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Review Article

EXTEMPORANEOUS DOSAGE FORM FOR ORAL LIQUIDS

Vipul P. Patel[1]*, Tushar R. Desai[2], Bindi G. Chavda[3], Ridhi M. Katira[3]

[1]* Department of Pharmaceutics, R.K. College of Pharmacy, Kasturbadham, Rajkot, India

[2] Department of Pharmacology, R.K. College of Pharmacy, Kasturbadham, Rajkot, India

[3] Research Scholar, R.K. College of Pharmacy, Kasturbadham, Rajkot, India

ABSTRACT

Access to a special dosage form of a medication is essential when administration to infants and children and selected other populations is required. Some drugs necessary for pediatric patients are not commercially available in dosage forms appropriate for use in this population. These drugs may be prepared extemporaneously for use in individual patients. Physical and chemical properties of drugs and excipients should be considered when preparing extemporaneous formulations. These formulations, however, may lack studies to document stability, bioavailability, pharmacokinetics, pharmacodynamics, efficacy and tolerability.

Keywords: Extemporaneous dosage form, Paediatric preparation, Paediatric medicines, Licensed liquid, Special products, Extemporaneous preparations, Compounding.

INTRODUCTION

Drug substances are usually administered as part of a formulation in combination with; nonmedical agents (otherwise known as inactive pharmaceutical ingredients or excipients) that have varied, specialized pharmaceutical functions. The proper design and formulation of a dosage form requires consideration of the physical, chemical, and biological characteristics of all drug substances and pharmaceutical ingredients to be used in formulating the product. The drug and pharmaceutical materials utilized must be compatible with one another to produce a drug product that is stable, efficacious, palatable, easy to administer, and well tolerated. The age of the intended patient also plays a role in dosage form design. Infants and children aged ~5 years or younger are unable to swallow a solid dosage form (eg, tablet, capsule). A solid dosage form containing a fixed dose (eg, 250 mg) would also be impractical to use in these patients because the dosage requirements vary based on body weight (eg, milligram, kilogram) or surface area (milligram!meter^2). Thus, pharmaceutical liquids, rather than solid dosage

forms, are preferred for oral administration to infants and young children. A single liquid pediatric preparation may be used for infants and children of all ages, with the dose of the drug varied by the volume administered.[1]

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.[2]

Stewart and Tucker 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.[3]

Lack of Commercial Products and the Implications for Infants and Children

Unless an illness largely affects infants and children, most drugs are not labeled for use in the pediatric population for a variety of reasons. These include relatively small market size (thus limiting return on investment), potential delay in marketing a drug for adults, and perception of greater legal liability and regulatory requirements for conducting studies in children instead of in adults. Consequently, nearly 75% of the drugs available in the United States for adults have not been labeled for use in infants and children (ie, those aged <12 years), even though these drugs may be needed in this population.[4,5] For example, seizure disorders occur in both adult and pediatric patients, but certain drugs-gabapentin, lamotrigine, tiagabine, and topiramate-were not fully labeled or available in a liquid dosage form for use in young pediatric patients (ie, those aged <12 years) at the time of their marketing for adults. Also, sildenafil was found to be effective in adults for the treatment of pulmonary hypertension, but it was not available in a liquid dosage form for use in neonates with this condition. Extemporaneous liquid formulations prepared from solid dosage forms were needed to make these drugs accessible to infants and children. 6 IV drugs (eg, morphine, phenobarbital) marketed for adults are too concentrated for accurate measurement of the small volumes (doses) needed for the treatment of neonates or infants. These drugs need to be diluted to minimize underdosing or overdosing; however, stability and sterility of these extemporaneously prepared formulations for parenteral use must be documented before administration to patients.[6]

When drugs are not commercially available in appropriate dosage forms, options include the following: delaying or omitting potentially effective therapies; us-ing a dosage form intended for adults without alteration; contacting the manufacturer for recommendations; and preparing an extemporaneous formulation, if reasonable, based on data in the literature or in consultation with peers. Examples of drugs not commercially available in suitable dosage form (ie, a liquid formulation) for infants and young children are listed in the table.[7]

Need for Pediatric Drug Formulations

Based on a survey of 57 hospitals, with 36 to 350 licensed pediatric beds, there was a need for >100 liquid formulations for use in pediatric patients. Similarly, a United States

Pharmacopeia (USP) survey identified the need for >70 formulations for oral administration in infants and children (personal communication, Claudia Okeke, PhD, Rockville, Maryland, January 15, 2008). The need is expected to grow because the majority of newly approved drugs are not labeled for use in pediatric patients, and an appropriate formulation usually does not exist unless the drug is approved for that population.[7]

Currently Available Information for Compounding Extemporaneous Formulations

Several hundred different formulations for pediatric use are compounded in various situations, including pharmacies in hospitals, nursing homes, and the community. Some have official monographs in the USP and may be published in the peer-reviewed literature. Before any USP monograph can be developed, however, valid stability studies must be undertaken to establish a beyond-use date for the compounded preparation. Formulations have been published in the professional and peer-reviewed literature.[6] Drops, syrups, and suspensions may be suitable for use in neonates, infants, and young children, while a tablet (eg, regular, chewable, disintegrating) or capsule may be preferable for older children and adolescents. Parenteral and rectal dosage forms can be used in all age groups. Drug absorption and bioavailability, however, may be unpredictable after oral, rectal, or 1M administration of certain drugs, especially among infants.[7]

Pharmaceutical Considerations in Preparing Extemporaneous Formulations

Before the formulation of a drug substance into a dosage form is planned, it is essential that the substance be chemically and physically characterized. Preformulation studies can include physical description, particle size, solubility, pKa, pH, stability, excipients toxicity, and other characteristics that provide the information needed to define the nature of the drug substance. This information then provides the framework for the drug's combination with pharmaceutical ingredients in the development of a dosage form. Understanding the physical description of a drug substance before dosage form development is important. The majority of drug substances used today occur as solid materials. Most of them are pure chemical compounds of either crystalline or amorphous constitution. Physical properties include such characteristics as its physical description, particle size, crystalline structure, melting point, and solubility. Biological properties relate to its ability to reach a site of action and elicit a biological response.[7,8]

Stability

When experience or shelf-storage experiments indicate that a preservative is required in a pharmaceutical preparation, selection of that preservative is based on various factors.

For example, an effective preservative should:

I. Inhibit growth of microorganisms likely to be involved;

II. Be sufficiently water soluble to achieve necessary concentrations;

III. Be in an undissociated form for penetration into microorganisms;

IV. Be nonirritating and nonsensitizing;

V. Have adequate stability;

VI. Be compatible with all other formulation ingredients; and

VII. Not adversely affect the preparation's container or the closure. When compounding, caution must be used to not alter the pH or dilute the preservative below its effective concentration to prevent microbial growth.[9]

The required preservative concentration will vary with the factors of pH and dissociation, as well as with the presence of other formulation ingredients (eg, syrup) with inherent preservative capabilities. The use of syrup contributes to the

preservation of the preparation and may lessen the amount of additional preservative needed in the formulation.[9]

Sterility and Endotoxins

Microbiologic testing for pharmacy sterile compounding may include sterility and endotoxin testing. Preservative effectiveness should also be considered for some preparations. Sterility tests can be conducted using commercial kits (QI Medical, Inc., Nevada City, California) or by developing and validating USP sterility testing protocols, which are more detailed than the commercial sterility test kits. Endotoxin tests can be conducted using commercially available kits (Associates of Cape Cod, Inc., East Falmouth, Massachusetts) or by purchasing the components separately. Endotoxin testing end points can be difficult to interpret, and in-house testing requires training.[7]

Taste, Odor, Palatability and Appearance

The proper selection of taste, odor, palatability, texture, color, and sweetness of a preparation may enhance patient adherence to the agent. Much work has been done and is ongoing on enhancing the palatability of oral drug formulations. The compounder has the option of using commercially available vehicles in which to incorporate the drug or to construct the entire preparation; this would include the use of viscosity enhancers, sweeteners, flavoring agents, preservatives, and colors.[10, 11]

Coloring agents are used in pharmaceutical preparations for purposes of esthetics. Certain agents-sulfur (yellow), riboflavin (yellow), cupric sulfate (blue), ferrous sulfate (bluish green), and cyanocobalamin (red)-have inherent color and are not considered pharmaceutical colorants in the usual sense of the term. Although most pharmaceutical colorants in use today are of synthetic origin, some are obtained from natural mineral and plant sources.[9]

Assurance of Quality and Safety

Testing for Potency, Stability and Sterility

A quality assurance program in compounding pharmacies includes some level of testing for finished compounded preparations. It is important for the compounder to understand pharmaceutical analysis so that valid results are obtained when tests are being conducted, whether they are done in-house or outsourced. It is incumbent on the compounding pharmacist to know the following: (1) when to test; (2) what to test; (3) what method(s) to use; (4) how to interpret the results; (5) the limits of the test; and (6) the importance of analytical testing in the overall quality assurance program in the pharmacy. This does not mean that one must be a pharmaceutical or chemical analyst or a microbiologist, but there should be a basic understanding of both the testing methods that are used and the sample handling requirements so that valid results are ensured. The goal in analytical testing is to produce results as accurately, efficiently, and reproducible as possible. Any analytical method used should be accurate, rapid, reproducible, and specific (stability-indicating). No single analytical method is ideally suited for all drugs; each method has its own strengths and weaknesses. Compounding pharmacies have two options when analytical testing is required. Some analytical methods can easily be performed in-house (in the pharmacy), but some must be outsourced to a contract laboratory. If done in-house, appropriate equipment must be obtained, validated either by the manufacturer before purchase or by the compounder on purchase, maintained, calibrated, and used properly. If outsourced, the compounder needs to determine what to outsource, how to select a laboratory, and how to "test" a laboratory; ongoing relationships should be developed with the laboratories chosen. Contract laboratories should follow USP General Chapter standards by using its official methods and techniques for preparation.[7]

Safety Considerations with Excipients

Although excipients are expected to be pharmacologically inactive, certain patients may experience a variety of adverse effects, ranging from hypersensitivity or allergic reaction associated with a coloring agent in an oral dosage form to intracranial hemorrhage with a benzyl alcohol preservative in an IV dosage form. All sweeteners containing sucrose and fructose may affect blood sugar; sorbitol and xylitol may cause osmotic diarrhea. Lactose should be avoided in patients who are lactose intolerant. Ethanol is a solvent minimally used in oral liquid formulations that has largely been replaced by other excipients. Propylene glycol is commonly used as a solvent in oral, topical, and injectable drugs (eg, phenobarbital, phenytoin, diazepam, lorazepam). This vehicle is especially useful to solubilize drugs with limited water solubility. Patients aged <4 years may accumulate propylene glycol due to decreased metabolism, and those receiving multiple drugs containing this solvent are at high risk of developing central nervous system depression and hyperosmolality. Certain extemporaneously prepared suspensions, without sufficient preservative, may pose risks associated with microbial contamination.[1, 7]

Challenges and Limitations

Lack of Stability/Sterility Studies

The use of some extemporaneous formulations in pediatric patients is based on experience rather than data from specific stability and sterility studies.[5,6] Furthermore, published clinical studies in pediatric patients may also lack information about the dosage forms used in those studies. Standing et al searched 10 highly cited journals (5 adult medicine and 5 pediatric medicine) for studies published over a 2-year period evaluating the use of oral medications in children aged <12 years.[12] They found that <40% of the 76 articles identified provided adequate information regarding the dosage form for the study to be accurately reproduced. In addition, 20% of the articles neglected to provide the formulation used in the study. These results thus question the validity and reliability of pediatric trials where oral dosage forms are utilized. Because highly cited journals have allowed studies with inadequate dosage form information to be published, the investigators hypothesized that less highly cited journals may tend to provide even less specific dosage form information, further decreasing reliability and validity of results. PubMed was searched using the terms administration, and oral or oral medication, limiting those results to the English language, those in children aged 0 to 12 years, and those published in the last 6 years (2001-2006).[13] This produced >650 citations, and the abstracts were analyzed for inclusion into the study. Initial review of the first 100 citations has produced results mirroring the findings of Standing et al and in some instances was worse; only 27% of studies provided adequate formulation information, 52% provided some, and 21% provided none. Interestingly, studies published in pediatric journals were more likely to provide no information than nonpediatric journals. More highly cited journals were no more likely to require authors to provide adequate information on the dosage form used than less-cited journals. Randomized, placebo-controlled, prospective trials did no better at reporting formulations than studies that were less rigorous. Only 43% of publications documented their administration procedure and only 14% documented education if a caregiver or parent was responsible for administration. Fifty-two percent assessed and documented adherence, and only 10% documented palatability and tolerability (taste and acceptance [not adverse effects]). Only 3 citations used extemporaneous preparations, but none have cited stability data. In no instance did impact factor have a statistically significant effect on dosage form reporting. Investigators speculated that results may show a substantial

problem in the pediatric clinical trial literature that could influence pharmacotherapy.[9]

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.[14] Usually the reaction rate or type is influenced by pH, for example, azathioprine is rapidly hydrolyzed to 6-mercaptopurine at alkaline pH but is relatively stable in acidic or neutral conditions.[15] Other factors which may increase the rate of reaction include the presence of trace metals which catalyse the oxidation of captopril.[16] methyldopa[17] or exposure to light which catalyses the oxidative degradation of 6-mercaptopurine.[18] 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.

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.[19,20] However it cannot be assumed in all cases that an extemporaneously prepared suspension is more stable than a solution. In a suspension, 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.[21]

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. 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.[22]

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 suspension 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. Refrigeration, whilst usually desirable to maximize chemical stability and reduce microbial growth, can also

increase the viscosity of a suspension making re-suspension more difficult 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 unionized phenobarbitone.[23-25]

Lack of Bioavailability and Pharmacokinetic /Pharmacodynamic Studies

Bioavailability and pharmacokinetic/Pharmaco-dynamic studies are rarely conducted for most extemporaneously prepared medications. When a tablet or capsulewith regular-release characteristics is used to prepare a suspension, it is assumed that the bioavailability and pharmacokinetics /pharmacodynamics will not be compromised in patients. However, those sustained-release properties can be lost when a tablet is crushed and converted to a liquid dosage form before administration. Bioavailability, pharmacokinetic, and pharmacodynamic studies are unlikely to be performed for most extemporaneous drugs due to lack of financial resources and the complexity of performing these studies at most health care facilities. Thus, treatments involving extemporaneous formulations should be observed to monitor efficacy and tolerability of these products in patients.[7]

Efficacy and Safety Concerns

Extemporaneous formulations have generally not been evaluated in controlled trials to establish effectiveness and tolerability in patients. Because these studies are even more expensive to perform than the bioavailability, pharmacokinetic, and pharmacodynamic studies, they are unlikely to be conducted for the majority of extemporaneous drug formulations. It is most important to monitor patients receiving extemporane-ously prepared medications to assure effectiveness and tolerability. Patients and caregivers should be encouraged to contact health care practitioners to confirm that the desired outcomes were achieved with therapies.[7]

Lack of Funding for Research

Most diseases are more prevalent in adults and thus the drugs are indicated for only this population at the time of approval by the US Food and Drug Administration (FDA). Manufacturers may have less interest in conducting expensive Phase I to III studies for labeling in pediatric patients-especially in neonates, infants, and young children-due to low return on investment. They may also be reluctant to fund studies nfor the development of pediatric drug formulations, as such funding may be viewed by the FDA as promoting a drug's use without conducting efficacy and safety studies in pediatric patients. The manufacturers of generic drugs would have even less interest in supporting such studies by independent researchers. Experience

in the past 20 years has shown that the National Institutes of Health and many foundations may view these studies as "too applied" for consideration of funding, and funding should be provided by the individual drug companies for their specific products. A national professional association in pharmacy defined the need but could not devote financial resources to conduct studies on extemporaneous formulations.[7,10]

Variations in Practice

The need for extemporaneous formulations at various health care facilities may be similar for selected drugs, and yet different drug concentrations, excipients, and methods may be used to prepare certain formulations. This occurs because of a lack of established or "standard" formulations or a lack of information in the literature regarding stable formulations. Lack of information about extended stability creates waste of drugs, increased costs, and inconvenience to patients and caregivers because prescriptions then have to be refilled more than

necessary. Conveniently located pharmacies may not have expertise in preparing extemporaneous formulations, and thus caregivers may have to travel to specialized pharmacies. The need for extemporaneous formulations may be unique at various facilities. In such cases, the facilities would have to make these drugs available in the desired formulation, even though the expertise to do so may not exist. This might include physicians and/or nurses preparing the formulation. If these practitioners are not well versed in the procedures, there is ample room for medication and compounding errors to occur.[7]

Poor Coordination and Sharing of Information

The efforts and activities of various health care facilities in preparing extemporaneous formulations are not generally coordinated. In addition, information and knowledge regarding these formulations may not be widely shared. Although investigators at academic institutions and health care facilities present papers and publish articles about extemporaneous formulations, most pharmacists involved daily with these activities may not do so. Thus, coordination and sharing of information must be improved to decrease duplication of efforts and to increase access to stable extemporaneous formulations for patients.[7]

Reimbursement and Payment Issues

Third-party payors do not always pay for compounded medications. They do pay for compounded medications in the hospital (eg, IV admixtures, pediatric formulations) but not always in the community pharmacy setting. This practice is undesirable for patients in the ambulatory setting, as caregivers must payout of pocket for the prescriptions when they are not covered by insurance.[7]

Adverse-Event Reporting

According to the USP compounding standards, adverse events occurring as the result of a compounded medication should be reported to the USP MEDMARX program. Some individual state boards request that these adverse events be reported to the FDA MedWatch program. However, neither of these programs is mandatory and neither was developed specifically to handle pharmaceutical compounding adverse events; rather, they were designed to handle adverse events from manufactured drug products.[7]

What Is Wrong With Extemporaneous Formulations?

In order to provide liquid formulations to administer drugs with no liquid preparation available, or to overcome „special" supply problems, extemporaneous formulations are needed. They can be prepared by dilution of existing liquid dosage forms (e.g. dilution of the injectable form of clonidine, Table 2) if formulation parameters such as excipients and pH are suitable orally; they can be prepared directly from raw materials/chemicals although there was no example in the cardiovascular therapeutic area. The procedure of crushing tablets and "dispensing/suspending" in water, food or beverages prior to administration is associated with the highest risk of errors in extemporaneous dispensing, mainly because they are difficult to track as there is no record or control of preparation. Extemporaneous preparations tend to have little or no compatibility study back up. Very few well-controlled stability studies are published on in vitro compatibility issues between manipulated solid dosage forms and food/beverages. Studies have been undertaken with drugs for the gastrointestinal system [26,27] (Johnson *et al.*, 2003; Carrier *et al*., 2004), 5HT3 antagonist drugs[28] (Yamreudeewong *et al*., 1995) and labetalol for the cardiovascular system [29] (Nahata, 1991). Standardization of recommendations for suitable alimentary vehicles is highly problematic. For example, manufacturer may recommend that the drug is stable when tablets are dissolved in apple juice [30] (Imatinib SPC,2004), but surely it cannot be

known whether the drug is stable in any apple juice or other juices, whose pH and ingredients may vary significantly between manufacturers and countries. There are few stability studies undertaken on extemporaneous products. In the literature, shelf-life is determined by chemical stability, mainly assessed by HPLC, for specials or some extemporaneous preparations formulated in pharmaceutical vehicles. Vehicles can be commercially available (e.g. Ora®plus, Ora®sweet, Keltrol®) or prepared in the dispensary (e.g. methylcellulose 1%, syrup NF). Mostly, stability testing does not include physical and microbial stability testing and does not mimic the „in-use" stability when the preparation encounters variable temperature and frequent opening during the treatment course. The bioavailability of extemporaneous products can be unpredictable. A gross formulation obtained from crushed solid dosage forms may not be bioequivalent with the dose form swallowed whole. In the past, the priority has been to provide a formulation that children can take rather than a formulation with optimized bioavailability.[31] Notterman *et al.* (1986) described an example of inadequate isoniazid bioavailability of crushed tablets and an extemporaneous preparation made from the injection, compared with a licensed liquid. As mentioned in Table 2, drug solubility is very important to consider in extemporaneous preparation. If the active is not soluble, it can lead to inaccuracy of dosing through a lack of dose uniformity and reproducibility. This is a major consideration when no suspending agents are used, especially when the person administering the dose is inexperienced and the dose is small (Tuleu *et al*., in press). [32] Other problems with extemporaneous dispensing include the expense of some drugs (bosentan, sildenafil,Table 2) and the consequences of production errors, which can be fatal (Anonymous, 2000). [33]

Is Dosing Accuracy A Problem?

Where „special" products are used, there is some degree of certainty that the drug will be present in the stated quantity within the expiry period. The main difference between „specials" and licensed liquids is that their bioavailability usually remains untested. This means that the bioavailability of „specials" may depend on the manufacturing technique used and may differ between manufacturers. There is little incentive for „specials" manufacturers to perform bioavailability/ bioequivalence studies as, without going to the considerable expense of attempting to license the drug, dosing recommendations based on such studies cannot be legally made. Extemporaneous preparation of doses by nurses or carers is probably the least accurate method. The weight of a split tablet can range from 50 to 150% of the actual half-tablet weight[35] (Teng *et al.*, 2002) and accuracy does not seem to be improved by using commercially available tablet cutters (Breitkreutz *et al.*, 1999). [36] Insoluble drugs are often crushed and dispersed in water to give a proportion of the dose. Without the use of suspending agents, this method provides highly variable dosing especially if the dose (volume) is small. Although drug dosing in children is often based on bodyweight, this can be a poor predictor of drug clearance (Anderson *et al*., 1997). [37] It is therefore questionable how much impacting inaccurate dosing will have on clinical outcomes, especially with anti-hypertensive medications where dose is titrated to response. The main problem will be with variability in dosing, which occurs most frequently when solid doses are manipulated immediately prior to administration. Warfarin is available as a special but the expense and short shelf-life along with the drug"s water solubility means that it is usually administered as tablets crushed and dispersed in water. In a cohort study of paediatric patients receiving warfarin therapy, children under one year took significantly longer to achieve the target international normalized ratio (INR), needed more INR tests per month and required more

dose changes per month compared with other age groups. Children under 6 years were more likely to have INRs below the target range[38] (Streif *et al.*, 1999). There are many factors which could explain these differences but one which the authors did not explore was formulation. Unfortunately, no details on the drug formulation were given but it would seem most likely that crushed tablets were used to administer the dose to younger age groups Using an inappropriate formulation leading to inaccurate dosing could have been a factor in these patients requiring more blood tests (potentially traumatic finger/heel pricks) and failing to reach target INR values as quickly. This example highlights the potential problem encountered when narrow therapeutic index drugs are not available in liquid formulation showing that in such situations, dosing accuracy is a problem.

Why Have Formulation Issues Not Been Addressed In the Past?

Drug formulation issues are frequently overlooked in the reports of paediatric clinical trials. One of the core principles in reporting scientific research is to give full details on how the experiment was carried out so that it can be repeated. Clinical trials involving medicines in children routinely fail to do this by omitting information on the drug formulation and how it was administered, impairing the reliability and validity of results and hindering the transferability into clinical practice. In the previous two sections, published trials on nifedipine[39] (Blaszak *et al*., 2001) and warfarin[38] (Streif *et al*., 1999) have been mentioned, neither of which gave full details of the formulation used and how the drug was administered. A study on the use of amlodipine in children with hypertension described how they were administered a weight-specific dose using a powder prepared from crushed tablets (Tallian *et al.*, 1999).[40] The report did not specify how the powder was administered. It is unlikely that each dose of powder was individually weighed out and as amlodipine is only sparingly soluble in water, dispersing the dose in water without using a suspending agent will lead to variable dosing. Another study[41] (Flynn *et al.*, 2000) on amlodipine in children recognized this problem by using a suspension formulated in the hospital pharmacy. These studies represent the variability of formulation and administration information provided in published paediatric clinical trials. The problem is not isolated to cardiology medicines (Standing and Wong, 2004).[42] A review of recent paediatric clinical trials in high impact factor journals[42] (Standing *et al.*, in press) found adequate formulation information is provided in only 37% of reports. Adequate formulation reporting was classified as providing sufficient information for the study to be repeated (formulation and manufacturer stated, where formulation was a tablet/capsule, an account of whether children were able to swallow the dose whole or how an aliquot of the dose was administered). Especially in the case of „special" or extemporaneous preparations, it is vital that a reference on the medicine"s formulation is given, as unlike licensed products, unlicensed preparations may not be bioequivalent between different manufacturers (or between batches). This result suggests that many authors and journal editors do not consider providing formulation information in paediatric clinical trials to be important, when its potential impact on the amount of drug received may have a profoundly negative effect on the reproducibility (reliability) and to a lesser extent validity of the results. In addition to clinical trials frequently not providing formulation information, therapeutic failure can often have a number of explanations. For example, the failure of amiodarone to control a patient"s arrhythmia may be due to a dosing with a proportion of a crushed tablet dispersed in water. Many drugs are sparingly soluble such as amiodarone, nifedipine, in water, in absence of a suspending agent; most of the drug will be in the solid form

at the bottom of the measuring device. Unless the mixture is thoroughly stirred immediately prior to giving the dose, the amount of drug received by the patient is likely to be very erratic[32] (Tuleu *et al*., in press). „Special" and extemporaneous products have almost never been tested for bioavailability and so patients may be under or over dosed compared with a level expected to be achieved by extrapolation data from licensed formulations in adults. It is therefore possible that therapeutic failure or adverse reactions due to overdose resulting from inappropriate formulations go unrecognized by paediatricians and pharmacists caring for the patient. Another important reason for inadequate formulation availability for children is a commercial one. At present in UK, there is no financial incentive for pharmaceutical companies to license paediatric medicines and develop suitable formulations due to the relatively small market and high cost of developing and producing them.

Proposed Solutions and Recommendation[43]

Access to age-appropriate drug formulations is critical to provide effective and well-tolerated medications to patients. As discussed here, there continues to be a need for extemporaneous formulations of brand and generic drugs for neonates, infants, and children. Given the multitude of challenges, we recommend a number of potential solutions.

Most-Needed Formulations

A prioritized list of needed formulations should be developed in consultation with physicians, pharmacists, and nurses at the local, regional, and national levels.

Funding of Centers of Excellence and Independent Research

Mechanisms for funding of studies to develop extemporaneous formulations should be established from local, regional, and national sources. The NICHD may consider funding of "Centers of Excellence," which could work collaboratively to conduct studies for the development of high-priority extemporaneous drug formulations. Individual investigators should also have mechanisms to compete for funding of such studies.

Dissemination of Data

Investigators and pharmacy practitioners involved in the development and use of extemporaneous formulations should share their data and experience with others through presentations at national meetings, publications in peer-reviewed journals, and postings on Web sites. Manufacturers possessing any data on drug stability in extemporaneous formulations should share this information through package information and Web sites. Some drugs (eg, captopril, spironolactone) are available commercially in countries other than the United States; information on preparing these drugs extemporaneously should be shared by the manufacturer.

Monitoring Clinical Effectiveness and Tolerability during Use and Sharing of Experience

Because most extemporaneous drug formulations have not undergone clinical studies, their effectiveness and tolerability should be monitored and studied systematically during clinical usage in patients. This clinical experience should be shared through presentations, publications, and Web sites.[43]

Do Children Need Access to Modified Release Products?

Nifedipine is unlicensed for use in children but is often prescribed for hypertension secondary to renal failure. In adults, short acting nifedipine is not recommended for use in hypertension due to the rapid drops in blood pressure it causes, leading to complications, such as reflex tachycardia (British National Formulary, 2005). The usual recommendation is to give a modified release (m/r) preparation to obviate large changes in blood pressure. However, the only

available m/r nifedipine preparations are in tablet form, and many children are unable to swallow whole tablets. As a result, children are prescribed short-acting nifedipine preparations, which include withdrawing the dose from soft capsules, crushing m/r tablets and using imported drops which have proved to give variable dosing. There is little evidence for the safety of using short-acting nifedipine in children, but a retrospective review did find it effective in producing large reductions in mean arterial blood pressure, albeit giving little information about how doses below 10mg were extracted from the capsules. Serious adverse effects of large decreases in blood pressure in children can include cerebral ischemia particularly when the patient has long-standing hypertension. This, along with a lack of prospectively collected safety data, is the reason that some paediatricians advise against the use of short acting nifedipine outside the specialist hospital environment. Nifedipine provides a prime example of the disparity which exists between medicines for children and adults. Licensing of nifedipine affords adults the benefit of once daily dosing, decreased risk of adverse effects and formalised post-marketing surveillance. Children, treated with the same drug, have to take the dose three times a day, and are placed at potentially increased risk of adverse effects because no m/r formulation is available. So, in answer to the question: do children need access to modified release products; the answer is yes; the challenge being to develop innovative drug delivery methods that children are able to take. Such strategies may include: m/r small platforms (minitablets, minicapsules), trans-dermal delivery (especially for neonates), m/r liquids (nano or microparticles) with suitable polymers.

Will Formulations Improve In the Future?

In September 2004, the European Commission adopted a legislative framework for regulation of medicinal products for paediatric use in order to work towards an ethical, effective and favourable environment for paediatric research and development (Medicines for Children, 2004). These arrangements are similar to the one established in USA during the late 1990s. The key objectives of the EU proposed regulation are to increase the development and authorization of paediatric medicines while ensuring they are subject to high quality research, but that no unnecessary clinical trials are carried out. The proposal also aims to improve the information available on medicines for children.[8]

Key elements in the proposal are[8]:

- A new expert committee within the European Medicines Agency (EMEA) to assess and agree Paediatric Investigation Plans (PIPs) presented by the pharmaceutical industry. A system of free scientific advice will also be provided by the EMEA.
- A requirement at the time of marketing authorization application that data is presented on the drug‟s use in children. A system of waivers and deferrals will ensure the requirements do not delay the authorization for medicines in adults.
- A reward for studying medicines for children of 6 months extension to the supplementary protection certificate; in effect, 6-month patent extension for the product (including adult use). - For off-patent medicines, 8 plus 2 years of data exclusivity on paediatric use of the product for new studies awarded via a Paediatric Use Marketing Authorization (PUMA). These incentives are very similar to those in USA but the EU proposal is more robust as it requires the sponsor to market the paediatric medicine for the approved indication within 12 months, speeding up the availability for patients. It does not distinguish between studies required (with claimed benefit to children) and those requested (with potential benefit to children) as in USA.

- Increased safety monitoring for children‟s medicines (pharmacovigilance).
- A compulsory submission by industry of existing studies in children, an inventory of the EU therapeutic needs of children and an EU network of investigators and trial centers to conduct studies required. The EU proposes a transparent approach to negative outcomes of the trials in children as any results (positive or negative) will be included in a database of ongoing or terminated studies; the results will also be incorporated on the drug label, regardless of whether the indication is approved or not. This awaited legislation is likely to become effective late 2006 and it is hoped that all future medicines for children will have been investigated in children and, where there is an appropriate indication, a licensed paediatric formulation will be produced.

However, delays are anticipated as the Medicines Investigation for the Children in Europe (MICE) fund, equivalent to the National Institute of Health and FDA set up to support old and commercially disregarded drugs in USA, has not yet been sourced. This is a real issue as generics manufacturers do not have substantial resources for research and development beyond equivalence studies. In the meantime, extemporaneous preparation, be it at the bedside, by pharmacists or „special‟ manufacturers will continue to be a major route by which paediatric oral medicines are prepared. As a result of strong national concern in UK (Safer and Better medicines for children, 2004; National Service Framework (Standard 10), 2004), the first edition of the British National Formulary for Children (BNF-C) is due to be published (British National Formulary for children, 2005). It will provide a practical, relevant, authoritative information source and guide prescribing, dispensing and administration of medicines to children up to 18 years of age. By reflecting current evidence on efficacy and safety of drugs within the limits of available clinical trial data, BNF-C will provide practical guidance on the „off label‟ use of medicines.

In addition to legislative and formulary developments,, innovations in pharmaceutical formulations should improve the ease in which children can access medicines. Innovative m/r preparations have previously been mentioned, and the following areas are also ripe for future developments and research:

- New routes of administration such as oraltransmusosal (buccal strips), intra-nasal and transdermal (for neonates mainly).
- More research into alternative safe excipients for children such as natural polymers (e.g. cyclodextrin to mask taste of drugs, improve solubility or protect drugs/patient).
- Children‟s ability to swallow and their preferences need to be investigated. This will direct future formulation research towards (mini) tablets, chewable tablets, dispersible tablets or more oral liquids.

Although new and innovative formulations are urgently needed, work on extemporaneous formulation should not be disregarded. Those findings reflect on numerous problems associated with the lack of suitable formulations for children. This emphasized the difficulty in prescribing and administering cardiovascular drugs as a proof of concept, which can be extended to many other therapeutic areas. In an era of evidence-based medicine, it is unacceptable that drug formulations given to children are not better designed to provide accurate and reproducible dosing. With the expected new European regulations and the obligation of clinical testing on the paediatric population, it will be important that a strategy for paediatric formulation research is put in place. The future of paediatric drug formulations seems bright, but legislation must be supported by innovative research on new and existing delivery methods.[8]

Preparation of an Extemporaneous Preparation-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 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 centers. It may be possible to adapt existing information from drug stability texts (e.g. solubility, 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 careers 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.[44]

CONCLUSIONS

The present article was described a many complex issues that have been described and to highlight some of the factors for pharmacists and paediatricians to consider in order to optimize drug therapy. Information sources such as specialized 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 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 extemporaneous preparation and research collaboration should be further encouraged especially between major paediatric hospitals and research centers to ensure that our patients receive the highest quality drug therapy.

Table 1: Examples of medications not available in a suitable dosage form (eg, a liquid formulation) for infants and young children.[7]

Acetazolamide	Albendazole	Amiodarone	Amitriptyline	Arginine
Biotin	Bupropion	Busulfan	Captopril	Carbenicillin
Cholestyramine	Clindamycin	Clobazam	Clonazepam	Clonidine

Dantrolene	Dexamethasone	Enalapril	Ethambutol	Ethionamide
Famciclovir	Glutamine	Hydroxyurea	Irbesarta	Lansoprazole
Leucovorin	Lisinopril	Lomustine	Mefloquine	Methimazole
Methotrexate	Methylphenidate	Minoxidil	Neomycin	Nicardipine
Nimodipine	Olanzapine	Pancrelipase	Paromomycin	Phenobarbital
Prazosin	Primidone	Probenecid	Procarbazine	Propafenone
Pyridoxine	Riboflavin	Saquinavir	Scopolamine	Sertraline
Sildenafil	Sotalol	Testosterone	Tiagabine	Topiramate
Ursodiol	Verapamil	Vigabatrin	Warfarin	Zinc sulfate

Table 2: Commonly used cardiovascular drugs for which no licensed liquid is available in UK.[34]

Drug	Paediatric License	Remarks
Amiodarone	No	Drug sparingly soluble in water. Special only has 1 month self life. Extemporaneous preparation can be made (suspension from tablets).
Amlodipine	No	Drug sparingly soluble in water. Special only has 1 month shelf life. Crushed tablets suspended in water often used.
Aspirin	No	Very water soluble drugs – use dispersible tablets.
Bosentan	No	Crushed tablets suspended in water, very expensive.
Captopril	No	Solution- must be refrigerated, only 1 month shelf life. Licensed solution in Australia, packed under nitrogen with only one month shelf life once opened. Easy dispersible low strength tablets crushed and mixed in water (these have recently been withdrawn from the market).
Carvedilol	No	Drugs sparingly soluble in water. Special only has one month shelf life. Crushed tablets suspended in water often used.
Clonidine	No	Dilution in water of the injection is often used, must be refrigerated. Special has 1 month shelf life.
Enalapril	No	Drug sparingly soluble in water. Crushed tablets suspended in water often used.
Hydralazine	No	Soluble tablets available. The injection can be diluted and used orally and kept 24 h at room temperature.
Nadolol	No	Drug sparingly soluble in water. Special only has 1 month shelf life. Crushed tablets suspended in water often used. Low strength tablets recently withdrawn in UK.
Nifedipine	No	Drops in macrogol 200 can be imported – Crushed modified release tablets or removal of nifedipine liquid from soft capsules used.

Pravastatin	No	Drugs freely soluble in water, crushed tablets often dissolved in water. Special has 1 month shelf life.
Prazosin	Yes	Manipulated solid oral dosage forms suspended in water.
Ramipril	No	Drug sparingly soluble in water. Crushed tablets suspended in water often used. Special only has 1 month shelf life.
Sildenafil	No	Crushed tablets suspended in water – expensive
Spironolactone	No	Large range of strength available.
Warfarin	No	Drug freely soluble in water, crushed tablets often dissolve in water. Special only has 1 month shelf life

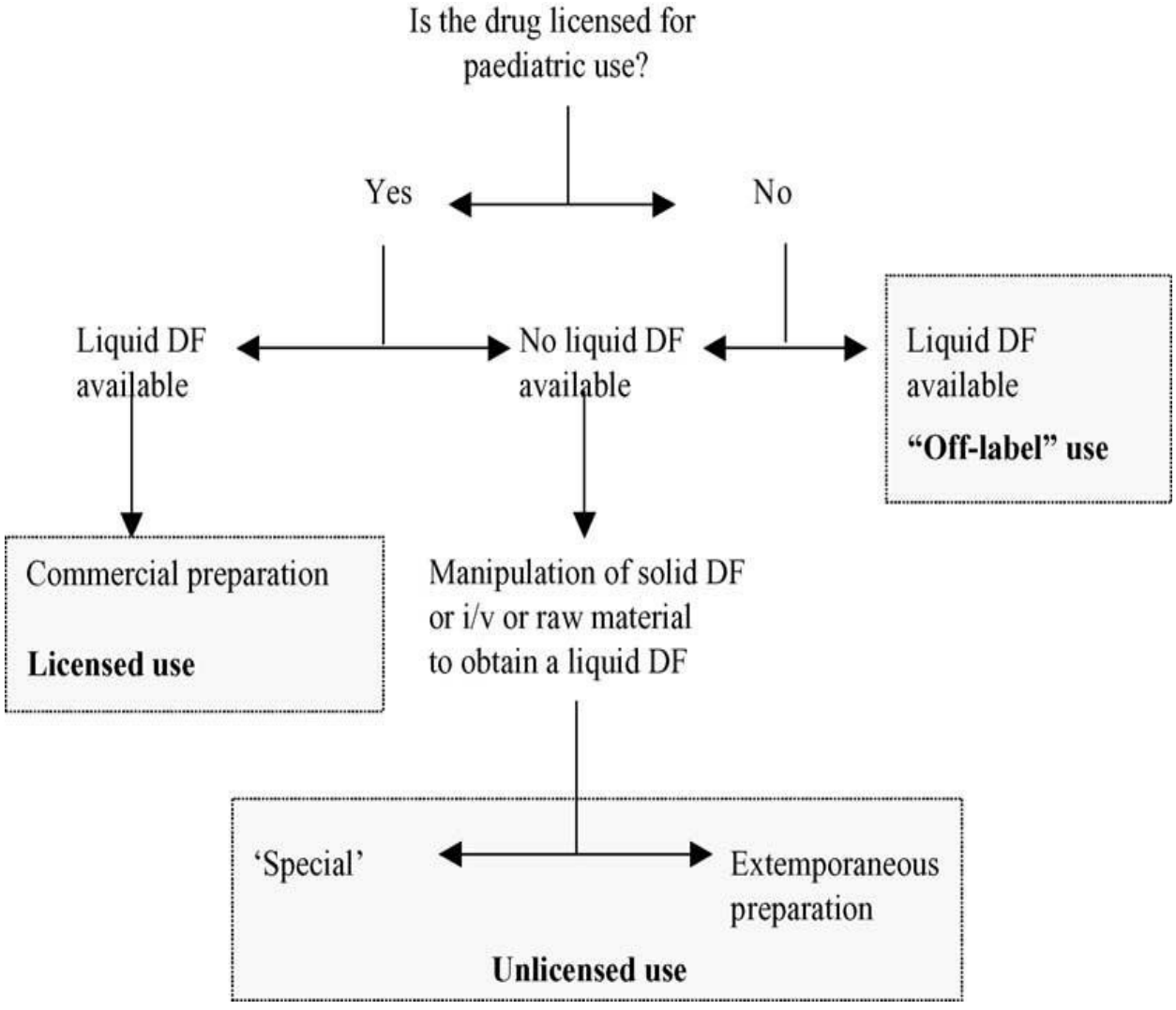

Figure1: Decision pathway for providing oral doses to children for whom whole tablets/capsules are unsuitable (DF: dosage form; i/v: intravenous).[8]

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