the vehicle, the excipients in the original dosage form (e.g. tablet or capsule) and the packaging.
- (ii) **physical stability** includes considering resuspension and the ability to administer an accurate dose, antifoaming agents to prevent excessive foaming from vigorous shaking prior to administering a dose, and caking or crystal growth that may arise during storage.
- (iii) **microbial stability** includes the use of preservatives at a suitable strength to prevent microbial growth in a predominantly water based preparation. A recent study by Ghulam *et al* (49),

showed that various suspending vehicles failed the BP 2007 efficacy of preservation tests when diluted in ratios greater than 1:1, and cautioned that such dilution represents a potential biohazard, especially to premature, newborn, or immunocompromised children. Another study by Salgado *et al* (50) on the microbial stability of spironolactone in Simple syrup NF, demonstrated the importance of the use of preservatives, since microbial contamination occurred in the preparation, even when stored at low temperatures.

- (iv) **palatability** includes the use of suitable flavours and sweeteners to mask bitter drugs, especially with young patients. It has also been suggested that administering chocolate syrup before medication administration or mixing the preparation with chocolate syrup (1:1 by volume) immediately before administration is recommended to mask the bitter aftertaste and improve

- palatability, for extremely bitter drugs (18,28,30).
- (v) **excipient suitability** includes limiting cosolvents such as alcohol for children and providing sugar free preparations for diabetic patients.
- (vi) **packaging** includes the use of amber containers not only for APIs sensitive to light, but also those ingredients in the vehicle, such as colours and flavours that may also be sensitive to light. Provision of child safety packaging is particularly important for oral liquids where a significant dose could be inadvertently administered when compared to tablets or capsules.
- (vii) **bioavailability**. It has been suggested that absorption and therapeutic efficacy of a drug in a suspension compounded from crushed tablets is unlikely to differ appreciably from those of the original dosage form (35). Careful consideration should be given when using commercial products designed for administration via another route (e.g. intravenous preparations) since there may be differences in bioavailability when these products are administered orally.
- (viii) **cost, compounding considerations and shelf-life**. The availability of starting materials and excipients and staff preparation time are important considerations (9,51,52), as is access to appropriate facilities and equipment and accurate calculations of ingredients in the final preparation. Some APIs are extremely sensitive to light, showing significant degradation in only a few hours, therefore exposure to light needs to be minimised during preparation. The source of the water used has also been shown to cause problems (53). Assigning an appropriate beyond use date or shelf-life in the absence of specific stability studies is also challenging, with many preparations given a very short shelf-life for safety purposes.
- (ix) **dose calculations**. A study on the stability of a 1 mg/ml tacrolimus suspension (34) has shown that careful consideration of the strength of the oral liquid (namely 1mg/mL as opposed to decimal amounts per mL) will facilitate several aspects of clinical care, For example, the 1:1 ratio of drug to suspension volume will decrease the

frequency of patient medication errors, as it allows for a more simplified and straightforward drug administration. This will also facilitate easier discharge medication instructions or any follow-up discharge instruction in the outpatient clinic when confirming and verifying dosing. Further, incremental dosing with the 1 mg/ml suspension allows for more accurate adjustment of therapy based on monitoring blood levels and paediatric dosing could result in better patient adherence owing to the small volume required for dosing.

#### Commercially available oral liquid vehicles

Commercially available vehicles, such as Ora-Plus and Ora-Sweet and Ora-Sweet SF are a convenient resource for pharmacists, since many practice settings may not stock a wide variety of excipients and many of the stability studies in the literature on oral liquids prepared extemporaneously utilise these commercial vehicles, as seen in Table 1. A number of medicines are stable at an acidic pH, for example thalidomide is not stable in a solution with a pH of greater than or equal to 6.0 (37). All of the above vehicles are buffered to a slightly acidic pH (pH~4.2) to reduce the degradation of medicinal agents through oxidation. The vehicles also contain effective preservatives, therefore microbial testing is not needed (22). Ora-Plus is a translucent, milky white oral suspending vehicle that can be diluted up to 50 % or more with other ingredients and still retain appropriate properties as a suspending agent. It also contains an anti-foaming agent, simethicone, to allow for vigorous shaking of the suspension with minimal production of foam. Ora-Sweet syrup is a flavouring vehicle for oral extemporaneous preparations. It contains glycerin and sorbitol to prevent "cap-lock", a problem associated with many syrups, due to sugar crystallization, and will retain its flavouring properties when diluted up to 50% with water or suspending agents. Ora-Sweet SF is a sugar-free version of Ora-Sweet with similar properties. Ora-Plus and either Ora-Sweet or Ora-Sweet SF can be combined in a 50/50 ratio to produce a pleasant tasting elegant suspension. The original formulas for the Ora-range of vehicles are available in the United States Pharmacopoeia/ National Formulary (USP/NF) and are referred to as *Vehicle for Oral Solution NF* (i.e. Ora-Sweet), *Vehicle for Oral Suspension NF* (i.e. Ora-Plus), and *Vehicle for Oral Solution, Sugar Free NF* (i.e. Ora-Sweet SF) (54).

A recent study (55) on the content uniformity of six different suspensions compounded from nifedipine tablets, showed that the suspensions compounded with methylcellulose 1% / syrup NF or hypromellose 1% required mixing by inverting the bottle 10 to 15 times, while the commercially available suspension vehicles (namely, Ora-Plus/Ora-Sweet, Ora-Plus/Ora-Sweet SF and SyrSpend SF Cherry) complied with the pharmacopoeial content uniformity test if the bottle was inverted only three times. This highlights the benefits of utilising commercially available vehicles.

Further usefulness of commercially available vehicles is highlighted in a review of the stability of captopril oral liquids (53). Due to the susceptibility of captopril to oxidation, the use of water-based captopril solutions is not recommended. This is due to the potential for the variable quality of water, particularly in terms of its metal ion content, to facilitate the oxidative degradation of captopril. The previous review (7) detailed a number of studies and the associated stability concerns with compounding captopril oral liquids. It has been suggested that alternative therapeutic agents such as lisinopril and ramipril should be preferentially used due to their improved stability in oral formulations, or commercially available captopril oral liquids sourced.

### **Management of oral liquid preparations in practice**

A recent review by Lam (56) on the extemporaneous preparation of oral liquid formulations for anticancer drugs showed that compounding formulae are available for only 46 % of oral anticancer agents and that there is a paucity of data in terms of stability, bioequivalence, and safety of these extemporaneously prepared oral formulations. The review detailed the challenges that health care providers, patients, and caregivers face with the limited availability of oral liquid formulations. Caregivers are often at an increased risk of exposure to these hazardous drugs when challenged with an oral tablet or capsule that the patient cannot swallow. The review also highlighted the important role that oncology pharmacists, as well as community pharmacists, can play as a resource for educating and monitoring patients receiving oral chemotherapy to ensure dosing accuracy, safe administration, and proper disposal of hazardous drugs.

The first review provided a flow chart, with explanations, for the management of oral liquids in practice (7). Due to the complexities involved in extemporaneously preparing oral liquids, it highlighted that (i) pharmacists should always consider a commercially available product (i.e. this may not necessarily be limited to an oral liquid and may include other alternative dosage forms, such as a transdermal patch or a dispersible tablet); (ii) if no suitable commercial product exists, a therapeutic alternative that is available in a suitable dosage form may be considered, in consultation with the prescribing doctor, and (iii) the importation of suitable oral liquid medicines licensed in other countries may also be considered.

Should none of these measures prove successful, a suitable formula for an oral liquid with a proven stability profile should be sought in the literature. Useful resources include, Allen's Compounded Formulations (57), Paediatric Drug Formulations (58), Trissel's Stability of Compounded Formulations (1), journals such as the *International Journal of Pharmaceutical Compounding* and the *American Journal of Health-System Pharmacy*, and the current and previous review article (7) showing examples of oral liquid dosage forms prepared by modifying an existing commercial medication.

Stability studies in the literature allow for increased shelf-life and cost savings, in addition to providing evidence for stable products. Further, the recent availability of commercial liquid vehicles in many countries now provides pharmacists with a convenient resource for preparing an oral liquid formulation. It is also promising to note that procedures to prepare stable oral liquids from commercial solid dosage forms have been provided by manufacturers in cases where an oral liquid is not available or temporarily out of stock (Table 3).

### **Alternatives to preparing oral liquids**

The previous review (7) provided details on dispersing tablets or capsules in water or mixing them with food immediately prior to administration, and the provision of powder packets in cases where the preparation of oral liquid dosage forms are not feasible. The disadvantages of these methods were outlined, namely potential for dosing inaccuracies, poor palatability leading to adherence issues, and risks associated with carers or patients crushing tablets which should not be crushed (e.g. sustained release tablets).

**Table 3.** Examples of instructions provided by manufacturers for the preparation of oral liquids

Drug Product with reference	API	Excipients	Packaging	Stability study data
Tamiflu® (59,60)	Oseltamivir	2 vehicles: Cherry Syrup; Ora-Sweet SF	Amber plastic bottle	6 mg/mL suspension stable for 35 days at 2-8 °C and 5 days at 25 °C.
Zestril®, Prinivil® (61,62)	Lisinopril	Vehicle: Purified water, Bicitra® diluent and Ora-Sweet SF®	Polyethylene terephthalate (PET) bottle	1 mg/mL suspension stable for four weeks at 25 °C.
Rifadin® (63)	Rifampin	4 vehicles: Simple Syrup NF; Simple Syrup (Humco Laboratories); Syrpalta® Syrup (Emerson Laboratories); or Raspberry Syrup (Humco Laboratories)	Amber glass or plastic (high density polyethylene, polypropylene, or polycarbonate) prescription bottle	10 mg/mL suspension stable for four weeks at 2-8 °C and 25 ± 3 °C.

The review by Lam (56) provides detailed guidelines in an Appendix for patients on what to do if they cannot swallow their oral anticancer medication.

#### ***Solid dosage forms that should not be crushed***

Information on the appropriateness of crushing tablets or opening capsules is available through resources such as the approved product information and the CMI (Consumer Medicine Information) of the commercial solid dosage form. Compiled lists of medicines that should not be crushed or modified are available, such as the Australian Don't Rush to Crush Handbook (64), the Handbook of Drug Administration via Enteral Feeding Tubes (65), the Australian Medicines Handbook (AMH) Aged Care Companion (66) and electronic resources such as the list provided by the Institute for Safe Medication Practices (67).

#### ***Short term stability of crushed medicines in food thickeners or water***

A recent study reported on the short term compatibility of risedronate sodium tablets with different food thickeners, namely Milani Thickenit®, Resource Thicken Up®, Thik & Clear®, Hormel Thick & Easy®, and Hormel NutraThik® (68). A risedronate sodium 35-mg tablet was added to a beaker and allowed to disintegrate without agitation. After two minutes, the water was stirred with a plastic spoon and an additional 4 oz of water was added to each beaker and stirred briskly for 30 seconds. The recommended amount of each food thickener was then added to each beaker. The risedronate tablets were shown to be stable for 24 hours with each of the food thickeners.

## **CONCLUSION**

Orals liquids for certain drugs are often not commercially available, due to market size and the many physicochemical factors that need to be considered when formulating a liquid dosage form (69). Since the physicochemical stability of a drug does not confirm either its safety or efficacy in a patient, there are a number of factors, including exercising good judgement, that the pharmacist must take into account when deciding to compound an oral liquid (70). The fact that the stability of an extemporaneous formulation prepared from commercially available products cannot be predicted based on a formulation using the pure drug powder, due to the effect of excipients, was highlighted in the previous review where 6 out of 83 (7.2%) oral liquids presented with stability concerns, largely due to drug-excipient interactions. This review, which includes 42 oral liquids extemporaneously prepared by modifying existing commercial dosage forms presents 6 out of the 42 orals liquids including the four APIs, clopidogrel, lansoprazole, temozolomide, and mercaptopurine for discussion.

However, it must be noted that the research and skill base in compounding has evolved since the previous review and that many improvements have been made to address the various formulation and stability issues in preparing extemporaneous oral liquids, from commercially available products, which is now common practice.

This review thus presents more complex stability issues, where the authors have proposed the inclusion of specific ingredients (excipients) to address some of the stability problems that have been identified in the past, including: the pH

adjustment of lansoprazole extemporaneous oral liquids by the addition of NaHCO<sub>3</sub> and the commercial availability of an oral suspension; the inclusion of antioxidants in mercaptopurine oral liquid; the addition of povidone K-30 to prevent crystal growth and citric acid to optimise pH in temozolomide oral liquid; and the adjustment of storage conditions to prevent enantiomeric conversion of clopidogrel.

This improved understanding of the role of excipients in the stability of extemporaneously prepared oral liquids from commercially available products will allow the pharmacist to meet the challenge in making an informed judgement when asked to address the needs of patients requiring the compounding of oral liquids.

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**Table 1 Oral liquid dosage forms prepared by modification of commercial medications**

API with reference	Extemporaneous modification		Excipients	Packaging	Stability study data	Stability considerations
	How?	Why?				
Acetylcysteine (8)	1e	2a, 2c	Vehicle: bacteriostatic 0.9% sodium chloride for injection.	3b (amber)	4a. 10 mg/mL and 100 mg/mL solutions were stable for 60 days at 20-25 °C.	API sensitive to oxidation. Note inhalation solution contains EDTA.
Acetylcysteine (9)	1e	2a	None. Bulk inhalation preparation repackaged into oral syringes.	3c	4a. 600mg/3mL solution was stable for 6 months at 3-5 °C and 23-25 °C.	
Acetylcysteine (10)	1e	*	Vehicle: 1:1 Sweetener and strawberry creamsicle flavouring (FLAVORx Inc).	3b (amber)	4a. 86.5 mg/mL solution was stable for 35 days at 3-5 °C and 23-25 °C.	Offensive smell and taste was effectively masked.
Aprepitant (11)	1b	2a	Vehicle: Ora-Blend	3a (amber); 3b (amber)	4a. 20-mg/mL suspension was stable for 90 days at 4 °C in amber glass or plastic. Storage at 23 °C accelerated degradation of the API.	
Celecoxib (12)	1b	2a, 2b	Vehicle: Ora-Blend	3b (amber)	4a. 10 mg/mL suspension was stable for 93 days at 5 °C and 23 °C.	
Clopidogrel (13)	1a	2a	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 5 mg/mL suspension was stable for 60 days at 2-8 °C and 23-25 °C.	Bitter aftertaste intensified slightly between 28-60 days, but remained fairly mild.
Clopidogrel (14)	1a	2a	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3a (amber)	1 mg/mL suspension was stable for 1 month at 4 °C and 2 weeks at 25 °C.	
Clozapine (15)	1a	2d	6 vehicles: Ora-Sweet; Ora-Plus; 1:1 Ora-Sweet: Ora-Plus; Simple syrup; 'Hospital for Sick Children suspending vehicle'; and 'Guy's pediatric mixture'.	3b (amber)	4a. 20 mg/mL suspensions were stable for 63 days at 23 °C.	
Cyclophosphamide (16)	1d	2a	2 vehicles: Simple syrup; and Ora-Plus.	3c (amber)	4a. 10 mg/mL solutions were stable for 56 days at 4 °C. Storage at 22 °C in Simple syrup and Ora-Plus reduced stability to 8 and 3 days respectively.	

Dexamethasone phosphate (17)	1d	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a.0.5 and 1.0 mg/mL suspensions were stable for 91 days at 4 °C and 25 °C.	Commercially available liquids contain alcohol or their strength is lower than desirable.
Glycopyrrolate (18)	1a	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 0.5 mg/mL suspensions were stable for 90 days at 23-25 °C.	
Lansoprazole (19)	1b	2d	2 vehicles: NaHCO <sub>3</sub> , water; 1 <sup>st</sup> vehicle + Ora-Sweet:Ora-Plus buffered with NaOH	3a (amber)	4a. 3 mg/mL suspensions were stable for 91 days at 4 °C and 25 °C. 1 <sup>st</sup> vehicle developed a more bitter taste by day 49, however this is for nasogastric and not oral use.	A 3 <sup>rd</sup> vehicle similar to the 2 <sup>nd</sup> vehicle but buffered with NaHCO <sub>3</sub> was deemed unpalatable.
Lansoprazole (20)	1a	2d	Vehicle: Ora Blend	Clear glass vial stored protected from light.	4a. 3 mg/mL suspension was stable for 3 days at 4.5-5.5 °C. Storage at 21-22 °C or the reduction of pH through addition of citric acid accelerated degradation of the API.	
Levetiracetam (21)	1a	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 50 mg/mL suspensions were stable for 91 days at 4 °C and 25 °C.	
Melatonin (22)	1a	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	1 mg/mL suspensions were stable for 90 days at 23-25 °C. Slight yellow colouring occurred over time.	
Melatonin and pyridoxine HCl (22)	1a	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	1 mg/mL (melatonin) suspensions were stable for 90 days at 23-25 °C. Slight yellow colouring and prolonged aftertaste occurred over time.	
Mercaptopurine (23)	1a	2a	4 vehicles: simple syrup, cherry syrup, water; 1 <sup>st</sup> vehicle + ascorbic acid; 1 <sup>st</sup> vehicle + sodium phosphate; and 1 <sup>st</sup> vehicle + ascorbic acid and sodium phosphate.	3a (amber)	50 mg/mL suspensions were stable for 35 days at 19-23 °C. Formulations stored in a refrigerator (4-8 °C) showed decreased stability and caking. Further studies on the microbial safety and efficacy of these vehicles were suggested.	API sensitive to oxidation, especially at basic pH. Antioxidant (0.1% ascorbic acid) increased shelf life, whereas buffer (sodium phosphate) decreased shelf-life.

Moxifloxacin (24)	1a	2d	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 20 mg/mL suspensions were stable for 90 days at 23-25 °C.	
Omeprazole (25)	1f	2d	Vehicle: water.	3b (amber)	4a. 2 mg/mL suspension was stable for 45 days at 3-5 °C. At 45 days, there was a very slight yellowish tint in all samples, which were creamy white when first prepared.	
Omeprazole (26)	1f	2d	Vehicle: water.	Clear plastic 50mL conical polypropylene tubes	4a. 0.6, 1.2, 2, 3 and 4 mg/mL suspensions were stable for 28 days at 4 °C (in the dark). Except for the 0.6 mg/mL preparations, suspensions stored at 22-25 °C in the light were stable for 7 days, despite turning yellow.	
Oseltamivir (6)	1b	2e	2 vehicles: Cherry Syrup and Ora-Sweet SF.	3a (amber); 3b (amber)	4a. 15-mg/mL suspensions were stable for 35 days at 5 °C. 2 <sup>nd</sup> vehicle was also stable for 35 days at 25 °C and for up to 13 days at 30 °C.	
Oseltamivir (5)	1b	2e	3 vehicles: SyrSpend SF; Cherry Syrup; and SyrSpend SF (for reconstitution).	3b (amber)	4a. 15-mg/mL suspensions were stable for 30 days at 2-8 °C.	Vehicles are ethanol- and sorbitol-free.
Oxandrolone (27)	1a	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 1 mg/mL suspensions were stable for 90 days at 23-25 °C.	Women who are or may become pregnant should wear a mask when compounding.
Phenobarbital (28)	1a	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 10 mg/mL suspensions were stable for 115 days at 23-25 °C.	Commercially available liquid contains alcohol.
Phenylbutyrate (29)	1f	2a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 200 mg/mL suspensions were stable for 90 days at 23-25 °C.	Both preparations were bitter with a strong, bitter aftertaste.
Rifaximin (30)	1a	2d	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 20 mg/mL suspensions were stable for 60 days at 23-25 °C.	
Rufinamide (31)	1a	2a, 2b	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet	3b (amber)	4a. 40 mg/mL suspensions were stable for 90 days at 23-25 °C.	

SF: Ora-Plus.						
Sulfasalazine (32)	1a	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3a (amber); 3b (PET and PVC) (amber)	100 mg/mL suspensions were stable for 91 days at 4 °C and 23 °C	
Sunitinib (33)	1b	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 10-mg/mL suspension was stable for 60 days at 4 °C and 22°C.	
Tacrolimus (34)	1b	2a, 2b	Vehicle: sterile water, 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 1 mg/mL suspension was stable for 4 months at 23-26°C.	
Tadalafil (35)	1a	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 5 mg/mL suspension was stable for 91 days at 23-25 °C.	
Temozolomide (36)	1b	2a, 2b	2 vehicles: citric acid, povidone K-30, 1:1 Ora-Sweet: Ora-Plus; and citric acid, povidone K-30, 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 10 mg/mL suspensions were stable for 60 days at 4 °C.	Storage at 23 °C accelerated degradation of the API.
Thalidomide (37)	1b	2d	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 20 mg/mL suspension was stable for 35 days at 3-5 °C.	Caregivers administering the liquid should avoid contact with the skin. Wear gloves and a mask when compounding.
Thalidomide (38)	1b	2d	Vehicle : tragacanth mucilage, sorbitol compound syrup, benzoic acid 5% solution, citric acid, distilled water.	Amber bottles	4a. 10 mg/mL suspensions were stable for 31 days at 21-23 °C.	See warnings above regarding protective measures.
Thioguanine (39)	1a	2a	3 vehicles: Simple syrup and methylcellulose; Ora-Sweet and Ora-Plus; and 2 <sup>nd</sup> vehicle + ascorbic acid.	3a (amber)	20 mg/mL suspensions were stable for 63 days at 19-23 °C. pH increased over the study period.	Addition of antioxidant (0.1% ascorbic acid) was not effective in consistently increasing shelf-life.
Vancomycin (40)	1d	2a, 2b	Vehicle: SyrSpend SF	3b (amber)	50 mg/mL suspension was stable for 90 days at 2-8 °C.	Vehicle is ethanol- and sorbitol-free.
Venlafaxine (41)	1b	2d	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and Simple syrup.	3b (amber)	4a. 15mg/mL suspension was stable for 28 days at 5 °C and 23 °C.	The capsules were a slow release dosage form. Capsule microspheres were ground to a powder.
Venlafaxine (42)	1a	2a, 2b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3a (amber)	4a. 5mg/mL suspension was stable for 15 days at 4 °C and 10 days at 22-28 °C.	

Venlafaxine (43)	1b	2c	2 vehicles: tragacanth mucilage, sorbitol compound syrup, benzoic acid 5% solution, distilled water; and 1 <sup>st</sup> vehicle without tragacanth mucilage.	3a (amber)	4a. 7.5 mg/mL suspensions were stable for 30 days at 20-24 °C.	The capsules were a slow release dosage form. Capsule microspheres were ground to a powder.
Warfarin (44)	1a	2d	Vehicle: Sodium phosphate, tragacanth mucilage, sorbitol compound syrup, Compound Hydroxybenzoate Solution APF (methyl and propyl hydroxybenzoate, propylene glycol), distilled water.	3a (amber)	4a. 1 mg/mL suspensions were stable for 28 days at 20-24 °C.	Warfarin is subject to pH-dependent sorption to polyvinyl chloride plastic. (1)
Ziprasidone mesylate (45)	1d	2a	Vehicle: Ora-Sweet.	3b (amber)	4a. 2.5 mg/mL solution was stable for 6 weeks at 5 °C. Storage in the light or at 20-22 °C accelerated degradation of the API.	The API is solubilised by complexation with β-cyclodextrin in the I/V preparation.
Zonisamide (46)	1b	2d	2 vehicles: Simple syrup NF; and 0.5 % methylcellulose.	3b (amber)	4a. 10 mg/mL suspension was stable for 28 days at 3-5 °C and 23-25 °C in the 1 <sup>st</sup> vehicle, and 28 days at 3-5 °C and 7 days at 23-25 °C in the 2 <sup>nd</sup> vehicle.	Significant microbial growth was observed in methylcellulose vehicle stored at 23-25 °C after 7 days.

1a. Tablet modified to an oral liquid mixture

1b. Capsule modified to an oral liquid mixture

1c. Liquid-filled soft gelatin capsule modified to an oral liquid mixture

1d. I/V preparation modified to an oral liquid mixture

1e. Inhalation preparation modified to an oral liquid mixture

1f. Granular powder preparation modified to an oral liquid mixture

2a. Lack of a commercially available oral liquid (paediatric) formulation for dose adjustment according to body weight or swallowing difficulties

2b. Ease of administration due to swallowing difficulties

2c. Nasogastric, jejunal, or feeding tubes

2d. All of the above – i.e. oral liquid dosage form not commercially available; including patients requiring a non-standard dose.

2e. Commercial oral liquid dosage form discontinued or unavailable

\* Unpleasant sulfurous smell and taste of the drug resulting from the slow release of hydrogen sulfide gas. As a result, patients may experience nausea and vomiting and have difficulties adhering to either oral or inhalation therapy.

3a. Glass prescription bottles

3b. Plastic prescription bottles

3c. Plastic oral syringes

4a. Analysis of organoleptic properties (e.g. colour, odour, taste) and visual inspection of physical stability (e.g. signs of caking, ease of pouring/ redistribution, microbial growth) and analysis of apparent pH revealed no appreciable changes throughout the storage period.