Stability considerations in liquid dosage forms extemporaneously prepared from commercially available products.

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The pharmacist, both in community and hospital pharmacy practice, is often challenged with the preparation of a liquid dosage form not available commercially for paediatric patients, those adults unable to swallow tablets or capsules and patients who must receive medications via nasogastric or gastrostomy tubes. Recognising the lack of information available to healthcare professionals, a general discussion of the various parameters that may be modified in preparing these dosage forms and a tabulated summary of the dosage forms presented in the literature is described, which, although not exhaustive, will provide information on the formulation and stability of the most commonly prepared extemporaneous liquid dosage forms. An extensive survey of the literature and investigation of 83 liquid dosage forms revealed that stability considerations were of concern for only 7.2 % of these liquid dosage forms, extemporaneously prepared from the following commercially available products: captopril, hydralazine hydrochloride, isoniazid, levothyroxine sodium, phenoxybenzamine hydrochloride and tetracycline hydrochloride. Inclusion of the antioxidant, sodium ascorbate in the liquid dosage form for captopril resulted in improved stability at 4ºC. Hydralazine hydrochloride, isoniazid and phenoxybenzamine hydrochloride were adversely affected due to interactions with excipients in the formulation, while the effect of the preservative in lowering the pH in a levothyroxine sodium mixture resulted in decreased stability. Interestingly, the instability in these formulations is primarily due to interactions between the drug substance and the excipients rather than degradation of the active pharmaceutical ingredient by standard routes such as oxidation, hydrolysis, photolysis or thermolysis. This low percentage however illustrates the low risk associated with these dosage forms investigated. It may be concluded that when considering the safety and efficacy of liquid dosage forms prepared extemporaneously, it is thus important to consider not only the stability of the drug substance but the entire formulation.

INTRODUCTION

The lack of commercially available oral liquid dosage forms is an ongoing problem in many practice settings. A pharmacist is often challenged to provide an extemporaneous oral liquid for (i) paediatric patients; (ii) patients who are unable to swallow solid dosage forms such as tablets or capsules; (iii) patients who must receive medications via nasogastric or gastrostomy tubes; and (iv) patients who require non-standard doses that are more easily and accurately measured by using a liquid formulation (1-10). It is common practice for these liquid dosage forms to be prepared from a commercially available oral solid dosage form by simply crushing tablets or opening a capsule and the subsequent addition of water or juice. However these dosage forms can become complex (2) due to the addition of excipients and while these measures are taken to improve compliance and stability of the extemporaneously prepared product, there are often limited data to support the stability or bioavailability of the final liquid dosage form, where potential interactions between the vehicle, preservative, buffering agent, flavouring agent, levigating agent, suspending agent, viscosity enhancer, storage container and the modified commercial product have yet to be established.

This review represents the first comprehensive summary of liquid dosage forms prepared from commercially available tablets and illustrates the low risk associated with these products if cognisance is taken,

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not only of the active pharmaceutical ingredient but all those ingredients contributed to the formulation as excipients from the commercially used product.

ORAL LIQUID PREPARATIONS

Oral liquid preparations for paediatric patients

Studies (2, 7, 9, 11-14) have identified that the preparation of liquid formulations for paediatric patients is both a daily experience and challenge for the pharmacist and paediatric health care provider. Appropriate formulations for administration to children exist for only a minority of commercially available drugs and the need for extemporaneously compounded formulations is escalating due to the release of many new drugs formulated for adults but with expected use in children (7, 9, 11). Children require titratable individualised doses in milligrams per kilogram of body weight and most children under six years of age cannot swallow tablets (15, 16).

A survey (14) into the informational needs of hospital compounding pharmacists providing pharmaceutical care to paediatric patients at 57 sites in the USA and Canada listed 76 extemporaneously prepared drug formulations as having adequate stability data, 109 formulations for which improved stability data were requested, and an additional 103 drug formulations prescribed by paediatricians that had no compounding or stability information available.

There are many reasons for the lack of commercially available paediatric formulations. The overall size of the paediatric market is much smaller than for adults, especially for common diseases such as hypertension. The industry is thus reluctant to commit resources to seek labelling for infants and children (unless a disease occurs exclusively or frequently in the paediatric population), since the formulation has to have been adequately studied in paediatric patients. Therefore, additional costs, limited financial returns, delay in marketing for adults, and perceived greater legal liability and regulatory requirements are impediments to developing and marketing a paediatric drug formulation (7, 17). It is encouraging to note, however, that according to a recent European memorandum, pharmaceutical manufacturers may be given incentives to manufacture and distribute medicines for a common paediatric market (14, 18). The FDA (Food and Drug Administration Act) Modernization Act (FDAMA) of 1997 provides incentives for the development and marketing of drugs for children. Under this Act, the FDA would waiver user fees for supplemental application for paediatric approval of new drugs already approved for use in adults. In addition, the market exclusivity period would be extended by six months for new drugs if the pharmaceutical industry can demonstrate health benefits in the paediatric population (18).

Tablets are often cut into smaller segments (halves or quarters) in the pharmacy or on the ward to obtain appropriately sized dosage units for children, however a major concern is that segments from tablets cannot be cut with great accuracy of dose (12, 19-21). McDevitt et al (20) conducted an extensive analysis on the ability to split a 25-mg hydrochlorothiazide tablet accurately by 94 volunteers. Of the 1752 manually split tablet portions, 41.3 % deviated from ideal weight by more than 10 % and 12.4 % deviated by more than 20 %. Gender, age, education, and tablet-splitting experience were consistently found not to be predictive of accuracy. Most subjects (96.8 %) stated a preference for commercially produced, lower-dose tablets, and 77.2 % were willing to pay more for them. The issue of cost containment in the treatment of hypertension has seen many physicians prescribing larger dosages of drugs and then instructing patients to split the tablets to receive the correct dose, and some health maintenance organisations are providing tablet splitters to patients while dispensing larger than prescribed doses (20). Modification of the commercial medication in this manner may be less expensive in the short term, but it has not been proven to be financially or medically effective and is of particular concern for drugs with steep dose-response curves or narrow therapeutic windows. The most appropriate device for splitting tablets is a further issue. Horn et al (19) conducted a study on captopril, clonidine, amlodipine, atenolol, carbamazepine, and setraline tablets to assess the reproducibility of tablet splitting using two different commercially available pill cutters, by examining the weight variation between the tablet parts (halves and quarters). Their results showed an inability for tablets to be

reproducibly split by both devices and it was suggested that paediatric practitioners and pharmacy administrators investigate alternative dosage forms, such as the extemporaneous compounding of solutions, when small dosages are required for paediatric patients.

It has been estimated that more than 40 % of doses given in paediatric hospitals require compounding to prepare a suitable dosage form (9) since crushing a tablet and/or sprinkling the contents of a capsule over food or mixing in a drink may lead to errors in preparation or delivery of doses (14).

Occasionally extemporaneous powders have been prepared by redistributing the powder from commercially available crushed tablets or opened capsules into smaller strength capsules or powder papers/ sachets, sometimes after dilution with lactose or similar material (12). This practice has been reported to be inflexible and time consuming (15, 22, 23) and further, usually requires the caregiver to reconstitute the powder form of the drug into a liquid dosage form immediately prior to drug administration, with the potential for the caregiver to be unable to accurately prepare and administer each dose (24, 25).

Another practice seen in paediatric care is to use injectable solutions for oral administration (13, 26). This is generally cost-prohibitive (27) and presents with many problems including the following: (i) drugs and/or vehicles may be mucosal irritants, vesicants, nauseants, or cauterants; (ii) drugs may undergo extensive first-pass metabolism or may have poor bioavailability after oral administration (e.g. cefuroxime and enalapril) (7); (iii) drugs and/or vehicles suitable for injection may be unpalatable; (iv) excipients included in the formulation may have toxic effects when cumulative oral ingestion is considered; and (v) co-solvents used in the commercial formulation may be diluted when mixed with syrup or water, thus allowing the drug to precipitate (13).

In most cases the pharmacist will therefore prepare an oral liquid dosage form with the active ingredient dissolved or suspended in a simple syrup or sorbitol mixture (7, 12, 18, 28). Since pure crystalline powders of drugs are not usually accessible to pharmacies, the active pharmaceutical ingredient (API) is often obtained by modifying a commercially available adult solid dosage form by crushing a tablet or opening a capsule. When a drug is formulated for paediatric use, several factors unique to paediatrics must be considered such as the immaturity of the intestinal tract and the subsequent influence on gastrointestinal absorption, and the fact that seriously ill neonates are often fluid restricted, limiting the volume of medications that can be received. Additives, including preservatives and sugar must be chosen carefully. Patients who are fructose intolerant have had significant adverse effects from sorbitol and there is a link between chronic use of sugar sweetened medication and dental caries (11). Formulations may also contain preservatives; an excipient considered to be largely inert in adults, however, may lead to life threatening toxicity in paediatrics when multiple doses of medications with the same preservative are employed. This is particularly the case with benzyl alcohol and benzoic acid (11).

The physical, chemical, microbial and therapeutic stability of the above paediatric extemporaneous preparations may not have been undertaken at all. This coupled with the increased potential for calculation or dispensing errors may prove the practice of modifying commercially available products to be extremely unsafe. Although information (29-31) is available detailing extemporaneous formulations for parenteral and oral use, however, only some of the formulations have documented stability data.

Oral liquid preparations for use in residential aged-care facilities

Many people in aged-care facilities have their medications modified for ease of administration. For example, nurses at nursing homes routinely use a mortar and pestle to crush oral solid medications for elderly patients with swallowing difficulties and sprinkle the crushed medication over the food (1, 32). While this practice aims to ensure residents receive necessary medications, there are also potential problems with this practice (4). Modifying a commercially available medication may lead to (i) increased toxicity, e.g. crushing an extended-release solid dosage form leads to dose dumping; (ii) undesirable side effects; (iii) decreased efficacy, e.g. crushing an enteric coated tablet may result in destruction of the active ingredient in the acidic environment of the stomach; (iv)

unpalatability, resulting in poor patient compliance; (v) instability of the medicine, affecting the rate of drug absorption; and (vi) create potential hazards to health care workers, e.g. crushing cytotoxics (1, 4, 5).

The processes by which medicines are modified in these facilities are also a cause for concern. In a study in South Australia (5), at least one medication was modified in 34 % of the 1207 occasions of medication administration observed within ten residential aged-care facilities. In all occasions where more than one medicine was modified, they were crushed together within the same vessel. In 59 % of occasions where the same vessel was shared amongst residents, the vessel was not cleaned between residents and in 70 % of cases where medicines were modified, spillage, and thus potential loss of dosage, was observed. The administration of the crushed medicines then poses a further concern, as in the majority of cases, the crushed medication was mixed in a small medication cup with a soft medium such as jam, custard or fruit. This raises questions as to the physicochemical stability of the active ingredient in the food medium, especially in the case of acid-labile active ingredients. In 2 % of the observations, the crushed medications were sprinkled over the resident's meal, questioning the dosage (5). In a study (6) involving 540 nurses (out of a potential 763) employed in nursing homes in England, 40 % admitted to crushing tablets every drug round, 29 % every day and 12 % at least every week. All of the tablets that the nurses admitted to crushing were available to be administered by other routes, in dispersible formulations or as a liquid. Reasons for crushing tablets were listed as "the GP tells me to" (58 %) and that the GP would be concerned about the cost of changing to a liquid formulation (60.9 %). Although the cost of alternatives is a justifiable concern, it must be viewed in the contexts of patient safety and professional liability (6).

The practice of crushing tablets may breach legal and professional requirements (33, 34). The important legal issues related to the act of tablet crushing and capsule opening are outlined by Wright (6) as follows: (i) the opening of a capsule or crushing of a tablet before administration will in most cases render its use to be "unlicensed". Consequently the manufacturer may assume no liability for any ensuing harm that may come to the resident; and (ii) under the Medicines Act 1968 only medical and dental practitioners can authorise the administration of "unlicensed" medicines to humans. It is, therefore, strictly illegal to open a capsule or crush a tablet before administration without the authorisation of the prescriber. When a medicine is authorised to be administered "unlicensed" by a prescriber, a percentage of liability for any harm that may ensue will still lie with the administrating nurse. The balance of this liability would be assessed in a court of law on an individual case basis (6).

Oral liquid preparations for use in enteral feeding

There is a growing interest in enteral feeding as a means of delivering medications and new feeding tubes are being designed in order to share the capacity for medication delivery (33). Although the newer feeding tubes share the capacity for medication delivery, their use for the administration of drugs may induce intolerance and/or result in less than optimal drug absorption, for example: (i) the bioavailability of the drug may be altered, resulting in unpredictable serum concentrations or tube occlusion; (ii) drugs may bind to the enteral feeding tube, reducing drug absorption; (iii) crushed tablets can block the enteral tube requiring it to be replaced and (iv) there may be interactions between the feed and certain drugs, such as the metal ions in antacids binding to the protein in the feed and subsequently blocking the tube (33, 35). The British Association for Enteral and Parenteral Nutrition (BAPEN) has published guidance on the safe administration of medicines via enteral feeding tubes (36). Liquid rather than solid medicines should always be administered to patients being fed by the enteral route.

LITERATURE REVIEW OF EXTEMPORANEOUSLY PREPARED ORAL LIQUID DOSAGE FORMS

A review protocol was developed with data identified from MEDLINE, EMBASE, Informit, reference texts related to the field, reference lists of articles and abstracts from conference proceedings. Searches were current as of September 2006.

This review presents 83 examples (Table 1) of oral liquids in practice, prepared

by modification of commercial medications, including the reasons, methods, excipients and packaging for the extemporaneous preparation and the outcome of the chemical and physical stability studies conducted. This review considers only those liquid dosage forms prepared from commercially available dosage forms as this is the situation most commonly encountered in the practice of pharmacy. Table 2 shows the contents of the various proprietary vehicles utilised to prepare the extemporaneous mixtures shown in Table 1.

Only those preparations that included chemical stability assessment via a stability-indicating high performance liquid chromatography (HPLC) method were reviewed and drugs were considered stable if they retained ≥ 90% of the initial drug concentration. The reason for this is best demonstrated by the results of study by Carlin et al (37) on the stability of isoniazid (INH) in INH syrup. Hydrazine, a known carcinogen and one of INH's principal degradation products, is also an amine and thus not distinguished from parent INH. The inadequacy of the then current compendial assay in failing to distinguish between INH and hydrazine prompted Carlin et al (37) to assess the stability of commercial INH syrup stored under various conditions over a 4-month period. At 0 ºC, no hydrazine was detected over the storage period, however, decomposition to hydrazine was observed at ambient temperature with a 5.5 – 6.0 fold increase in decomposition rate when the storage temperature was raised to 40 ºC. The formation of hydrazine was linear with time.

Where more than one stability-indicating study had been conducted for each API and demonstrated similar results, only the most recent study is reported in the table. Prior studies to those presented in Table 1, that (i) include chemical stability assessment and (ii) are prepared by modifying an existing commercial medication, have been performed on the following API's: acetazolamide (38, 39), allopurinol (40), azathioprine (40), baclofen (41), bethanechol chloride (42, 43), captopril (44), cisapride (45, 46), clonazepam (47), diltiazem hydrochloride (48), enalapril maleate (49, 50), famotidine (51), flecainide acetate (52), flucytosine (53, 54), hydralazine hydrochloride (55), hydrocortisone (56), itraconazole (57), labetalol hydrochloride (58), metoprolol tartrate (59), metronidazole (60), midazolam (61-64), mycophenolate mofetil (65, 66), nifedipine (67), norfloxacin (68), omeprazole (69), procainamide hydrochloride (70, 71), pyrazinamide (72), rifampin (73-75), sotalol (76), spironolactone (59, 77-79), tramadol (80), ursodiol (81) and verapamil hydrochloride (82).

The highlighted (shaded) areas in Table 1 indicate those preparations (6 of the total 83) with stability concerns and are further reviewed in the discussion.

DISCUSSION OF STABILITY CONSIDERATIONS IN THE PREPARATION OF ORAL LIQUID DOSAGE FORMS

Of the liquid dosage forms reviewed in the literature, stability was considered to be unfavourable for only 6 of the 83 dosage forms – a small percentage, 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.

Captopril liquid dosage forms

The formulation of captopril, used to treat hypertension and congestive heart failure in infants and young children, in a liquid dosage form from commercially available tablets, has proved problematic with many and varied results reported in the literature (77, 138-140). Utilising stability data in the literature that captopril oxidation yields captopril disulphide, Nahata et al (44) decided, in addition to investigating the stability of captopril in water and syrup, on the inclusion of the antioxidant, sodium ascorbate in distilled water. For these researchers the application of existing knowledge on the susceptibility of captopril to oxidation allowed them to extend the shelf-life of the extemporaneously prepared captopril mixture (in distilled water) from 14 days at 4 ºC and 7 days at 22 ºC to 56 days and 14 days respectively (in distilled water and sodium ascorbate). This confirms the need for the pharmacists to utilise their understanding of

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?				
Acetazolamide (53)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 25 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Optimum pH 4-5.
Allopurinol (53)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 20 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Alprazolam (83)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 1 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Stability in the vehicles tested may be partly attributed to the drug's poor aqueous solubility.
Amiloride hydrochloride (84)	1a	2d	2 vehicles: Glycerin BP 40 % w/v and sterile water; Glycerin BP 40 % w/v, sterile water and 0.1% Compound hydroxybenzoate solution APF.	3d (amber)	4a. 1 mg/mL mixture, with or without preservatives, stored in the dark was stable for 21 days at 5 ºC and < 7 days at 25 ºC. Mixtures prepared from pure powder are stable for 60 days at 25 ºC.	Mixtures prepared from pure powder were more stable than those prepared from tablets.
Aminophylline (85)	1d	2a,b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3a (amber)	4a. 3 mg/mL suspension was stable for 91 days at 4 and 25 ºC; 21 mg/mL suspension was stable for 91 days at 25 ºC.	21 mg/mL suspension was not stable when stored at 4 ºC; white crystals formed that were not redispersible.
Amiodarone (86)	1a	2a,b	Vehicle: Simple syrup NF, methylcellulose, distilled water.	3a,b	4a. 5 mg/mL mixture was stable for 91 days at 4 ºC and 42 days at 25 ºC.	
Azathioprine (53)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 50 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Baclofen (87)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF:	3c (amber)	4a. 10 mg/mL mixture stored in the dark was stable for 60	

Table 1 continued						
			Ora-Plus; and cherry syrup.		days at 5 and 25 ºC.	
Bethanechol chloride (88)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 5 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Captopril (87)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 0.75 mg/mL mixture stored in the dark in was stable for less than 10 days at 5 and 25 ºC in the 1st two vehicles and only stable for 2 days in cherry syrup under the same conditions.	In aqueous solution captopril undergoes an oxygen-facilitated first-order oxidation by free radicals. Antioxidants (sodium ascorbate), decrease oxidation of captopril (44).
Chloroquine phosphate (83)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 15 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Drug has a bitter taste.
Cisapride (83)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 1 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	pH must be adjusted (sodium bicarbonate) to neutral.
Clonazepam (53)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 0.1 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Clonazepam must be prepared as a suspension, since in solution it adsorbs to polypropylene/ PVC.
Clonidine hydrochloride (89)	1a	2d	Vehicle: Purified Water USP, Simple Syrup NF.	3a (amber)	4a. 0.1 mg/mL suspension stored in the dark was stable for 28 days at 4 ºC.	Similar results were obtained from a solution prepared in the same vehicle with pure drug powder.
Dantrolene (22)	1b	2d	2 vehicles: consisting of citric acid monohydrate, water, syrup BP, with and without 0.15% w/v methyl hydroxybenzoate.	3d (amber)	4a. 5 mg/mL suspension, with or without preservatives, stored in the dark was stable for 150 days at 5, 25 and 40 ºC.	The presence of excess citric acid in the formulation ensures dantrolene sodium is converted to the insoluble free acid. Suspension has a high

Table 1 continued

						viscosity when stored at 5 ºC.
Dapsone (90)	1a	2a,b	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and simple syrup NF, citric acid, distilled water.	3c (amber)	4a. 2.0 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	Slight yellow colouration was observed from day 28 at 25 ºC.
Diltiazem hydrochloride (87)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 12 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Optimum pH ~5. Choice of sugars as excipients greatly influences drug stability (48).
Dipyridamole (87)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 10 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Dolasetron mesylate (91)	1a	2d	2 vehicles: 1:1 Ora-Plus: (8:1.5 Simple syrup NF: strawberry fountain syrup); and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 10 mg/mL suspension was stable for 90 days at 3-5 ºC and 23-25 ºC.	2nd vehicle is sugar-free and useful for patients on a ketogenic or diabetic diet.
Domperidone (92)	1a	2a,b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 1 and 10 mg/mL suspensions were stable for 91 days at 4 ºC and 25 ºC.	
Enalapril maleate (83)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 1 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Optimum pH ~3.
Etoposide (93)	1d	2a	Vehicle: 0.9% sodium chloride injection.	3f	10 mg/mL mixture was stable for 22 days at ~22 ºC.	
Famotidine (94)	1a	2e	Vehicle: Water for Irrigation USP, 1:1 Ora-Sweet: Ora-Plus. pH 5.8.	3c (amber)	4a. 8 mg/mL mixture stored was stable for 95 days at 23-25 ºC.	Stability is pH dependent.
Flecainide acetate (87)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 20 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Fluconazole (95)	1a	2b,c	Vehicle: deionised water.	3a	1 mg/mL mixture stored in the dark was stable for 15 days at 4, 23 and 45 ºC.	
Flucytosine (96)	1b	2d	2 vehicles: 1:1 Ora-Plus:	3b (amber)	4a. 50 mg/mL suspension was	

Table 1 continued						
			(8:1.5 Simple syrup NF: strawberry fountain syrup); and 1:1 Ora-Sweet SF: Ora-Plus.		stable for 90 days at 3-5 ºC and 23-25 ºC.	
Gabapentin (97)	1b	2a,b	2 vehicles: 1:1 Simple syrup NF: 1% methylcellulose; and 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 2.0 mg/mL suspension was stable for 91 days at 4 ºC and 56 days at 25 ºC.	
Ganciclovir (98)	1b	2b	2 vehicles: Ora-Sweet; and Ora-Sweet SF.	3c (amber)	4a. 100 mg/mL suspension was stable for 123 days at 23-25 ºC.	Sugar-free formula useful since ganciclovir has a diabetogenic effect.
Granisetron (99)	1a	2a	2 vehicles: 1:1 Simple syrup NF: 1% methylcellulose; and 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 0.05 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	
Hydralazine hydrochloride (83)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 4 mg/mL mixture stored in the dark was stable at 5ºC for only 1 and 2 days in vehicles 1 and 2 respectively. No stability was observed for cherry syrup.	Sugars have deleterious effect on the drug. The tablets used in this study contained lactose.
Hydrocortisone (100)	1a	2a	Vehicle: Polysorbate 80, sodium CMC, syrup BP, methyl- and propyl-hydroxybenzoate, citric acid monohydrate and water (Apparent pH ~3.4).	3d (amber)	4a. 2.5 mg/mL suspension stored in the dark was stable at 5 and 25 ºC for 90 days. Uniformity of dose was confirmed.	Maximum stability at pH 3-4 (citric acid used to lower pH). Mixtures prepared from pure powder were more stable than those prepared from tablets.
Isoniazid (101)	1a	2a	Vehicle: Purified water BP, citric acid, sodium citrate, glycerol, compound hydroxybenzoate solution APF.	3a (amber)	4a. 10 mg/mL mixture stored in the dark showed > 10 % loss of active within 3 days at 4 and 25 ºC. A mixture prepared with pure drug powder was stable for 30 days at 4 and 25 ºC.	An excipient (lactose) in the tablet caused rapid degradation of isoniazid.
Isradipine (102)	1b	2b,c	Vehicle: Simple Syrup NF, Glycerin USP (wetting agent).	3a (amber)	4a. 1 mg/mL suspension was stable for 35 days at 4 ºC.	Similar results were obtained from a

Table 1 continued

						suspension prepared in the same vehicle with pure drug powder.
Itraconazole (103)	1b	2a,b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 20 mg/mL suspension was stable for 56 days at 4 and 25 ºC.	
Ketoconazole (104)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 20 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Labetalol hydrochloride (82)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 40 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Optimum pH 3-4.
Lamotrigine (25)	1a	2a,b	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3c (amber)	4a. 1 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	2nd vehicle is sugar-free and useful for patients on a ketogenic or diabetic diet.
Lansoprazole (105)	1b	2d	Vehicle: 8.4 % sodium bicarbonate injection solution USP.	3f (amber)	4a. 3 mg/mL suspension was stable for 14 days at 4 ºC and 8 hours at 22 ºC. Microbiologically stable; formulation prepared in a vertical flow laminar air hood.	The vehicle decreases gastric acid degradation of the drug and prevents clogging of feeding tubes. Suspension became a thick paste when stored at 22 ºC.
Levodopa-Carbidopa (15)	1a	2a,b	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet: Ora-Plus and 2 mg/mL ascorbic acid.	3b (amber)	4a. 5 and 1.25 mg/mL (levodopa: carbidopa) suspension was stable for 28 days at 25 ºC and 42 days at 4 ºC in the 1st vehicle; and 14 days at 25 ºC and 28 days at 4 ºC in the 2nd vehicle.	Samples became darker yellow in colour during storage at 25 ºC.
Levofloxacin (8)	1a	2d	Vehicle: 1:1 Ora-Plus: Strawberry Syrup NF.	3b (amber)	4a. 50 mg/mL suspension was stable for 57 days at 3-5 and 23-25 ºC.	Drug has a bitter taste.
Levothyroxine sodium (106)	1a	2a	Vehicles: 40 % glycerol; and 40 % glycerol with	3d (amber)	4a. 25 μg/mL suspension stored in the dark was stable	A solution prepared in the same vehicles with

Table 1 continued			methylhydroxybenzoate solution APF.		for 8 days at 4 ºC in the 1st vehicle. The acidic preservative in the 2nd vehicle caused increased degradation (degradation increases at lower pH).	pure drug powder showed increased degradation.
Lisinopril (107)	1a	2a,b	Vehicle: Bicitra, purified water and Ora-Sweet SF.	3c (amber)	4a. 1 mg/mL mixture was stable for 28 days at 25 ºC. Microbiologically stable.	Bicitra used to control pH to maintain efficacy of a preservative in Ora-Sweet SF.
Metolazone (104)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 1 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Metoprolol tartrate (82)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 10 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Mexiletine (108)	1b	2a,b	2 vehicles: distilled water; and sorbitol.	3b (amber)	4a. 10 mg/mL suspension was stable for 70 days at 25 ºC and 91 days at 4 ºC in distilled water; and 14 days at 25 ºC and 28 days at 4 ºC in sorbitol.	
Midazolam (109)	1d	2a	Vehicle: Simple syrup USP, pure orange extract, red and yellow food colour, distilled water.	3d.	4a. 0.35, 0.64 and 1.03 mg/mL solutions were stable for 120 days at 23 ºC.	Drug has a bitter taste.
Mycophenolate mofetil (110)	1b	2a,b	Vehicle: Ora-Plus, 0.4 % artificial cherry flavouring, FD&C Red No. 40, aspartame 3mg/mL.	3e (amber)	4a. 100 mg/mL mixture was stable for 120 days at 23-25 ºC.	Vehicle is sugar free. Refrigerate product to preserve cherry odour.
Naratriptan hydrochloride (111)	1a	2b	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and Syrpalta.	3c (amber)	4a. 0.5 mg/mL mixture was stable for 90 days at 4 ºC and 7 days at 23 ºC in the 1st two vehicles. An adequate	

Table 1 continued

					suspension was not achieved with Syrpalta.	
Nifedipine (112) (113)	1a	2c	Vehicle: Autoclaved 1.0 % hypromellose.	3f	4a. 1 mg/mL suspension stored packed in a black, plastic bag was stable for at least 21 days at 6 and 22 ºC. pH, viscosity, density, osmolality and surface tension unchanged. Microbiologically stable.	Significant photodegradation after only 3 hours storage if not protected from light. Formulation is used for nasogastic medication.
	1c	2a	2 vehicles: 13:1 Simple syrup NF: 1% methylcellulose; and 1:1 Ora-Sweet: Ora-Plus.	3b	4a. 4 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	
Norfloxacin (114)	1a	2d	Vehicle: 1:1 Ora-Plus: (8:1.5 Simple syrup NF: strawberry fountain syrup).	3b (amber)	4a. 20 mg/mL suspension was stable for 56 days at 3-5 ºC and 23-25 ºC.	2nd vehicle is sugar-free and useful for patients on a ketogenic or diabetic diet.
Omeprazole (105)	1b	2d	Vehicle: 8.4 % sodium bicarbonate injection solution USP.	3f (amber)	4a. 2 mg/mL suspension was stable for 45 days at 4 ºC and 14 days at 22 ºC. Microbiologically stable; formulation prepared in a vertical flow laminar air hood.	The vehicle decreases gastric acid degradation of the drug and prevents clogging of feeding tubes.
Ondansetron (27)	1a	2a	3 vehicles: Ora-Sweet; Ora-Sweet SF; and Syrpalta.	3b (amber)	4a. 0.8 mg/mL mixture was stable for 42 days at 4 ºC.	
Pantoprazole (115)	1a	2d	Vehicle: Water for Irrigation USP, 8.4 % sodium bicarbonate.	3c (amber)	4a. 2 mg/mL mixture was stable for 62 days at 2-8 ºC.	Degradation increases with decreasing pH.
Pentoxyifylline (116)	1a	2a,b	Vehicle: Distilled water.	3a,b (amber)	4a. 20 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	Crushing an extended release tablet may modify the drug's pharmacokinetic properties. Drug has a bitter taste in water.

Table 1 continued						
Phenoxy-benzamine hydrochloride (117)	1b	2a	Vehicle: Syrup, 0.15 % citric acid, 1 % propylene glycol.	3a (amber)	4a. 2 mg/mL mixture was stable for 4 days at 4 ºC.	Drug decomposes rapidly in pH > 4.5 and in the presence of sugars. Propylene glycol has potential toxicity in paediatric patients.
Procainamide hydrochloride (104)	1b	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 50 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Propafenone (118)	1a	2a	Vehicle: Pomegranate syrup.	3b (amber)	4a. 1.5 mg/mL suspension was stable for 90 days at 3-5 and 15 ± 5 ºC.	
Propylthiouracil (119)	1a	2a,b	2 vehicles: 1:1 Simple syrup NF: 1% methylcellulose; and 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 5 mg/mL suspension was stable for 70 days at 25 ºC and 91 days at 4 ºC.	
Pyrazinamide (88)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 10 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Pyrimethamine (120)	1a	2a,b	Vehicle: 1:1 Simple syrup NF: 1% methylcellulose.	3a,c (amber)	4a. 2 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	
Quinapril (121)	1a	2a	3 vehicles: 15:15:70 Kphos:Bicitra:Ora-Sweet; 15:15:70 Kphos:Bicitra:Ora-Sweet SF; 15:15:70 Kphos:Bicitra:Simple syrup.	3c (amber)	4a. 1.0 mg/mL suspension was stable for 6 weeks at 5 ºC.	Optimum pH 5.5-6.5. The presence of basic excipients in the tablets increased complexity and buffering capacity of liquid formulation.
Quinidine sulphate (88)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 10 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Ranitidine (122)	1a	2d	Vehicles: Simple syrup, distilled water.	3a (amber)	15 mg/mL suspension was stable for 7 days at 25 ºC.	Rapid particle sedimentation – dose to be taken immediately after shaking.
Rifabutin (123)	1b	2a,b	2 vehicles: 1:1 Ora-Sweet:	3c	4a. 20 mg/mL suspension was	

Table 1 continued						
			Ora-Plus; and cherry syrup.		stable for 84 days at 4, 25 and 30 ºC.	
Rifampin (88)	1b	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 25 mg/mL mixture stored in the dark was stable for 28 days at 5 and 25 ºC.	
Saquinavir (124)	1c	2a	Vehicle: 10% syrup, 0.5 % citric acid, 20 % ethanol. pH 4.	3a (amber)	4a. 60 mg/mL mixture was stable for 30 days at 5 and 25 ºC.	Degradation increases in pH > 4. Ethanol has potential toxicity in paediatric patients.
Sildenafil citrate (125)	1a	2a,b	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Simple syrup NF: 1% methylcellulose.	3b (amber)	4a. 2.5 mg/mL suspension was stable for 91 days at 4 and 25 ºC.	
Sotalol (126)	1a	2a,b	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and 1:2.4 simple syrup: 1% methylcellulose gel.	3a (amber)	4a. 5 mg/mL suspension was stable for 12 weeks at 2-8 ºC and 20-25 ºC.	The 1st two vehicles had superior redispersibility compared to the 3rd.
Spironolactone (104)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 25 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	Optimum pH ~4.5.
Spironolactone with hydro-chlorothiazide (82)	1a	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. Spironolactone 5 mg/mL plus hydrochlorothiazide 5 mg/mL mixture stored in the dark was stable for 60 days at 5 and 25 ºC.	
Sumatriptan succinate (127)	1a	2a,b	3 vehicles: Ora-Sweet; Ora-Sweet SF; and Syrpalta.	3a (amber)	4a. 5 mg/mL suspension stored in the dark was stable for up to 21 days at 4 ºC.	All liquids were free of microbial growth for at least 28 days.
Tacrolimus (23, 128)	1b	2d	Vehicle: 1:1 Ora-Plus: Simple Syrup NF.	3a,b (amber)	4a. 0.5 mg/mL suspension was stable for 56 days at 24-26 ºC.	Note: the drug adsorbs to PVC.
Terbinafine hydrochloride (129)	1a	2a,b	Vehicle: 1:1 Ora-Sweet: Ora-Plus.	3d (amber)	4a. 25 mg/mL suspension was stable for 42 days at 4 and 25 ºC.	

Table 1 continued

Terbutaline sulphate (130)	1a	2a,b	Vehicle: Purified Water USP, Simple Syrup NF.	3a (amber)	4a. 0.1 mg/mL mixture stored in the dark was stable for 55 days at 4 ºC. Microbiologically stable for 35 days.	Similar results were obtained from a solution prepared in the same vehicle with pure drug powder.
Tetracycline hydrochloride (88)	1b	2d	3 vehicles: 1:1 Ora-Sweet: Ora-Plus; 1:1 Ora-Sweet SF: Ora-Plus; and cherry syrup.	3c (amber)	4a. 25 mg/mL mixture stored in the dark was stable for 28 days at 5 and 25 ºC in the 1st vehicle; 10 days at 5ºC and 7 days at 25ºC in the 2nd vehicle; and only stable for 7 days at 5ºC and 2 days at 25ºC in cherry syrup.	This study recommends that tetracycline base powder should preferentially be used in preparing an oral liquid.
Theophylline (131)	2a,b	1a	2 vehicles: 1:1 Ora-Sweet: Ora-Plus; and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 5 mg/mL suspension was stable for 90 days at 23-25 ºC.	Drug was obtained from a 300 mg extended-release tablet.
Tiagabine (16)	1a	2a	2 vehicles: 6:1 Simple syrup NF: 1% methylcellulose; and 1:1 Ora-Sweet: Ora-Plus.	3b (amber)	4a. 1 mg/mL suspension was stable for 42 days at 25 ºC and 91 days at 4 ºC in the in the 1st vehicle and 70 days at 25 ºC and 91 days at 4 ºC in the 2nd vehicle.	
Tramadol HCl-acetaminophen (132)	1a	2d	2 vehicles: 1:1 Ora-Plus: (8:1.5 Simple syrup NF: strawberry fountain syrup); and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 7.5 mg/mL tramadol hydrochloride and 65 mg/mL acetaminophen suspension was stable for 90 days at 3-5 ºC and 23-25 ºC.	2nd vehicle is sugar-free and useful for patients on a ketogenic or diabetic diet.
Trimethoprim (133)	1a	2a,b	Vehicle: 1:1 Simple syrup NF: 1% methylcellulose.	3a,b	10 mg/mL mixture was stable for 91 days at 4 ºC and 42 days at 25 ºC.	Change in pH: ~8.0 to 7.7 at 25 ºC.
Ursodiol (134) (135)	1a	2a,b	2 vehicles: 1:1 Ora-Plus: (8:1.5 Simple syrup NF: strawberry fountain syrup); and 1:1 Ora-Sweet SF: Ora-Plus.	3b (amber)	4a. 50 mg/mL suspension was stable for 90 days at 3-5 ºC and 23-25 ºC.	

Table 1 continued	1b	2a	Vehicle: Glycerin, Ora-Plus and Orange Syrup NF.	3b (amber)	4a. 25 mg/mL suspension stored in the dark was stable for 60 days at 2-6 ºC and 22-23 ºC.	Use of a suspending agent is recommended.
Valacyclovir hydrochloride (136)	1a	2a,b	3 vehicles: Ora-Sweet; Ora-Sweet SF; and Syrpalta.	3a (amber)	4a. 50 mg/mL suspension was stable for up to 21 days in the 1st two vehicles and up to 35 days in the 3rd vehicle at 4 ºC.	All liquids were free of microbial growth for at least 28 days.
Valganciclovir (137)	1a	2b	Vehicle: Water for Irrigation USP, cherry-chocolate syrup. pH adjusted to 3.2 with HCl.	3c (amber)	4a. 90 mg/mL suspension was stable for 125 days at 2-8 ºC.	Optimum pH ≤ 3.5.
Verapamil hydrochloride (24)	1a	2a,b	Vehicle: 1:1 Simple syrup NF: 1% methylcellulose.	3a,b	4a. 50 mg/mL mixture stored in the dark was stable for 91 days at 4 and 25 ºC.	Optimum pH 3.2-5.6.

1a. Tablet modified to an oral liquid mixture (solution/ suspension)
1b. Capsule modified to an oral liquid mixture (solution/ suspension)
1c. Liquid-filled soft gelatin capsule modified to an oral liquid mixture (solution/ suspension)
1d. I/V preparation modified to an oral liquid mixture (solution/ suspension)

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

3a. Glass prescription bottles
3b. Plastic prescription bottles
3c. Polyethylene terephthalate prescription bottles
3d. High density polyethylene prescription bottles
3e. Polyethylene terephthalate glycol prescription bottles
3f. 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.

Table 2. Contents of the various proprietary vehicles utilised to prepare the extemporaneous mixtures shown in Table 1

Proprietary vehicle	Ingredients	Manufacturer/ Supplier
Bicitra	Sodium citrate dihydrate (500 mg/5 mL) and citric acid monohydrate (334 mg/5 mL).	Draxis Pharma, USA
Cherry syrup	Cherry syrup concentrate diluted 1:4 with Simple Syrup, NF as per label instructions. pH 3.2 after dilution. Note: content uniformity of cherry syrup differs between manufacturers.	Cherry syrup concentrate from Robinson Laboratory Inc., San Francisco, USA
Cherry-chocolate syrup	Simple syrup (containing 0.1 % sodium benzoate), artificial cherry flavouring, Hershey's chocolate syrup.	Strong Memorial Hospital, Rochester, USA
Kphos	852 mg dibasic sodium phosphate anhydrous, 155 mg monobasic potassium phosphate, 130 mg monobasic sodium phosphate monohydrate. Yields approximately 250 mg phosphate, 298 mg sodium (13.0 mEq) and 45 mg of potassium (1.1 mEq) per tablet.	Beach Pharmaceuticals, USA
Ora-Plus	Purified water, microcrystalline sucrose, carboxymethylcellulose (CMC) sodium, xanthan gum, flavouring, citric acid, sodium phosphate, simethicone, methylparaben, and potassium sorbate. pH 4.2.	Paddock Laboratories, USA
Ora-Sweet	Purified water, sucrose, glycerin, sorbitol, flavouring, citric acid, sodium phosphate, methylparaben, potassium sorbate. pH 4.2.	Paddock Laboratories, USA
Ora-Sweet SF	Purified water, glycerin, sorbitol, sodium saccharin, xanthan gum, flavouring, citric acid, sodium citrate, methylparaben, propylparaben, potassium sorbate. pH 4.2. Sugar-free.	Paddock Laboratories, USA
Pomegranate syrup	Not known	La Madrileña, Mexico
Strawberry fountain syrup	Not known	Gordon Food Service, Grand Rapids, USA
Syrpalta syrup	Sucrose, purified water, synthetic flavour, certified colour, sodium benzoate, and inert ingredients. pH 4.7.	Humco Laboratory, Inc., Texarkana, USA

mechanisms of degradation in order that these liquid dosage forms can be formulated to minimise risk and optimise stability. Similarly, Allen et al (87) reported on the stability of a captopril mixture prepared from tablets in a 1:1 mixture of Ora-Sweet and Ora-Plus, 1:1 mixture of Ora-Sweet SF and Ora-Plus, and cherry syrup stored in amber, clear polyethylene terephthalate bottles. As expected the results achieved were not superior to those achieved by Nahata et al (44), with stability of 10 days or less achieved. Comment is made regarding the susceptibility of captopril to oxidation and that fact that this reaction is pH dependent. Although it is recommended that captopril be dispensed to patients as a solid dosage form and crushed in liquid prior to administration by a caregiver, it should be noted that the formulation containing sodium ascorbate which is stable for 56 days when stored at 4 ºC is preferable, as the caregiver is required only to refrigerate this liquid dosage form.

Hydralazine hydrochloride liquid dosage forms

A liquid dosage form of hydralazine hydrochloride 4 mg/mL was prepared using commercially available tablets in a 1:1 mixture of Ora-Sweet and Ora-Plus, a 1:1 mixture of Ora-Sweet SF and Ora-Plus, and a cherry syrup stored in amber, clear polyethylene terephthalate bottles at 5 and 25 ºC (83). The hydralazine hydrochloride was found to have limited stability in these vehicles with not even

one day stability achieved at 25 ºC and only one day at 5 ºC. Previous work by Alexander et al (55) resulted in an aqueous formulation containing maltitol, edetate disodium, sodium saccharin, methyl paraben, propyl paraben, propylene glycol and orange flavouring, with acetic acid used to adjust the pH to 3.7, which was only stable for 5 days at 25 ºC, possibly due to an incompatibility between hydralazine and edetate sodium. Further studies were conducted by Gupta et al (141) on aqueous solutions of hydralazine containing various sugars including dextrose, fructose, lactose and maltose, where substantial degradation of the drug was noted. Further research proved that the hydrolysed sucrose in simple syrup caused 93-95 % of the drug to be lost in one day, whereas unhydrolysed sucrose and sorbitol solutions proved to be more appropriate vehicles with 10 % in 7 days and between 4 and 8 % in 21 days at 24 ºC was reported. The problem has arisen in this study by Allen et al (83) due to the fact that tablets containing lactose as the filler have been used in the study, which is capable of forming an osazone, thereby increasing the degradation rate of hydralazine. A similar situation is reported below for the preparation of a liquid dosage form of isoniazid (INH) from INH tablets containing lactose (101).

Isoniazid liquid dosage forms

Due to the fact that an oral liquid of INH for the treatment of tuberculosis is not commercially available, there have been reports on the formulation and stability evaluations of extemporaneously prepared INH mixtures. In a study (101) using commercially available tablets and a formulation based on that in the British Pharmaceutical Codex (BPC) (142) containing citric acid, sodium citrate, glycerol and compound hydroxybenzoate solution APF (Australian Pharmaceutical Formulary), the compounded mixture showed significant degradation (≥ 10 % after 3 days at both 4 and 25 ºC), whereas the control (using pure INH powder) retained the desired stability of > 90 % after 30 days, as specified in the BPC, under identical conditions. A replicate control formulation spiked with lactose, produced statistically similar degradation profiles to that of the compounded mixture. A similar result achieved by Gupta et al (143) for a mixture prepared extemporaneously, containing INH (as a powder), sorbitol, methyl and propyl paraben in water, showed this preparation to be stable at room temperature for 42 days.

INH is susceptible to hydrolysis and oxidation and is known to interact with dosage form ingredients, particularly reducing sugars, to form hydrazones (37, 142, 144). The hydrazone formed by the reaction of INH with lactose (pH 1.0-6.0) is 1-isonicotinoyl-2-lactosylhydrazine (144). In the report by Gupta et al (143), the physical appearance changed from almost colourless to dark brown. Although the BPC claimed 28 days stability for the extemporaneously prepared INH mixture, the use of INH powder, as opposed to INH tablets, was specified, highlighting the importance of stability considerations for any modifications to existing formulae.

Levothyroxine sodium liquid dosage forms

There have been some issues raised recently about the stability of thyroxine (solid state) to light, heat and humidity (145). This has resulted in measures being taken to recommend storage of the tablets at a constant 4-8 ºC. It has been suggested that for children and patients unable to swallow tablets, the tablets should be crushed in 10-20 mL of water, breast milk or non-soybean formula, and the resulting mixture used immediately (145).

In an earlier article by Boulton et al (106), comment was made of the availability of levothyroxine sodium as a lyophilized powder for injection which, although it could be administered orally, was not cost effective. This was suggested as an alternative to crushing tablets prior to administration, which may be a problem due to the number of different dosages required. They suggested the preparation of an oral liquid from powder and tablets with and without methyl paraben as preservative, stored at refrigeration (4-8 ºC), room temperature and 23-27 ºC and, in the dark. Significant degradation was observed in all the formulations studied by this group, with those formulations including the preservative proving to be more unstable than those without the preservative, attributed to the reduction of pH due to the presence of the preservative. Results indicated that levothyroxine sodium in the formulation prepared from tablets without

the preservative is stable for the longest period (8 days at 4-8 ºC) attributed both due to the lack of the preservative and the buffering effect of the tablet excipients.

Phenoxybenzamine hydrochloride liquid dosage forms

Phenoxybenzamine oral liquid, used to treat hypertensive episodes in paediatric patients after cardiac surgery, prepared using the hydrochloride salt (2 mg/mL) in 1 % propylene glycol, 0.15 % citric acid and distilled water, was stable for 7 days at 4 ºC (117). The fact that phenoxybenzamine has been reported to be stable in acidified (ideally between pH 2-3) nonaqueous solutions, but unstable in neutral or alkaline solutions (146), has presented a challenge to the preparation of a liquid dosage form. In addition, the inclusion of syrup to improve palatability reduced the stability of the phenoxybenzamine to 4 days as opposed to the 7 days mentioned when only water was used as the vehicle. This instability may be due to a reaction occurring similarly in the sugar catalysed hydrolysis of penicillins (147). Because of the improved stability of phenoxybenzamine hydrochloride in propylene glycol, it is prepared as a stock solution which is stable for 30 days when stored at 4 ºC and diluted with syrup prior to administration in order to reduce the concentration of propylene glycol delivered. However, on dilution, this mixture is required to be administered immediately as it was only stable for up to 1 hour at 4 ºC.

Tetracycline hydrochloride liquid dosage forms

Allen et al (88) presented a study on tetracycline hydrochloride extemporaneously compounded in an oral liquid using the Ora range and conditions of 5 and 25 ºC. Stability was defined as the retention of not less than 90 % of the original drug concentration. Results indicated that tetracycline hydrochloride 25 mg/mL was stable in Ora-Sweet: Ora-Plus (1:1) for 28 days at both temperatures, in Ora-Sweet SF: Ora-Plus (1:1) for 10 days at 5 ºC and 7 days at 25 ºC, and in cherry syrup for 7 days at 5 ºC and 2 days at 25 ºC. The authors suggest preparation of a suspension formulation through the use of tetracycline base powder which, due to its limited solubility, would improve stability, as opposed to the hydrochloride salt which was used in this case due to its availability in the commercial capsules.

MANAGEMENT OF ORAL LIQUID PREPARATIONS IN PRACTICE

A management flow chart to address the issues of liquid preparations in practice is outlined in Figure 1 and discussed below. It has been recommended (148) for patients who cannot swallow whole tablets or capsules that the most logical approach is to use a liquid formulation of the same medication or to use a chemically different but clinically similar medication available in liquid form. If this is not possible, the pharmacist is usually consulted to determine if a liquid formulation can be prepared extemporaneously.

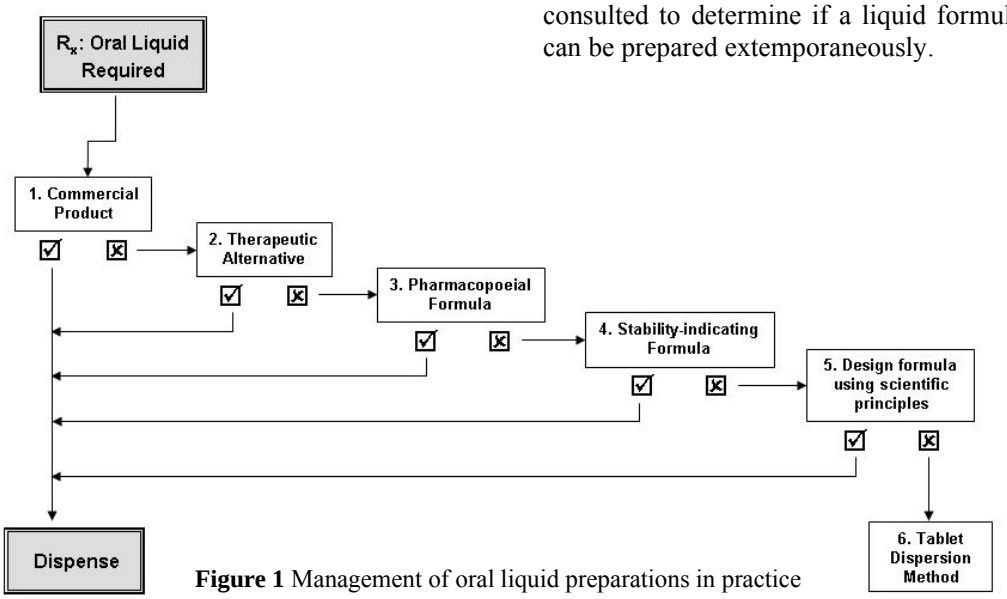

Figure 1 Management of oral liquid preparations in practice

Management flow chart

Step 1: Commercial product

Always consider a commercially available product. This may be an oral liquid, transdermal patch or dispersible tablet (149). As mentioned previously, when crushing tablets, patient safety and contravention of legal and professional standards must be taken into account (6, 33, 150). Licensed liquid formulations of drugs are preferable as their efficacy is supported by clinical trial data, the dose is easy to adapt to weight or body surface area, there are fewer problems with swallowing, and prescribing information is readily available (151).

Step 2: Therapeutic alternative

If no suitable commercial product exists, consider a therapeutic alternative that is available in a suitable dosage form. This must be discussed with the physician.

Step 3: Pharmacopoeial formula

Consult the relevant pharmacopoeial formulary, such as, amongst others, the BP, United States Pharmacopoeia (USP), APF or Martindale. If the formulary requires the API to be in powder form (as opposed to crushing a tablet containing the required API), this must be utilised. If the API is not available in the pure form, a literature search for a suitable stability-indicating formula utilising tablets or capsules for the API must be sought (see step 4 for further detail). It is important to remember that the modification of an existing commercial preparation, such as a solid dosage form, to prepare an oral liquid would be an unlicensed use of the original product and as such would have important legal implications for the pharmacist (6, 33, 34).

Step 4: Stability-indicating formula

A suitable stability-indicating formula should be sought in the literature. Suitable sources include, amongst others, *Allen's Compounded Formulations* (30), *Nahata and Hipple's Paediatric Drug Formulations* (29), *Trissel's Stability of Compounded Formulations* (31), and the current article, which presents a review of 83 examples (Table 1) of oral liquids in practice, prepared by modifying an existing commercial medication, where over 90 % of the preparations are stable and safe.

Step 5: Design formula using scientific principles

If no suitable formula can be found in the literature, the pharmacist will be required to design a formula based on sound scientific principles. This is a lengthy process and would require careful consideration of the following: (i) potential degradation of the API by standard routes such as oxidation, hydrolysis, photolysis or thermolysis; (ii) storage and packaging considerations and assigning a suitable shelf-life to the formulation; and (iii) interactions between excipients and the API, especially if tablets or capsules are utilised as the active ingredient.

The manufacturer of the solid dosage form may also be in a position to provide useful stability information. The following examples illustrate the relative merit of adopting this approach. In a review (152) to identify clinical reports describing alternative methods of administering proton pump inhibitors to patients (i.e. patients with nasogastric, jejunal, or feeding tubes; patients with swallowing disorders; critically ill patients; geriatric patients; and paediatric patients), four basic methods were described, all of which involve modification of the original commercial product: (i) opening capsules and simply flushing intact granules with water; (ii) preparing a sodium bicarbonate-based suspension; (iii) administering intact granules in acidic fruit juices; and (iv) sprinkling intact granules on applesauce and yogurt. All methods used to administer omeprazole were successful in the published trials and reports, however current lansoprazole experience was limited to administration of intact granules in healthy adults (152). The first method found that liberal flushing with water was needed for proper delivery of medication since the granules become soft and sticky on contact with water and although the process is simple, it is time and labour intensive and fluid restricted patients might be excluded from use of this method. Administration of proton pump inhibitor granules in acidic fruit juices is intended to provide an acidic environment to ensure the enteric-coated granules remain

intact until they reach the alkaline duodenal region, thus protecting omeprazole or lansoprazole from destruction in the gastric acid. The manufacturers of omeparazole and lansoprazole have tested the integrity of the enteric-coated granules mixed with various juices, including apple, cranberry, grape, orange, prune, and V-8 and found the integrity of the enteric coating to be maintained for a minimum of 30 minutes (152). Utilisation of sodium bicarbonate-based suspensions is the option most widely described to date, demonstrating advantages in patients with nasogastric, jejunal, or feeding tubes since it is the method least likely to clog tubes and eliminates the problems of intact granules adhering to syringes or tubes during administration with water or fruit juices. In fact, according to a manufacturer of a dolasetron mesylate injection, the injection form may be mixed in apple or apple-grape juice for oral administration in paediatric patients, and the diluted product may be kept for up to two hours at room temperature before use (91).

It would be advantageous for drug companies to provide suitable stability data or perhaps fund relevant stability studies to enable pharmacists to prepare extemporaneous formulations when required with confidence concerning stability (24).

Step 6: Tablet dispersion method

The tablet dispersion method provides an alternative to extemporaneous compounding (3, 153), whereby tablets are placed in a beaker/ cup of water, stirred by swirling the beaker/ cup until they have dispersed, and then administered to the patient. In an Australasian study (153), 258 (51 %) of 509 tablets tested were regarded as dispersible, with a maximum dispersion time of 5 minutes. The tablets were sourced from stock commonly held at an Australian and New Zealand hospital, and controlled release products were excluded from the study. The authors have published (153) the dispersion times of the respective tablets. Similarly, in a study at the University Hospital of Wales (UHW) (3), a poster was produced and displayed in all wards detailing the dispersibility in water of tablets commonly used at UHW. Nurses were instructed to administer the dispersed tablets immediately as stability studies had not been carried out. A consideration, however, is that bitter or unpalatable medications may cause compliance issues (153).

One disadvantage of this method is that the dose has to be prepared at the time of administration by the patient or caregiver, providing a potential for inaccurate dosing. When dispersing tablets in water and taking an aliquot of the dispersion, it is necessary to know whether the medication becomes soluble or the dispersion achieves an adequate suspension to measure an accurate dose (149). There are also many solid dosage forms which should not be crushed. Pharmacists should consult the labelling/ package insert of commercial products to determine which drug products preclude crushing, for example, formulations that are: (i) sublingual/ buccal preparations; (ii) enteric-coated; (iii) extended release formulations; (iv) products with carcinogenic potential since aerosolisation of particles will expose healthcare workers who handle these products; and (v) products that contain drugs that are extremely bitter, irritate the oral mucosa, or contain dyes or inherently could stain teeth and mucosal tissue (148).

Alternatives in current practice

Other options, which may not be recommended by the authors include: (i) mixing solid dosage form with food or juice; (ii) powder packets.

Mixing solid dosage form with food or juice

Crushing a tablet and/or sprinkling the contents of a capsule over food or mixing in a drink may lead to errors in preparation or delivery of doses (14). Many vehicles, such as fruit juices (pH 4-4.5) or cola drinks (pH 2-2.5), are easily accessible to mix the contents of tablets or capsules, however, the physicochemical properties of the drug should be considered in these vehicles. Since these vehicles do not contain any suspending agents, drugs that are insoluble or partly soluble will not be uniformly distributed, leading to inaccurate dosing (97).

The stability and compatibility of various actives from crushed tablets in selected foods and beverages, such as fruit juices e.g. apple, orange, Gatorade Lemon Lime, Ocean Spray Cran-Grape, vegetable juices (V8), soup (Campbell Soup), milk, applesauce, yoghurt,

and chocolate-hazelnut spread has been studied (154-157). However, the process of extracting a drug from a complex food mixture can lead to a non-homogenous mixture and incomplete sampling making the stability assessment and shelf-life difficult to ascertain. Further, the co-administration of medicines with fruit juices, especially grapefruit juice, is known to affect the pharmacokinetic and pharmacodynamic profiles of certain drugs (156, 158-160). There are also difficulties with drug products such as omeprazole capsules, which contain enteric coated beads to prevent acid degradation of the parent compound (105). Since it is common practice to mix the contents of the capsule with fruit juice, apple sauce and other acidic mixers (152), should the enteric coated granules be crushed or chewed during the mixing/ administration process, the active will be subject to degradation prior to reaching the site of action.

Powder packets

Extemporaneous powders have been prepared by redistributing the powder from commercially available crushed tablets or opened capsules into smaller strength capsules or powder papers/ sachets, sometimes after dilution with lactose or similar material (12). This practice has been reported to be inflexible and time consuming (15, 22, 23) and further, usually requires the caregiver to mix the powder form of the drug in a liquid or soft food prior to administration, with the potential for the caregiver to be unable to accurately prepare and administer each dose (24, 25, 123).

Bronzetti et al (161) reported the significant potential for medication error in the provision of paper packets containing incorrect dosages of powder obtained from crushed tablets. It was noted in a number of cases that the amount of active in the powder packet was lower than that prescribed due to a failure to consider the weight of the excipients in the tablet when weighing the crushed tablet powder.

CONCLUSION

Liquid dosage forms are often not commercially available for certain drugs due to many factors including lack of market size and various physicochemical factors which need to be considered. Many drugs widely used in infants and children are not labelled by the FDA for use in paediatric patients and although they can be prescribed justifiably, their optimum dose or duration is often unknown especially during the first few years after their availability in adults (15). Since efficacy and safety of unlabelled drugs has not been adequately studied in the paediatric population, extemporaneous formulations should be used with caution, and clinical experience should be reported in the literature, so that dosage guidelines can be developed for the paediatric population for the optimal use of the drug (16). It is also important to note that the physical and chemical stability of a drug does not necessarily equate with its efficacy and safety in patients (15). Patients, however, should not be denied useful drugs simply because they are not commercially available in a suitable dosage form (108).

The safety, efficacy, and other quality attributes of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation conditions and procedures, and prudent pharmaceutical judgment (162). The pharmacist is also responsible for allocating a justifiable beyond-use date for the compounded product. It is important to clinically monitor patients receiving a new formulation to ensure its efficacy and safety. In addition, studies have emphasized the danger of using kinetic data for the decomposition of a control formulation made from pure drug to predict the stability of an extemporaneous formulation prepared from crushing commercially available tablets (84, 101).

This review provides an extensive survey of the literature and investigation of 83 oral liquid formulations extemporaneously prepared by modifying an existing commercial dosage form. The results demonstrated that a small percentage (7.2 %) of these preparations exhibited stability concerns 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 are able to further minimise the risk involved and thus confidently dispense an oral liquid dosage form.

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