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Paediatric mixtures

By Dr Alison Haywood and Professor Beverley Glass

Learning objectives

After reading this article you should be able to:

- Describe when compounding oral liquids to meet specific requirements for children is necessary, and the precautions to be taken by pharmacists in undertaking this task.
- Describe compounded oral liquids, including the components, methods of preparation, packaging, storage and labelling.
- Counsel patients/carers on the appropriate use of these compounded oral liquids.

Competencies addressed:
4.2.2, 5.1.2, 5.1.3, 5.2.7

Rationale for compounding medicines for children

In many practice settings, pharmacists are frequently challenged with providing a suitable formulation for patients who are unable to swallow solid dosage forms. Children often require titratable individualised doses in milligrams per kilogram of body weight and most children under six years of age cannot swallow tablets.[1] There are a limited number of suitable dosage forms commercially available for children, not only due to the size of the market but also the resulting lack of financial viability for the pharmaceutical industry of such dosage forms. In addition there are complexities associated with the formulation of liquid dosage forms due to various physicochemical factors.[2] The preparation of oral liquids extemporaneously by pharmacists, recently reviewed by Nahata[3] and Giam[4], therefore provides an important solution to this problem for paediatric patients. This article will assist in informing pharmacists on the preparation of safe, stable oral liquids for children in those cases where suitable dosage forms are not available.

Compounding oral liquids

Active ingredient

In most practice settings, sourcing the active pharmaceutical ingredient (API) as a powdered raw material is not always practical or possible and

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thus commercially available tablets and capsules are often used in compounding oral liquids. These solid dosage forms however contain many excipients, which although compatible in the solid state have the potential to interact both in solution/suspension, adversely affecting the potency of the active ingredient and thus impacting on the shelf life of the compounded oral liquid. There are also certain tablets or capsule contents that should not be crushed (e.g. sustained-release products). The pharmacist should consult the CMI to determine potential risks associated with crushing the solid dosage form. Further useful resources are detailed in previous articles in this series[5,6] and include the *Clinical Monographs* of the *APF21*,[7] *APAC guidelines for medication management in residential aged care facilities (Appendix F)*,[8] *AMH Aged Care Companion*,[9] *Handbook of Drug Administration via Enteral Feeding Tubes*,[10] and electronic sources such as the list provided by the Institute for *Safe Medication Practice*.[11]

Designing a suitable formula

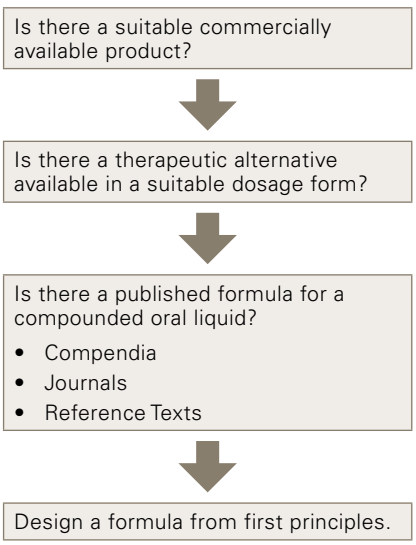
Because of the presence of excipients in tablets and capsules and their potential ability to interact with the active drug in the liquid dosage form, there are problems associated with using stability data for an oral liquid made from powdered raw material and in making the assumption that oral liquids prepared from commercial tablets or capsules will have comparable stability and thus shelf life (see case study).

A review in 2006 of 83 oral liquids extemporaneously prepared by modifying an existing commercial dosage form revealed that only 7.2% of those compounded oral liquids exhibited stability concerns.[13] This review is a useful comprehensive summary of liquid dosage forms prepared from commercially available tablets/capsules and illustrates the low risk associated with these products, if cognisance is taken not only of the active ingredient but all those excipients present in the commercial dosage form. Pharmacists should be encouraged to use the following process to assist in the compounding of safe, stable oral liquids (Figure 1).

Case study: Caution when modifying existing formulae.

A study investigating the stability of an isoniazid (INH) liquid prepared using commercially available tablets and a *British Pharmaceutical Codex* (BPC) formula showed significant degradation of the INH (≥10% after three days at both 4 and 25°C), whereas the control (using pure INH powder) retained the desired stability of >90% after 30 days, as specified in the BPC, under identical conditions.[12] A replicate control formulation spiked with lactose (an excipient present in the commercial tablets), produced similar degradation profiles to that of the compounded oral liquid. INH is susceptible to hydrolysis and oxidation and is known to interact with reducing sugars (e.g. lactose) to form hydrazones. 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. This highlights the importance of considering not only the stability of the active drug but also the potential for interaction with excipients when modifying existing formulae.

Figure 1. Compounding medicines for children



In the absence of existing commercially available dosage forms or therapeutic alternatives in a suitable dosage form, a compounded oral liquid is best prepared by searching for a suitable formula. It is important that the stability of these compounded oral liquids is evaluated by methods of analysis that are '*stability-indicating*'.[14] Examples of journals containing stability-indicating methods of analysis include the *Journal of Pharmacy Practice and Research*, the *International Journal of Pharmaceutical Compounding*, and the *Journal of American Health-System Pharmacists*. However, a suitable search engine will provide results from a wider range of journals. For example, the following are available online (free access):

- *Medline* – www.ncbi.nlm.nih.gov/pubmed
- *Google scholar* – http://scholar.google.com.au/schhp?hl=en&tab=ws

Useful texts include *Allen's Compounded Formulations*,[15] *Paediatric Drug Formulations*,[16] and *Stability of Compounded Formulations*.[17] However, it is important to check whether there is evidence for the stability of these formulations. Should no suitable formula be available in the literature, the pharmacist may design a formula from first principles. Appropriate excipients and methods of preparation are detailed below.

Excipients

Excipients used in extemporaneous oral liquids commonly include suspending agents/viscosity enhancers, sweeteners and preservatives. They may also contain flavours, colours and buffers. Commercial *liquid vehicles* are available that contain a combination of sweeteners, flavours, viscosity enhancers/suspending agents and preservatives (contact your local pharmaceutical supplier for details). Some contain non-nutritive sweeteners and are therefore suitable for diabetic patients. It is not always necessary to colour a product. If a colouring agent is used, it should match the flavour (e.g. red for cherry) and should be used in minimal quantities to produce light-moderate density colours. The TGA has a recently updated list of colourings

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permitted in medicines for oral use.[18] Mixtures may be required to be buffered to an optimum pH, or pH might need to be taken into account when using certain preservatives such as benzoic acid solution which requires an acidic pH to be effective.

Many stability studies are available in the literature that utilise commercial liquid vehicles, thereby making them a convenient resource, especially since various practice settings may not hold a wide variety of excipients in stock. If the commercial liquid vehicle is not suitable, and a formula for a compounded oral liquid supported by a stability-indicating method of analysis is not available, see Table 1 for a general formula (adapted from the APF).[7]

Table 1. General formula for a compounded oral liquid

Ingredient	Amount
API	qs
Suspending agent	qs* (APF21 – p48)
Sweetener/flavour	qs* (APF21 – p55)
Preservative/ preservative solution	qs* (APF21 – p54)
Purified water to	100 mL

*See APF21 for appropriate concentrations of excipients.

Method

Since most oral liquids will be prepared using a commercially available solid dosage form (tablet or capsule) which may not readily dissolve in water-based vehicles, a general method for preparing oral suspensions is described. Particle size reduction followed by the adequate wetting of solids are important steps in the preparation of a good suspension.

1. Crush the tablets in a dry mortar to a fine powder. For capsules, carefully open the capsules and empty the contents.
2. The fine powder should then be wetted with a minimum amount (i.e. enough to produce a thick paste) of a suitable wetting agent (e.g. glycerin) or a portion of the vehicle.
3. After the preparation of a thick paste, the vehicle and any other excipients should be added with constant stirring.
4. The preparation should then be transferred to an airtight medicine bottle with a child-resistant cap and appropriately labelled. Should the active drug or any of the excipients be sensitive to light, a coloured medicine bottle is recommended (note that many colouring and flavouring agents are sensitive to light).

Packaging and storage

Oral liquids should be stored in an airtight container with a child-resistant cap. Should the active drug or other excipients be sensitive to light, a coloured medicine bottle should be used. In the absence of any published stability data, *APF21* recommends an expiry date 28 days from the date of manufacture.[7] Oral liquids should be stored at less than 25°C unless otherwise specified.

Labelling

Compounded products are to be labelled according to regulatory requirements[19] and should include the approved pharmacopoeial name (where applicable) and the name and strength of any preservatives used. The label must also be in accordance with the relevant state law.[7] A complete list of ingredients and their amounts/ proportions should be included when non-pharmacopoeial products are prepared. Ancillary labels should be used to indicate specific storage conditions, provide an expiry date and indicate specific usage conditions. Containers should always be labelled SHAKE THE BOTTLE to ensure even distribution of the drug content throughout the liquid vehicle to ensure an accurate dose is administered.

Quality control and self-inspection

The pharmacist is responsible for ensuring the quality of extemporaneously prepared products, and should verify that products are prepared according to documented procedures and meet product specifications before release to the patient.[7] Self-inspections should also be conducted at regular intervals to identify areas for improvement and the resulting actions should be documented.[7]

Counselling and instructions for carers

- Store the oral liquid as per instructions.
- Discard the preparation after the expiry date (e.g. after 28 days, unless otherwise specified), and if the recommended storage temperature is 2–8°C do not freeze.
- Do not remove all or part of the oral liquid from its original container as storage in a coloured medicine bottle will protect the active drug, if necessary, from light.
- SHAKE WELL before use to ensure that the patient receives an accurate dose.

Key learning points

- Pharmacists should determine whether commercial tablets/ capsules can be used in the preparation of oral compounded liquids.
- Pharmacists should consult reputable sources when compounding oral liquids including compendia (e.g. *APF21*) and journals.
- Due to the potential for interactions of multiple ingredients, KEEP IT SIMPLE and reduce the number of ingredients in oral compounded liquids.

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Questions

A score of 3 out of 4 attracts three quarters of a credit point.

1. Oral liquids are still required to be compounded by pharmacists due to:

a) Paediatric patients being able to swallow tablets and capsules.
b) The lack of availability of commercially available oral liquids.
c) The physicochemical stability of the active drug and the excipients.
d) Increased financial viability to the pharmaceutical industry of manufacturing these dosage forms.
e) b and c.

2. Given the following formula from the APF for baclofen suspension CF-5 mg/mL – what is the role of the glycerin in the formula?

Baclofen	*500 mg*
Glycerin	*4 mL*
Methylcellulose mucilage APF	*25 mL*
Compound hydroxybenzoate solution	*0.8 mL*
Syrup APF to	*100 mL*

a) Active drug.
b) Vehicle.
c) Thickener/suspending agent.
d) Wetting agent.
e) Preservative.

3. Given the formula from the APF for propranolol mixture CF-5 mg/mL – rationalise why sodium benzoate is able to be used as a preservative:

Propranolol hydrochloride	*500 mg*
Citric acid monohydrate	*1 g*
Sodium benzoate	*100 mg*
Syrup	*40 mL*
Purified water to	*100 mL*

a) Sodium benzoate is the sodium salt of benzoic acid and is water insoluble.
b) The pH of the mixture is within an acceptable range for the preservative to be effective.
c) Citric acid is included as a buffer to maintain the pH of the mixture in an acceptable range (acidic).
d) b and c.
e) a, b and c.

4. Labelling and storage requirements for orally compounded liquids are as follows:

a) Storage need not be in an airtight container.
b) Storage should be at less than 35 °C unless otherwise stated.
c) Labels are required to include only the name of the preservative.
d) Storage of all oral liquids should be in an amber bottle.
e) Labelling should always include SHAKE THE BOTTLE to ensure even distribution of the active drug throughout the mixture and that the patient receives an accurate dose.