Managing Extemporaneous Oral Liquids in Practice

Alison Haywood, Beverley Glass

ABSTRACT

Oral liquid preparations are often the dosage form of choice in paediatric and geriatric populations. Many drugs are not available in oral liquid dosage forms because of the complexity of formulating liquids and the small market size. Pharmacists are often challenged with the extemporaneous preparation of oral liquids from commercially available products. Most problems associated with the stability of these preparations have been attributed to interactions between the drug substance and excipients (tablet and formulation) rather than the degradation of the drug substance by standard routes. However, a review of 83 such dosage forms revealed that only 7.2% exhibited stability concerns. To address these challenges pharmacists may consider the management plan for oral liquid dosage forms presented in this paper to ensure the provision of safe, effective and quality drug products to patients.

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INTRODUCTION

Studies have identified that extemporaneously prepared oral liquid formulations present a challenge for hospital pharmacists who are required to provide suitable dosage forms for a wide spectrum of patients. These include paediatric patients, patients who are unable to swallow solid dosage forms, patients who must receive medications via nasogastric or gastrostomy tubes and patients who require non-standard doses that are more easily and accurately measured by using a liquid formulation that allows for the dose to be reliably and reproducibly measured.¹⁻⁹ It is common practice for these liquid dosage forms to be prepared from a commercially available solid dosage form such as a tablet/capsule. Although a number of parameters need to be considered in the formulation of both a stable and bioavailable liquid dosage form, there are limited formulation and stability data available.

PHYSICOCHEMICAL STABILITY

The extemporaneous preparation of oral liquid dosage forms can be complex due to the addition of excipients to improve compliance and/or the stability of the final product and those excipients in the commercial product. The latter excipients may be more problematic as they are often not identifiable by pharmacists. In many cases, the potential interactions between the drug in the commercial product and the excipients, such as the vehicle, preservative, buffering agent, flavouring agent, wetting and suspending agent, viscosity enhancer, storage container, have yet to be established. In addition, studies have emphasised the problems associated with 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 tablets and capsules.^{10,11} Further, drugs may be less stable in solution or suspension than in the solid state. A review of 83 oral liquid formulations extemporaneously

prepared by modifying an existing commercial dosage form revealed that only 7.2% exhibited stability concerns and that the instability was primarily due to interactions between the drug substance and the excipients in the formulation, rather than degradation of the active pharmaceutical ingredient by standard routes (oxidation, hydrolysis, photolysis, thermolysis).¹²

Drug product stability is an important factor in ensuring a successful therapeutic outcome. Drug stability encompasses chemical, physical, microbiological, therapeutic and toxicological stability not only of the drug substance, but when taking account of the excipients, also the drug product.¹³ Stability has been defined as the extent to which a product retains within specified limits and throughout its period of storage and use the same properties and characteristics that it possessed at the time of its manufacture.¹³ Stability of dosage forms is routinely confirmed by the manufacturer, where stability studies on packaged dosage forms are conducted by means of 'real-time' long-term tests and accelerated stability tests at specific temperatures and relative humidity that represent storage conditions experienced in the distribution chain of the climatic zones of the concerned country or region.

Although stability of a dosage form is the responsibility of the manufacturer, the modification of a commercial product, such as a solid dosage form for ease of administration (i.e. crushing a tablet and mixing with a patients' food) or to prepare an extemporaneous oral liquid is an unlicensed use of the original product and may have legal implications for the prescriber, pharmacist and/or healthcare worker.^{7,14,15}

AVAILABILITY

Liquid dosage forms are often not commercially available due to many factors, including small market size and physicochemical factors. Many new drugs used in paediatrics have not been labelled in full by the US Food and Drug Administration (FDA) for use in this population. However, it may be neither practical nor clinically appropriate to restrict drug use in children only to licensed drugs. Health professionals are obliged to treat children to the best of their ability and this invariably involves 'unlicensed' and 'off-label' prescribing.¹⁶ In 1997 new FDA regulations, including special incentives such as patent extension or tax reduction, encouraged manufacturers to study their prescription drugs in paediatric patients. Recently a study quantifying the economic return to industry for completing paediatric exclusivity trials has been reported.¹⁷ It was also shown that one-third of the drugs tested under the FDA's paediatric exclusivity program had different effects in children than in adults. Of the 59 drugs tested, 12 were found to be ineffective in children, 5 required dosing changes, and 9 resulted in new safety information for children. Since the program began, 300 drug studies in children have resulted in 122 drug labelling changes for paediatric use. Of note is the 'black box' warning added to certain antidepressants and a hepatitis drug because paediatric studies indicated increased risk for suicidal thoughts or behaviour.¹⁷ In February 2007 the US Congress debated the renewal of the paediatric exclusivity program. Critics are advocating either eliminating the program or reducing the pharmaceutical patent extensions from 6 to 3 months. Either step could limit the benefits to children since a shortened time of patent extension would reduce the incentive and the number

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of paediatric studies conducted.¹⁸ It has also been suggested that only ‘blockbuster’ drugs will be studied and that drugs providing less income, such as anticonvulsants and hepatitis drugs will not be studied, despite their tendency to be the drugs that children really need.¹⁸ Therefore, limited resources may lead to a lag time between the approved labelling for adults and children and many drugs may not be viewed as important for children at the time of marketing. Thus, extemporaneous oral liquid dosage forms will continue to play an important role in many practice settings, especially clinical paediatrics.

ORAL LIQUID PREPARATIONS IN PRACTICE

Pharmacists have an important role to play in the delivery of safe, effective and high quality drug products. Patients should not be denied useful drugs simply because they are not commercially available in a suitable dosage form. When considering the physicochemical stability of drug substances and the complex design of their subsequent pharmaceutical delivery systems, it can be reasonable to suggest that when confronted with the unavailability of an appropriate commercial drug product, a suitably prepared extemporaneous oral liquid may be the preferred alternative to crushing a tablet and/or sprinkling the contents of a capsule over food or mixing in a drink, as this practice may lead to errors in preparation or delivery of doses.^{2,3,5} More importantly, once patients leave the hospital, continuity of care may be compromised as patients will have to self administer their medication and may adopt a variety of methods and mixers that may affect the stability and efficacy of the drug product. The following practical suggestions are provided to assist pharmacists in managing liquid dosage forms for oral administration in their practice (Figure 1).

Figure 1. Management plan for liquid dosage forms for oral administration in practice

Commercially Available Products

Pharmacists should always consider a commercially available product, however, this may not necessarily be limited to an oral liquid and may include other alternative dosage forms, such as a transdermal patch or a dispersible tablet. If no suitable commercial product exists, a therapeutic alternative that is available in a suitable dosage form may be considered, in consultation with the prescribing doctor. The importation of suitable medicines licensed in other countries may also be considered. Oral administration of injectables is not advised due to the many stability concerns surrounding this practice.¹⁹

Preparation of an Extemporaneous Oral Liquid

A number of parameters need to be considered in the formulation of both a stable and bioavailable liquid dosage form. 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 judgement. Pharmacists are also responsible for allocating a justifiable beyond-use date for the compounded product. It is also important to clinically monitor patients receiving a new formulation to ensure its efficacy and safety. With these measures in place, a suitable formula with a proven stability profile for the preparation of an extemporaneous oral liquid should be sought in the literature, such as *Allen's Compounded Formulations*, *Paediatric Drug Formulations*, *Stability of Compounded Formulations*, *International Journal of Compounding*, *Paddock Laboratories* <www.paddocklabs.com/secundum_artem.html> and the review article showing 83 examples of liquid dosage forms for oral administration in practice, prepared by modifying an existing commercial medication.^{12,20-22} Relevant pharmacopoeial formularies, such as the *British Pharmacopoeia*, *US Pharmacopeia* or *Martindale* may also be used.²³⁻²⁵

If no suitable formula can be found in the literature, pharmacists may be required to design a formula based on sound scientific principles. This is a lengthy process and would require careful consideration of:

- potential degradation of the active ingredient by standard routes such as oxidation, hydrolysis, photolysis or thermolysis;
- storage, preservation and packaging considerations and assigning a suitable shelf-life to the formulation; and
- interactions between excipients and the active ingredient, especially if tablets or capsules are used as the source.

The manufacturer of the solid dosage form may also be in a position to provide useful stability data.²⁶

Tablet Dispersion Method

Due to the inherent time constraints involved in the design and development of stable liquid dosage forms from first principles, pharmacists may need to consider the ‘tablet dispersion method’ as an interim alternative until a suitable formula with a proven stability profile can be devised. This method involves tablets or capsule contents being placed in a beaker or cup of water, stirred by swirling the beaker or cup until they have dispersed, following immediate administration to the patient.^{4,27} In an Australasian study, 258 (51%) out of 509 tablets tested were regarded as dispersible, with a maximum dispersion time of 5 minutes.²⁷ The dispersion times of the tablets studied were published (controlled-release products were excluded). Similarly, in a study at the University Hospital of Wales, a poster was produced and displayed in all wards detailing the dispersibility in water of tablets commonly used at the hospital.

Table 1. Potential risks associated with modifying oral solid dosage forms²⁵

Dosage forms that should not be crushed	Potential risks
Extended or sustained-release	Increased toxicity, adverse effects
Enteric coat protecting an acid-labile active ingredient	Decreased efficacy, altered drug absorption
Film coat protecting a light-sensitive active ingredient	Decreased efficacy, altered drug absorption
Delayed-release coat designed to release the active ingredient at a defined site in the gastrointestinal tract	Decreased efficacy, altered drug absorption
Enteric coat protecting the upper gastrointestinal tract from the active ingredient	Increased local irritant effect
Sugar or film coat disguising a poor tasting active ingredient	Unacceptable taste, poor compliance
Cytotoxic or teratogenic	Potential hazards to healthcare workers

Nurses were instructed to administer the dispersed tablets immediately as stability studies had not been carried out.⁴ When using this method the following should be considered:

- bitter/unpalatable drugs may cause compliance issues;
- doses to be prepared at the time of administration by the patient or caregiver, may provide a potential for inaccurate dosing;
- when taking an aliquot of the dispersion for the purpose of administering a reduced dose, it is necessary to know whether the medication becomes soluble (data on drug solubility may be obtained from Martindale) or the dispersion achieves an adequate suspension to measure an accurate dose; and
- many solid dosage forms should not be crushed/altered. Pharmacists should consult the approved product information and consumer medicine information of commercial products to determine which drug products preclude crushing or altering, to prevent the risks associated with this practice. Further, many Australian hospitals may have their own internal guidelines on tablet crushing and dispersion which may serve as a convenient quick reference for healthcare workers. The *Australian Pharmaceutical Formulary* outlines a six-step process to assist pharmacists in the modification of oral formulations, including information on medications that should not be crushed or altered.²⁸ This information has been adapted and is presented in Table 1.

CONCLUSION

The stability of a drug substance in an extemporaneous oral liquid can be compromised by the addition of excipients. When considering the safety and efficacy of liquid dosage forms prepared extemporaneously, it is important to consider not only the stability of the drug substance but the entire formulation. Pharmacists are to be encouraged that by considering various factors such as drug stability, mechanisms and routes of degradation, potential interactions with excipients in the tablets and/or capsules, and the availability of formula (including methods and materials) for stable liquid dosage forms for oral administration in the literature, they are able to confidently dispense an oral liquid dosage form. However, clinical experience, including an assessment of bioavailability whenever possible, with extemporaneous liquid dosage forms for oral administration should be reported in the literature to further support health professionals in this necessary area of practice. It would be advantageous if this information were disseminated to health professionals to ensure that safe, effective and quality drug products are delivered to patients.

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