

Extemporaneous formulations of Oral Liquids

A Guide

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1. Introduction

Pharmacists and paediatricians are often faced with the problem of modifying an oral dose form intended for adult use into a suitable form for paediatric administration. Texts and research papers freely describe paediatric doses without exploring the logistics of dose administration. Tablets and capsules are generally unsuitable for administration to children aged under four years and a suitable tablet strength might not be available for use in older children. The range of commercially available paediatric oral liquids and tablets is narrow because the relatively specialised use of these products makes industrial product development, manufacture and registration financially unattractive. Availability varies between countries and very few products are available in countries which constitute a small market. There are, however, anomalies to this theory in that some oral liquids (for example, captopril liquid, metronidazole suspension and rifampicin suspension) that are not available in North America are freely available in other countries such as New Zealand.

In the absence of a ready-made product a frequent approach by pharmacists is to prepare an oral liquid from tablets, capsules or powdered drug dispersed or dissolved in a suitable base. These are often referred to as extemporaneously prepared formulations and the practice occurs on an international scale. A survey of 210 pharmacists in the USA identified the eleven most frequently compounded preparations and the authors concluded that efforts by manufacturers and professional associations are required to supply pharmacists with information on the compounding and stability of extemporaneous preparations.¹ Stewart and Tucker² surveyed Australian hospitals and showed that 116 drugs were extemporaneously compounded into 270 different formulations for paediatric use. Frequent problems identified in this survey included disguising unpleasant taste, achieving dose uniformity and a lack of chemical and physical stability data. This lack of stability information is a common problem and formularies of extemporaneous formulations have been published in an attempt to provide some guidance on the preparation of paediatric oral liquids. The first widely available book was published in the UK in 1978³ and is mainly a collation of individual

hospitals' formulas and recommendations made by pharmaceutical companies with little reference to published data. This publication is now considered outdated and obsolete. Over the last 20 years researchers have studied the stability of many extemporaneous formulations and these are summarised in three formularies which have been published in North America.^{4,5,6} However, the authors of these publications still describe a significant number of formulations which are not based on previously published data which indicates the requirement for further research. Recently more comprehensive books have been published which give much more detail of published stability studies, physicochemical stability data on each drug and some discussion on alternative methods of preparing paediatric doses.^{7,8}

The formulation of an oral liquid for paediatric use requires careful consideration of many factors to ensure that the product is of optimum quality and efficacy. Compounding an oral liquid from crushed tablets should only be considered if there are adequate stability data and it should be recognised that there are often simpler or more reliable methods of preparing the dose. Before discussing the formulation of oral liquids it is important to briefly consider these alternatives some of which are perhaps under utilised.

2. Alternatives to formulation of oral liquids

(i) An alternative drug which is available commercially in liquid form could be selected.

For example, it is usually preferable to use captopril oral solution rather than prepare enalapril solution from tablets.

(ii) Tablet dispersion

The practice of crushing tablets or opening capsules and adding the powder to a palatable drink or sprinkling onto solid food is a time-honoured alternative, but there are few circumstances when this method is appropriate or necessary. It is difficult to ensure that a complete dose has been taken and the practice of nurses or carers handling powdered drug may present health concerns.⁹ Tablet dispersion is a simpler, more reliable and potentially safer method.^{9,10}

If the tablet disperses in water, it can be dispersed in a small volume and the dose given when a suspension is formed, mixed with a flavoured vehicle if required. Not all tablets disperse readily but some form a suspension in seconds.¹⁰

If the tablet disperses readily and the drug is soluble, dispersing the tablet in a known volume of water allows a fractional dose to be accurately measured with a syringe as in the case of captopril.¹¹ As extraction of soluble drug from the tablet excipients may be incomplete^{12,13} the suspension should be shaken or stirred prior to measuring the dose and not filtered unless it has been established that active drug is not removed. In the case of an insoluble drug, the measurement of a fractional dose by taking an aliquot from a suspension formed in this way cannot be recommended due to probable rapid sedimentation of insoluble drug and resultant dosage inaccuracy. Tablet dispersion may not always be practical for infants when the doses required are the equivalent of small tablet fractions.

(iii) Oral administration of the injection

This is possible for some drugs but there are important factors which must be considered when evaluating whether the injection is suitable for oral use. This can be illustrated with some examples.

- (a) If the injectable form of the drug is the same as the oral form (for example labetalol hydrochloride, ondansetron hydrochloride) it can be assumed that the drug will be absorbed from the injectable formulation. However, as the drug is in solution more rapid absorption and higher peak levels may occur compared to slower absorption from a solid dose form.
- (b) Some injectable drug forms are produced by reaction of the insoluble oral form with sodium hydroxide to give a soluble salt (for example acetazolamide sodium, sodium folate). In the acidic conditions of the stomach the oral form (acetazolamide, folic acid) will be generated.
- (c) The injectable form of drugs which are chemically degraded by gastric acid (for example omeprazole) are unsuitable for oral administration.

- (d) The oral use of the injectable form of a drug which is subjected to extensive first-pass metabolism, resulting in poor oral bioavailability, may be impractical due to the large volume required. For example, a volume of 15 mL (15 ampoules) of 1 mg per mL is required if propranolol injection is used to give an oral dose of 15 mg.
- (e) Drugs such as cefuroxime and enalaprilat which are administered orally as pro-drugs (cefuroxime axetil and enalapril maleate) have relatively poor bioavailability and are not suitable for oral administration.
- (f) Injections may contain excipients and adjuvants that are undesirable in some patients. For example propylene glycol and ethanol.¹⁴
- (g) The cost of using the injectable form orally may be prohibitive. For example, the cost of giving dantrolene injection orally is approximately 60 times the cost (per mg of drug) of using the oral form.

(v) Powder Papers or Repacked Capsules

Fractional doses can be prepared by repacking dosage aliquots of powdered tablets or capsule contents, or mixing with a diluent such as starch or lactose prior to repacking into powder papers or empty capsules. This method can be used for drugs which are unstable in aqueous solution and was used to prepare paediatric doses of captopril before a stabilised solution was made commercially available.¹⁵ These methods can still significantly compromise drug stability and extreme care must be taken in ensuring uniform drug distribution. Further limitations are the time and cost of the operation and inflexibility of dosage. There are few situations where this option is necessary.

3. Preparation of Oral Liquids; Practices and Problems.

If alternatives are not possible or the convenience and flexibility of a ready prepared product is preferred an extemporaneously compounded oral liquid might be considered.

The most frequently used method is to grind the required number of tablets to a fine powder in a mortar and form a slurry by adding a small volume of water. Excipients such as antimicrobial preservatives, suspending agents and flavouring agents are added to make the final product. A frequently used base is a mixture of glycerol or syrup, a suspending agent

such as methylcellulose, and para-hydroxybenzoates (parabens) as a preservative. Other agents sometimes added include alternative solvents such ethanol, particularly when the drug is poorly soluble in water, and buffer systems to provide the optimum pH for drug stability or activity of the antimicrobial preservative. Whilst ostensibly simple, such formulations can be complex comprising a mixture of the base and a suspension or solution (usually a combination of both) of tablet excipients and active drug. If the drug is water soluble there is a temptation to filter out the insoluble tablet excipients to leave a clear solution but filtration can remove significant amounts of drug if extraction from tablets is incomplete.^{12,13} Insoluble tablet excipients are in suspension and may compromise product appearance whereas soluble excipients may reduce drug stability, for example, by altering the pH of the preparation.¹⁶ Thus there may be several advantages in using pure drug powder instead of tablets but the powder may not be easily obtainable.

The expiry date or “shelf-life” of an extemporaneously prepared oral liquid is assigned empirically or based on published information on a particular formulation. A conservative approach must be adopted when assigning an expiry date because of lack of information on drug stability or limitations in either the design or the conclusions of a published report. Also, it may be impractical to entirely reproduce the conditions of a study which was performed in another institution or country under the controlled conditions of an experiment rather than clinical use. Most studies base their expiry date recommendation on chemical stability but do not address possible physical or microbiological spoilage which may be significant during actual use of the product. For these reasons it is the author’s opinion that extemporaneously prepared oral liquids should only be used for a maximum of one month from the date of preparation to minimise any unrecognised product deterioration. Longer expiry dates may be applied if more extensive testing is performed.

Finally, when deciding on a formulation it is important to consider any possible adverse effects of the “inactive” components of the preparation. Sucrose (in syrup) can promote the formation of dental caries, ethanol can cause hypoglycaemia and para-hydroxybenzoates can cause hypersensitivity reactions and exacerbate the symptoms of asthma.¹⁴ It has also been suggested that benzoates and para-hydroxybenzoates can aggravate neonatal hyperbilirubinaemia by displacing bilirubin which is bound to plasma proteins but this effect has not been demonstrated *in vivo*¹⁴ and the amounts present in oral formulations are

unlikely to pose any risk.¹⁷ Limits for the inclusion of ethanol in paediatric formulations have been proposed by the American Academy of Pediatrics.¹⁸

Deterioration of an oral liquid may be due to chemical, physical or microbiological instability which can lead to a sub-therapeutic dose of drug, exposure to toxic degradation products or ingestion of unacceptable numbers of micro-organisms. It is important for pharmacists, clinicians and nursing staff to be aware of potential problems caused by instability to ensure that drug therapy is effective and safe.

Chemical instability

Drugs in extemporaneously prepared liquids may be susceptible to chemical reactions leading to degradation. The most common reactions are hydrolysis, oxidation and reduction.¹⁹ Usually the reaction rate or type is influenced by pH, for example, azathioprine is rapidly hydrolysed to 6-mercaptopurine at alkaline pH but is relatively stable in acidic or neutral conditions.²⁰ Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril,²¹ methyldopa²² or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine.²³ The rate of chemical degradation usually increases with temperature, a factor which is the basis for accelerated stability trials of pharmaceutical formulations. Preparations made from tablets contain excipients such as binders and disintegrating agents in addition to the active drug. These excipients may reduce chemical stability by changing the pH to a value at which more rapid degradation occurs. This probably explains why amiloride solution prepared from pure drug is more stable than an oral liquid prepared from tablets.¹⁶

The drug in the preparation may be totally or partially in solution or predominantly in the solid state as a suspension. Drugs in solution are more susceptible to chemical degradation than drugs in the solid state (ie. suspensions), thus suspensions of acetazolamide and chlorothiazide are more stable than solutions.^{24,25} However it cannot be assumed in all cases that an extemporaneously prepared suspension is more stable than a solution. In a suspension, an equilibrium exists between drug in the solid state and drug in solution and even though the amount of drug dissolved may be minimal the conditions could be optimal

for degradation. Frusemide is a notable example which undergoes hydrolysis in acidic conditions where the solid state is predominant, but is much more stable at alkaline pH where it is totally in solution.²⁶

Microbiological Instability

Microbial growth in an oral liquid may cause foul odour and turbidity and adversely effect palatability and appearance. High titres of micro-organisms may be hazardous to health especially in very young or immunocompromised patients. By-products of microbial metabolism may cause a change in the pH of the preparation and reduce the chemical stability or solubility of the drug. Microbial contamination during preparation must be minimised by using clean equipment, sterile water (Water for Irrigation BP) and avoiding contaminated raw materials and containers. If sodium benzoate or benzoic acid are used as antimicrobial preservatives the final pH must be less than 5 so that the active unionised form is predominant.²⁷ Consequently the drug must also be stable at this pH.

Effective preservative systems require rigorous evaluation which is seldom performed on extemporaneous formulations. Many factors can reduce the effectiveness of the preservative including use of contaminated materials, chemical degradation, binding of preservative to suspending agents or tablet excipients, incorrect storage or unhygienic use of the final product..

Physical Instability

Extemporaneously prepared oral suspensions may be susceptible to sedimentation of insoluble drug causing caking. Difficulty in re-suspending the drug or rapid sedimentation following shaking can lead to erratic dosage measurement as demonstrated with chlorothiazide suspension²⁸ and this inherent problem with extemporaneously prepared formulations is of considerable concern. Some spironolactone suspensions have been reported to be excessively thick and almost un-pourable.²⁹ Refrigeration, whilst usually desirable to maximise chemical stability and reduce microbial growth, can also increase the viscosity of a suspension making re-suspension more difficult³⁰ or cause the precipitation of active drug or preservatives. It is important to consider the effect on pH of all components of the formulation and the possible impact on stability. Syrup, for example, is relatively acidic

and if used in phenobarbitone sodium oral solution it will cause the precipitation of unionised phenobarbitone.

4. Conclusions

The guide (see below) is an attempt to summarise the many complex issues that have been described and to highlight some of the factors for pharmacists and paediatricians to consider in order to optimise drug therapy. Information sources such as specialised formularies, drug stability texts and the advice of pharmaceutical companies are invaluable. Most pharmaceutical companies will attempt to provide stability information and can sometimes recommend a specific formulation. Practitioners must continue to lobby for the development and availability of more paediatric oral liquids and paediatric strength tablets some of which may be obtainable in other countries. In order to make information more accessible investigators of clinical drug use should describe the formulation details of the preparation used in their research. This information is often omitted from the publication and can be extremely difficult to source especially when required rapidly. Investigators engaged in stability studies should aim to make the results of their research universally acceptable by designing simple formulations and avoiding the use of unnecessary or difficult to use ingredients. Valid protocol design for the stability study is essential^{31,32} and ideally the study should be carried out on formulations prepared from pure drug as well as tablets and the pure drug formulation used in practice whenever possible.

Finally, sharing information on paediatric formulations and research collaboration should be further encouraged especially between major paediatric hospitals and research centres to ensure that our patients receive the highest quality drug therapy.

Preparation of a Paediatric Oral Liquid-A Guide

- Consider an alternative drug
- Consider an alternative method, for example, tablet dispersion or oral administration of the injection
- Consult the latest information data-bases and publications. Prepare a formulation according to a published study and follow the conditions of this study as closely as possible. Modifications to published formulations are only appropriate if there are no

detrimental effects on stability. A maximum expiry date of one month from preparation is recommended and liquids without an antimicrobial preservative should be given a shorter expiry date.

- If there are no data from a published study consult pharmaceutical manufacturers, other paediatric hospitals and research centres.
- It may be possible to adapt existing information from drug stability texts (e.g. solubility, pH stability profile) or from the formulation details of the injection or oral liquid available elsewhere.
- Monitor use of the product and observe for any signs of physical instability such as colour change or difficulty in re-suspension.
- Provide information to carers to ensure correct use of the product (e.g. storage conditions, use of an oral syringe, shaking before administration).
- Ensure that formulations details are available to all practitioners involved in the patients care to ensure that the product is consistent in appearance and quality. Prescriptions could contain full details of the formula and hospital pharmacists could provide details to their community colleagues.

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