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# 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 not only of the active

## 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

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

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),

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 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.

**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- | 3c (amber) | 4a. 1 mg/mL mixture stored in the dark was stable for | Stability in the vehicles tested may be partly |

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