EXTEMPORANEOUS PREPARATION OF PAEDIATRIC ORAL FORMULATIONS

Studies conducted in nifedipine powders, capsules and suspensions in a hospital pharmacy

Licentiate Thesis in Pharmacy

Minna Helin-Tanninen
Department of Pharmacy
Kuopio University Hospital
September 2008
ABSTRACT

Despite efforts made to improve the availability of suitably licensed and manufactured drug products for children, the gap between supply and demand is still wide. Suitable dosage forms formulated at many different strengths by including harmless excipients would be needed to medicate children of different ages. Therefore, extemporaneously prepared products are still required to ensure that accurate doses and suitable dosage forms are available for children's drug therapy. Extemporaneously prepared products are produced mainly in hospital and community pharmacies.

The use of extemporaneous preparations can be considered as unlicensed drug use and these raise concerns about quality, stability, bioavailability, efficacy and safety. Currently, there are no appropriate and comprehensive published standards, and thus decisions in different steps of preparation process have to be done by applying professional pharmaceutical skills. The uniformity of content, selection of safe excipients and stability issues are part of the main challenges faced in the preparation of extemporaneous drug products.

The present study examined the chemical stabilities and content uniformities of extemporaneously prepared nifedipine oral dosage forms to be used in newborns and infants. In addition, physical and microbiological stability of the suspension preparations was assessed. Individually weighed oral powders, manually filled capsules and unit dose syringes were prepared either by using nifedipine drug powder or a crushed commercial tablet. A reproducible and validated stability-indicating high performance liquid chromatography method was developed in order to measure nifedipine concentrations and to assay the photodegradation of nifedipine.

The results indicate that both solid and liquid oral dosage forms may provide suitable solutions to treat newborns and infants. The content uniformities of the nifedipine suspensions, powders and capsules met the requirements of the European Pharmacopoeia. Due to the light sensitivity of nifedipine, it required handling in dimly lit room and storage protected from light. When exposed to light, 20–30% photodegradation occurred within three hours.

Nifedipine unit dose suspensions formulated with hypromellose 1% and packaged in capped syringes were found suitable also for nasogastric administration through feeding tubes. The nifedipine suspensions were stable over the four week study period. Autoclaved drug-free hypromellose 1.0% solutions were stable for at least 6 months.

It was found that the total mass of the nifedipine unit powder prepared with lactose monohydrate or microcrystalline cellulose had to be 300 mg or more to ensure accurate dosage and to prevent significant drug loss. When the mass was 100 mg or 50 mg, the nifedipine amount was less than 80% of the theoretical value. Three quarters of the missing amount was located on the emptied powder papers. Oral powders were stable for up to one year. Nifedipine capsules, whose contents were simply emptied prior to use, were faster to prepare and when comparing the quality, do represent an alternative to oral powders. Nifedipine recovery remained acceptable in all three sizes of emptied capsules.

In conclusion, nifedipine oral powders and suspensions were stable throughout the study periods when protected from light, whereas on exposure to light, nifedipine degraded rapidly. Content uniformities of the formulated nifedipine oral preparations met the established requirements. However, the loss of nifedipine was significant, especially in oral powders with low total weights. Thus, nifedipine capsules represent an alternative to oral powders in preparing paediatric medications.
ACKNOWLEDGEMENTS

The present study was carried out in the Department of Pharmacy, Kuopio University Hospital and in the Department of Pharmaceutics, University of Kuopio, during the years 1996–2006. The starting point of this study was the need to produce neonatal nifedipine medication in special health care with pharmacy prepared drug products in the situation where no commercial products exist. One feature of this practical research was multidisciplinary co-operation –though that was not self-evident during the first years of the study. Departments that co-operated in this study were Pharmaceutical Technology and Chemistry, Neonatal Intensive Care, Clinical Microbiology, Clinical Chemistry, and also the Department of Environmental Science, which helped in the light measurements.

My supervisors, the principal supervisor of my work, Chief Pharmacist Toivo Naaranlahti, Ph.D., and Kirsi Kontra, Pharm.Lic., deserve my sincere gratitude for all their efforts, guidance and patience during these years, their fantastic sense of humour and smooth cooperation as a team to create a feeling of synergy and affinity. Their constant support and encouragement during my studies and daily work in the Department of Pharmacy was critical in ensuring the completion of this project. I am also very grateful to my supervisors, City Manager, Professor Petteri Paronen for his assistance in helping me obtain the facilities that made this work possible and Professor Tiina Järvinen for her expert advice and valuable comments during the final stages.

I would like to acknowledge official reviewers, Docent Eetu Räsänen, Ph.D. and Anna Liisa Jäppinen, Ph.D. I would like to express my respectful thanks to my co-authors Docent Kari Wallenius, Ph.D., Tarja Ojanen, Ph.D., and Docent Kari Savolainen, Ph.D., for their pleasant collaboration. I warmly thank the advice and cooperation of Docent Kirsti Heinonen, M.D. (paediatrician) and Anneli Martikainen, M.D. (paediatrician, neonatologist). I am also grateful to thank Docent Hannu Taipale, Ph.D., Aarne Martinsen, Ph.D., Mr Jukka Knuutinen and Timo Oksanen, engineer, for their technical support, and Docent James Callaway, Ph.D. and Ewen MacDonald, Ph.D., for revision of the language of my manuscripts and the Licentiate Thesis.

In addition, my warm thanks belong to the personnel of the Department of Pharmacy for creating a convivial atmosphere and many fluent years of daily work. Finally, I deeply thank my nearest and dearest, the whole of my family, for supporting and yielding to the demands of my postgraduate studies during these 12 years.

This work was supported by grants from Association of Finnish Pharmacies, Alpharma and Bayer Finland.

Kuopio, June 2008
Minna Helin-Tanninen
**GLOSSARY**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEMPORANEOUS PREPARATION</td>
<td>A product, which is dispensed immediately after preparation and not kept in stock (Pharmaceutical Inspection Convention, 2008)</td>
</tr>
<tr>
<td>INFANT AND TODDLER</td>
<td>Age range from 28 days to 23 months (Costello et al., 2007)</td>
</tr>
<tr>
<td>OFF LABEL USE OF DRUGS</td>
<td>Defined by FDA: “Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labelling.” (European Society of Clinical Pharmacy, 2008)</td>
</tr>
<tr>
<td></td>
<td>An agreed definition is still under discussion in Europe (TEDDY, 2007)</td>
</tr>
<tr>
<td>PRETERM NEWBORN INFANT</td>
<td>Born before 37 weeks’ gestation (Costello et al., 2007)</td>
</tr>
<tr>
<td>‘SPECIALS’</td>
<td>Extemporaneous preparations that are made in larger volumes by licensed manufacturers (Costello et al., 2007)</td>
</tr>
<tr>
<td>TERM NEWBORN INFANT</td>
<td>Age range from 0 days to 27 days (Costello et al., 2007)</td>
</tr>
<tr>
<td>UNLICENSED USE OF DRUGS</td>
<td>Unlicensed use includes: modifications to licensed drugs, drugs that are licensed but the particular formulation is manufactured under a special licence, new drugs available under a special manufacturing licence, use of chemicals as drugs, drugs used before a licence has been granted, and imported drugs (Turner et al., 1998)</td>
</tr>
<tr>
<td></td>
<td>An agreed definition is still under discussion in Europe (TEDDY, 2007)</td>
</tr>
</tbody>
</table>
LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original papers referred to in the text by Roman numerals I–IV:


## CONTENTS

1 INTRODUCTION 8

2 REVIEW OF THE LITERATURE 10

2.1 Use of off-label and unlicensed medicines 10
  2.1.1 Problems with off-label and unlicensed drug use 10
  2.1.2 Improvements in regulations 11

2.2 Prevalence of extemporaneous preparation use in paediatric patients 12

2.3 Quality of extemporaneous preparations 14
  2.3.1 Stability of extemporaneous formulations 16
    2.3.1.1 Chemical stability 16
    2.3.1.2 Physical stability 18
    2.3.1.3 Microbiological stability 19

2.4 Oral dosage forms for neonates and infants 20
  2.4.1 Active ingredient 21
  2.4.2 Excipients 23
  2.4.3 Oral solid dosage forms 27
    2.4.3.1 Oral powders 27
    2.4.3.2 Hard gelatine capsules 29
    2.4.3.3 Splitting of tablets 30
  2.4.4 Oral suspension 31
    2.4.4.1 Sedimentation and redispersion 32

3 AIMS OF THE STUDY 34

4 MATERIALS AND METHODS 35

  4.1 Materials 35
    4.1.1 Nifedipine 35
    4.1.2 Excipients 35
    4.1.3 Packaging materials 36
    4.1.4 Standards for high performance liquid chromatography (HPLC) 37
1 INTRODUCTION

“Parents should be taught how to administer their infant’s drugs and then encouraged to do so whenever possible.” “Infants should be spoken to softly and in high-pitched tones. They should be handled gently and should be held and cuddled before and after administration” (Pagliaro, 2002).

Unfortunately, only a few products have been designed and tested specifically for paediatric use (Costello et al., 2007; Pawar and Kumar, 2002). However, the situation is hopefully going to change in European Union (EU). The aim of the EU Paediatric Regulation (2007) is to promote safer medicines for children for example by development and availability of medicines and by ensuring that medicines for use in children are of high quality, ethically researched, and appropriately authorised (EMEA, 2008). In addition, paediatric medicinal products is one focus area in National Agency for Medicines (NAM) in Finland (National Agency for Medicines, 2008a).

The lack of appropriate paediatric formulations is a worldwide problem (Giacoia et al., 2007a). Pharmaceutical companies manufacture special preparations for paediatric patients mainly if the products are likely to be marketable and will generate profit for the manufacturer (Pawar and Kumar, 2002). The range of doses used may be wide for paediatric patients, because of the developmental changes that occur during a child lifetime (Costello et al., 2007). Of all the active substances that were licensed by the European Agency for the Evaluation of Medicinal Products (EMEA) in the period October 1995 to September 2005, only 33% were licensed for paediatric use, 23% for use in infants and only 9% in newborns (Ceci et al., 2006). Since many drugs are not labelled for use in paediatric populations, the manufacturer does not usually market suitable dosage forms for children, e.g. a liquid dosage formulation (Pai and Nahata, 2001).

Therapeutic advances (e.g. modified-release forms) are rarely available for children. Expertise and facilities in hospital pharmacies limit the preparation of modern dosage forms, but pharmaceutical companies have appropriate facilities and should be encouraged to make them available for children (Brion et al., 2003).

The reasons mentioned for the absence of approved prescribing information and specific dosage forms for children include difficulties in evaluating the safety and efficacy of medicines (Giam and McLachlan, 2008). There are problems with recruiting children for
clinical trials and ethical considerations if invasive procedures need to be performed. Clinical trials for several different age groups are perceived as expensive. Suitable paediatric formulation requires further development and testing. Markets for children’s medicines tend to be small and this impacts significantly on commercial decisions. This lack of suitable dosage forms for use in paediatric patients is a contributor to the widespread need for extemporaneous preparations. Extemporaneous preparations are prepared mainly in hospital and community pharmacies.

In this licentiate thesis, the extemporaneous preparation of oral paediatric formulations is examined. In the literature review, the prevalence and quality of extemporaneous preparations are discussed as well as some technological and stability aspects in oral formulations to the extent to which they relate to the aims of this study. In the experimental part of this work, three essential oral dosage forms were investigated: oral powders, capsules and suspensions. A calcium channel blocker, nifedipine, was chosen as a problem drug substance both due to its chemical properties, which are insolubility in water and sensitivity to light and constant off-label and unlicensed use in the paediatric population, also in preterm newborn infants. Pulmonary hypertension and bronchopulmonary dysplasia are treated with extemporaneously prepared nifedipine products because no suitable dosage form is marketed. This study is restricted to preterm newborn infants, term newborn infants, infants and toddlers (Costello et al., 2007). Children over 2 years old and adolescents up to 18 years of age are excluded.
2 REVIEW OF THE LITERATURE

2.1 Use of off-label and unlicensed medicines

Many medicines licensed for use in adults are not licensed for use in infants even though their use may be accepted as the current standard of care (Giam and McLachlan, 2008). In the absence of specific clinical trial-based data in children, clinicians are forced to rely on results of studies conducted in adults, although children have different metabolism to adults and their response to medicines can be unpredictable (‘t Jong et al., 2001). This represents an ethical difficulty for the clinician: to prescribe a medicine for which there is not enough safety data or to avoid its use thus depriving a child of the potential therapeutic benefits. Prescription, dispensing and administration of unlicensed and off-label medicines are allowed by legislation in most countries, including EU countries (Giam and McLachlan, 2008).

Many children are treated with unlicensed medicines or adult’s medicines used off-label. In a prospective study in neonatal intensive care unit (NICU), general paediatric ward and paediatric surgical ward in Kuopio University hospital (KUH) it was found that of all prescriptions (n=629), 51% were for licensed drugs, 36% for off-label use and 13% for unlicensed drugs (Lindell-Osuagwu et al, submitted). Most of the prescriptions for unlicensed drugs, 71%, were used in the NICU. This is evidently due to lack of suitable formulations of drugs for use in pre-term and term neonates and infants. According to Lindell-Osuagwu et al. (submitted), the overall proportion of prescriptions for unlicensed drugs (13%) was similar to that in other studies (10–12%) in paediatric intensive care units in France, Australia, Brazil and Italy. The most frequent reason for prescriptions of unlicensed drugs was the modifications of licensed drugs. The age groups most commonly receiving unlicensed drugs were neonates, infants and children less than 2 years old.

2.1.1 Problems with off-label and unlicensed drug use

Drug products intended for adults are often not available in a concentration low enough for accurate and precise measurement of small doses (Nahata, 1999). Concentrated liquid and solid oral dosage forms may be associated with irritating effects on the gastrointestinal system, resulting in nausea, vomiting, or diarrhoea (Pagliaro, 2002). Errors may occur in measuring doses under 0.1 ml (Nahata, 1999). Measurement errors
with potent drugs like morphine and digoxin have been reported to cause intoxication in paediatric patients. If one wishes to achieve an appropriate strength, then it may sometimes be necessary to dilute the concentrated commercial preparations, a practice which may also render the preservatives ineffective (Costello et al., 2007; Nahata, 1999). Many cases of tenfold dosing error in children have been reported in the literature and several have resulted in tragic outcomes, thus, each step of a calculation should be written to permit double checking (Costello et al., 2007).

The lack of suitably adapted medicines and calculated individualized doses for children may increase the risk of adverse reactions and ineffective treatment (under- or over-dosing) (Costello et al., 2007; Pagliaro, 2002). Unsuitable formulations and routes of administration and the use of extemporaneous or officinal formulations to treat the paediatric population may be of poor quality (Regulation (EC) No 1901/2006). There is elevated risk in newborn infants, because they are more likely to be predisposed to adverse drug reactions due to their physiological immaturity (Costello et al., 2007). Most doses for children are based on weight, although body surface area may reflect the physiological differences more accurately. There is a wide variation in body mass thus the range of doses used may be wide. Seriously ill neonates are often fluid restricted, limiting the volume of medications that can be administered (Glass and Haywood, 2006). The skill and judgement of physicians and pharmacists are critical in ensuring appropriate drug, dosage form and dosing regimen.

2.1.2 Improvements in regulations

The Regulation of the European Parliament and of the council on medicinal product for paediatric use, which came into force in January 2007, obliges the pharmaceutical industry to undertake clinical trials also in the paediatric population (Regulation (EC) No 1901/2006). The Paediatric Regulation also requires marketing authorisation holders to submit to the competent authors all paediatric studies completed by the date of entry into force of the legislation.

It is stated in the Regulation: “This Regulation aims to facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric populations. These objectives should be achieved without subjecting the
paediatric population to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations” (Regulation (EC) No 1901/2006).

EMEA and the Paediatric Working Group (PEG), in consultation with paediatric learned societies, have drawn up a priority list of off-patent products for which studies are required in (EMEA/197972/2007). In that list, it is mentioned that one of the group of compounds for which studies are required are the calcium channel blockers which are used in the treatment of chronic hypertension in all paediatric age groups.

In the United States of America (USA), a mandatory regulation that requires manufacturers to assess the safety and effectiveness of new drugs and biological products in paediatric patients came into force almost ten years earlier than in Europe, in the year 1998. Later, in 2002 the authority to require certain research into drugs used in paediatric patients was given to US Food and Drug Administration (FDA) (FDA/Pub L No. 107–109, 2002). It was only in 2007, that the European Commission (EC), EMEA and FDA agreed to expand their current cooperative activities, particularly those in paediatrics.

2.2 Prevalence of extemporaneous preparation use in paediatric patients

Despite efforts to improve the availability of suitable licensed and manufactured medicine products for children, extemporaneously prepared products are still needed to ensure that accurate and effective doses and dosage forms are available to achieve optimal drug therapy for children. Extemporaneous preparation is one facet of unlicensed drug use and includes modifications to commercially manufactured products such as the preparation of suspension or powders from tablets or the preparation of a product from the individual raw materials. Instead, dividing solid forms, dissolving tablets in water or administering fractions of a liquid to children, which is done on the wards by nurses, is not extemporaneous preparation. The use of extemporaneously prepared products is one way that prescribers are able to overcome the problems associated with the lack of approved medicines for children (Giam and McLachlan, 2008).

Giam and McLachlan (2008) reviewed 20 published studies to identify the relative extent of extemporaneous product use reported in the paediatric population and the implications for pharmacy practice. On general medical/surgical wards, the frequency of extemporaneous or ‘special’ product use was reported to range from 2% to 26%. On neonatal wards, extemporaneously prepared products or ‘specials’ were dispensed in 5–
11% of the prescriptions. In the United Kingdom (UK) it was reported that of the 9.9% extemporaneous products prescribed, 4.6% had been prepared extemporaneously by the pharmacy with the remaining 5.3% being prepared by ‘specials’ manufacturers. The use of extemporaneous products and ‘specials’ was similar across all paediatric ages and conditions. Although the cost of manufactured ‘specials’ has been reported to be much higher than for pharmacy-prepared extemporaneous products, the ‘specials’ industry in the UK has been noted to be thriving. Extemporaneous products are used most frequently in countries such as Netherlands where pharmacy preparation services are readily available. It has been estimated that more than 40% of doses given in paediatric hospitals require compounding to prepare a suitable dosage form (Glass and Haywood, 2006).

Methods of extemporaneous preparation vary in different European countries (Brion et al., 2003). Liquids are predominantly (> 60% of doses) prepared in Denmark, England, Ireland, Norway and Sweden, capsules in Belgium, Croatia, France and Switzerland and powders in Finland, Italy and Scotland. The practice in Germany, Spain and Slovenia involves the preparation of a less well-defined combination of liquids, powders and capsules. The study of Brion et al. (2003) collected information from 16 European countries with Kuopio University Hospital being one of the participants. In the USA and Canada, practicing pharmacists answered the questionnaire by stating that the most common extemporaneously prepared dosage form was a liquid formulation and the most common route of administration for drug products was oral and/or gastric or nasogastric tube delivery (Pai and Nahata, 2001).

The same drug may well be prepared in several different dosage forms, reflecting the different traditions of extemporaneous preparation in the different countries (Brion et al., 2003). Many different concentrations were prepared for each dosage form. It was noted that 15 of the top 20 oral liquid preparations, 15 of the top 20 capsules and 6 of the top 20 powders prepared extemporaneously were marketed as suitable licensed paediatric formulations in other European countries, North America or Australia. Thus, a total of 60% of those most important extemporaneous products could have been available as licensed products if there had only been more convenient ways to locate and import those medicines. Licensing authorities need to cooperate to ensure consensus of data to allow licensing in all European countries. In addition, there should be free movement of licensed medicines between European countries and information on availability should be readily available.
2.3 Quality of extemporaneous preparations

The European Pharmacopoeia (2007) is used as an official regulation for extemporaneous preparation. General instructions of the extemporaneous preparation are presented in Medicinal products for human and veterinary use: Good manufacturing practice (Eudralex, 2007) and in PIC/S Guide to good practices for the preparation of medicinal products in healthcare establishments (Pharmaceutical Inspection Convention, 2008). Other relevant pharmacopeial formularies are British Pharmacopoeia (BP), United States Pharmacopeia (USP), Australian Pharmacopoeia Formulae (APF) and Martindale (Glass and Haywood, 2006). Suitable sources for finding stability-indicating formula include Allen’s compounded formulations, Nahata and Hipple’s Pediatric drug formulations and Trissel’s Stability of compounded formulations.

However, extemporaneous preparation presents a range of challenging issues of concern when compared to off-label use of registered products or unlicensed use of commercially manufactured products and it is important to be aware of those potential problems (Table 1) (Giam and McLachlan, 2008). There are no appropriate and comprehensive published standards for the process of extemporaneous preparation (Brion et al., 2003; Giam and McLachlan, 2008). To ensure product quality, harmonization of extemporaneous formulations and quality-control procedures are needed and collected data should be published as standards and uniformly implemented in all countries, and these should lead to the creation of a monograph in a pharmacopoeia (Brion et al., 2003; Ghulam et al., 2007; Giacoia et al., 2007b; Giam and McLachlan, 2008).

In the USA and Canada, a questionnaire was sent to practicing pharmacists. It was noted that 103 drug formulations prescribed by paediatricians had no compounding and/or stability information available due to a lack of published stability-indicating analytical methods in peer reviewed journals (Pai and Nahata, 2001). Adequate stability data was found for 76 drug formulations. However, longer or better stability data were requested on 109 formulations, such as captopril, hydralazine, spironolactone, ursodiol and nifedipine. Of the liquid dosage forms reviewed in the literature, the stability was considered to be unfavourable for only 6 of the 83 dosage forms (Glass and Haywood, 2006; Haywood and Glass, 2007). In an unpublished UK survey, it was noted that 54% of 112 paediatric extemporaneous formulations had inadequate data on stability (Brion et al., 2003).
<table>
<thead>
<tr>
<th>Problem</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of published standards</td>
<td>Brion et al., 2003; Costello et al., 2007; Ghulam et al., 2007; Giacoia et al., 2007b</td>
</tr>
<tr>
<td>Lack of access to various publications containing stability data on different drug formulations</td>
<td>Pai and Nahata, 2001</td>
</tr>
<tr>
<td>Lack of information about chemical, physical and microbiological stability data, short shelf-life</td>
<td>Brion et al., 2003; Giam and McLachlan, 2008; Pai and Nahata, 2001; Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Lack of information about validation and reproducibility</td>
<td>Costello et al., 2007; Paediatric Formulary Committee, 2007</td>
</tr>
<tr>
<td>Lack of proof of dose uniformity</td>
<td>Costello et al., 2007</td>
</tr>
<tr>
<td>Lack of adequate dosage form</td>
<td>Costello et al., 2007; Glass and Haywood, 2006</td>
</tr>
<tr>
<td>Need to manipulate adult dosage form of the available tablet, capsule or injection, lack of pure drug substances</td>
<td>Costello et al., 2007</td>
</tr>
<tr>
<td>Cutting, crushing or dissolving of controlled-release tablets: release of the whole drug content at the same time that may lead to significant overdose</td>
<td>Pagliaro, 2002; Paediatric Formulary Committee, 2007</td>
</tr>
<tr>
<td>Inability to swallow solid dosage forms</td>
<td>Pai and Nahata, 2001</td>
</tr>
<tr>
<td>Several different strengths prepared extemporaneously or as 'special' products, 10-fold difference in available strengths</td>
<td>Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Alternative routes of administration for commercial products: e.g. oral liquids rectally, eye drops in the ear or injectable solution orally leading to irritability and altered kinetics of absorption and bioavailability</td>
<td>Costello et al., 2007; Glass and Haywood, 2006</td>
</tr>
<tr>
<td>Dilution of commercial formulations leading to dilution of co-solvents thus leading to the precipitation of the drug</td>
<td>Glass and Haywood, 2006</td>
</tr>
<tr>
<td>Microbiological contamination in multidose extemporaneous preparations with insufficient preservation leading to potential risks, especially in the premature and newborn</td>
<td>Ghulam et al., 2007</td>
</tr>
<tr>
<td>Variability in overall compounding practices and training</td>
<td>Treadway et al., 2007</td>
</tr>
<tr>
<td>Concern about ingredient compatibility</td>
<td>Giam and McLachlan, 2008</td>
</tr>
<tr>
<td>Concern about compatibility between manipulated solid dosage forms and food/beverages</td>
<td>Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Taste of the drug or the preparation itself</td>
<td>Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Inaccuracy of dosing (dose uniformity and reproducibility)</td>
<td>Paediatric Formulary Committee, 2007; Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Concern about bioavailability and efficacy</td>
<td>Giam and McLachlan, 2008; Paediatric Formulary Committee, 2007; Standing and Tuleu, 2005</td>
</tr>
<tr>
<td>Concern about safety</td>
<td>Giam and McLachlan, 2008</td>
</tr>
<tr>
<td>Difficulty in monitoring adverse reactions</td>
<td>Giam and McLachlan, 2008</td>
</tr>
</tbody>
</table>
In the future, it is presented that there will be a continuing requirement for extemporaneous preparation by pharmacists (Giam and McLachlan, 2008). An accreditation process has been implemented in the USA and is under discussion in Australia (Treadway et al., 2007). Pharmacists need to be provided with information about the stability, formulation and compatibility and equipped with the skills to produce effective, safe and stable preparations (Allen, 2006; Treadway et al., 2007). In the meantime, due to a general lack of information and peer-reviewed research in this field, a product should be dispensed extemporaneously only when no product with a marketing authorisation is available and if there are no alternatives (Brion et al., 2003; Paediatric Formulary Committee, 2007).

2.3.1 Stability of extemporaneous formulations

Stability refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination (USP Pharmacists’ Pharmacopeia, 2008). The shelf life of a pharmaceutical product is the period during which, if stored correctly, it is expected to retain within specified limits, and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of preparation (Barnes, 2007, Jew et al., 2003). Extemporaneous preparations are often given arbitrary shelf-lives or shelf-lives based on published information (Costello et al., 2007). It is important to ensure that an extemporaneous formulation packaged in a specific container will remain within its physical, chemical and microbiological specifications during storage for a specified time (Florence and Attwood, 2006).

A short expiry period may be inconvenient for patients. The main causes for limited stability are: 1) loss of drug (by degradation), 2) loss of vehicle (by evaporation), 3) loss of uniformity (by caking of a suspension), 4) change of organoleptic characteristics (appearance), 5) change of bioavailability, 6) appearance of a degradation product that is irritant or toxic (Costello et al., 2007).

2.3.1.1 Chemical stability

Each active ingredient has to retain its chemical integrity and labelled potency within the specified limits (Allen, 2002). The limits of shelf life vary somewhat between different references. Usually the shelf life can be assumed to be the time taken for the concentration of the drug to be reduced to 95% of its value when originally prepared.
(Florence and Attwood, 2006). On the other hand, a reduction of content down to 90% of theoretical value (with possible 95% confidence bounds) is generally regarded as the maximum reduction acceptable (Barnes, 2007). Thus the limit of ≥ 90% of the initial concentration is also used (Glass and Haywood, 2006).

Chemical degradation reactions can be sub-divided into hydrolysis, oxidation, isomerisation, polymerisation, and photochemical decomposition (Florence and Attwood, 2006). Should these occur, then there will be a loss of potency of the drug, often accompanied by changes in the appearance of the product (e.g. discoloration, formation of a precipitate).

Primary photochemical reaction occurs when the wavelength of the incident light is within the wavelength range of absorption of the drug, so that the drug molecule itself absorbs radiation and becomes degraded (photolysis) (Barnes, 2007; Florence and Attwood, 2006). Photodegradation may also occur as a consequence of absorption of radiation by excipients which transfer the absorbed energy to the drug (Florence and Attwood, 2006). The degradation of photolabile drugs depends on both the intensity and spectral distribution of the light source (Thoma, 1996). Different numbers and structures of photodegradation products can be obtained by irradiating the drug in the solid state or in solution.

In contrast to drug solutions, photodegradation in the solid state only takes place at the surface (Figure 1) (Thoma, 1996). The rate of decomposition is influenced by the size and surface of particles, the colour and crystalline structure, and layer thickness and excipients. The smaller the particle size, the greater the reactivity of the product (Allen, 2002). Coating tablets with a polymer film containing ultraviolet absorbers is one method to achieve protection from light (Florence and Attwood, 2006). The layer thickness of the coloured and pigmented coating correlates strongly with the photoprotective effect (Thoma, 1996). Some light protecting pigments, e.g. titanium dioxide and iron oxide, can be added to the coatings. Iron oxide in particular has been demonstrated to possess a strong protection capacity with potent absorption of wavelengths below 400 nm. If the coating of the tablet is crushed, which is the case in extemporaneous preparation process, the photoprotection has to be assured with tinted packing materials. For example, coloured light-resistant containers and storage in the dark protects from photoinduced decomposition (Florence and Attwood, 2006).
Suspension formulations are often more stable than a formulation of the same drug in a solution because much of the drug is protected within the insoluble particles (Barnes, 2007). The solubility of the suspended drug changes with increase in temperature (Florence and Attwood, 2006). In suspensions, the concentration of solute drug usually remains constant because, as the decomposition reaction proceeds, more of the drug dissolves to keep the solution saturated.

Figure 1. Photoinstability of nifedipine crystals (≤ 5µm) compared with nifedipine solution:
-●- nifedipine crystals; -○- nifedipine solution, \( c_0 = 3 \text{ mg/50 ml} \) (adapted from Thoma, 1996). About 20 % of the crystalline nifedipine has become decomposed within 40 minutes, subsequently, further degradation does not occur during the next 40 minutes whereas a solution decomposes completely during the period.

The determination of the shelf life of a formulated product needs to be performed on the actual product at a realistic storage temperature, normally at room temperature or in a refrigerator (Barnes, 2007). An accurate, specific, reproducible and stability-indicating analytical method, e.g. high-performance liquid chromatographic technique should be used (Nahata, 1999). A specific protocol for testing the photostability of new drugs and products is described in the ICH Guideline (ICH Harmonised Tripartite Guideline, 1998).

2.3.1.2 Physical stability

Physical stability means that the original physical properties, including appearance, palatability, uniformity, dissolution and suspendability, have been retained (Allen, 2002). Physical instability can either spoil the product’s appearance or reduce its effectiveness (Barnes, 2007). Potential problems may also be loss of drug due to sorption, evaporation or contamination of the product by extractives.

Physical changes indicating instability in capsules could include changes in the physical appearance or consistency, including softening or hardening of the shell, or discoloration,
expansion or distortion of the gelatine capsule (Allen, 2002). Caking instead of free
flowing may occur in powders. Furthermore, discoloration and release of pressure upon
opening may possibly occur.

Physical instability in dispersed systems such as suspensions is expressed as caking of
sediment or particle growth (Barnes, 2007). It is recommended that the rate of
sedimentation of solids undissolved in the preparation should not be too rapid (Costello et
al., 2007). The particles that settle onto the bottom of the container must not form a hard
cake, but should be readily dispersed into a uniform mixture when shaken. Redispersion
of the preparation can be affected by the changes in viscosity. Precipitation of active
ingredients or excipients can lead to erratic dosing or affect the quality of the preparation.
Hurtado and Moffett (2007) reported one case of a neonate readmitted with an arrhythmia
because an amiodarone suspension had been incorrectly compounded and the solids had
settled into a hard mass at the bottom of the container.

The particle size of the active ingredient in suspension can affect the uniformity of content
since large particles will settle faster than their smaller counterparts (Costello et al., 2007).
Particle size may increase as a result of sedimentation, aggregation or crystallization,
which can occur due to Ostwald ripening, changes in storage temperature or the
appearance of polymorphic forms. Thus, the suspension needs to be observed for
uniformity, settling, caking, crystal growth and difficulty in resuspending, as well as odour
and loss of volume (Allen, 2002). Viscosity should also be monitored as changes can
affect the redispersion and pourability of the product, and impair dosing. In practice,
adequate testing includes the ease of redispersion in parallel with the dose uniformity
(Costello et al., 2007).

2.3.1.3 Microbiological stability

Microbial quality or resistance to microbial growth has to be retained according to the
specified requirements (Allen, 2002; European Pharmacopoeia 6.1, 2007). Products
containing sufficient water to permit bacteria or fungi growth are vulnerable to spoilage
(Hodges, 2007). Only spore-formers survive well in dry conditions. Most bacteria have an
optimum pH for growth near neutrality, whilst most fungi favour slightly acidic conditions.

Products contaminated with pathogenic organisms may be an infection hazard (Hodges,
2007). The occurrence of microbiological growth in aqueous medicines can affect the
organoleptic characteristics of the product, producing turbidity, bad odour or taste
(Costello et al., 2007; Ghulam et al, 2007). Deterioration of the product due to bacterial or mould growth can either render the product unacceptable, harmful or toxic to the patient (Barnes, 2007; Costello et al., 2007; Hodges, 2007). The presence of micro-organisms and their metabolites can even impair the chemical or physical stability and the drug solubility by affecting the pH (Costello et al., 2007; Hodges, 2007). For example, air contamination of a cellulose syrup mixture or unhygienic use of the product can also lead to microbiological contamination (Costello et al., 2007; Nahata et al., 2003).

There are pharmacopoeial requirements for microbiological quality of oral preparations, i.e. not more than $10^3$ bacteria and not more than $10^2$ fungi per gram or per millilitre, and the absence of *Escherichia coli* (European Pharmacopoeia 6.1, 2007). Hygienic manufacture, sterilization and suitable preservatives are used to prevent the presence or growth of microorganisms in the product (Billany, 2007). The factors impacting on the hygienic manufacture of medicines are air, building, equipment, work surfaces, raw materials, both ingredient and cleaning water, formulation and personnel (Hodges, 2007). Health, hygiene, clothing and training of the personnel may all have an impact on product contamination.

### 2.4 Oral dosage forms for neonates and infants

The ideal oral drug preparation should be effective, well tolerated, stable, affordable, and have good palatability, e.g. acceptable taste, after-taste and smell (Pawar and Kumar, 2002). This is important since the taste buds and olfactory receptors are well developed in children and therefore flavouring and sweetening are needed for many drugs with an unpleasant taste (e.g. chloral hydrate), smell (e.g. phenytoin) or texture (e.g. liquid antacids) (Allen, 2002). The age-related differences in the taste and smell has to be taken into account (Pawar and Kumar, 2002). Drugs with an acidic taste can be blended with citrus fruit flavours (Allen, 2002). Salty, sweet and sour tastes can be used to mask the bitter taste of high molecular organic compounds. The addition of a slightly salty taste may decrease sourness and increase sweetness. In patients with nasogastric tubes, the taste of the product is not relevant (Pawar and Kumar, 2002).

If the formulation is unsuitable administration of medications to paediatric patients can be stressful, traumatic and sub-therapeutic (Costello et al., 2007). Oral liquid dosage forms should be administered to infants when they are in the same position as for breast- or bottle feeding to prevent aspiration of the drug and to prevent the drug from running out of
the infant’s mouth (Pagliaro, 2002). In the newborn, oral liquids need to be dispensed via a plastic nipple to take advantage of their strong suckling reflex. If the infant refuses the nipple, the drug can be delivered via a plastic oral drug syringe. Small amounts of the drug should be placed between the infant’s cheek and gum toward the back of the mouth. The infant’s throat can be gently stroked outside in a downward motion to facilitate swallowing.

For many infant patients, drugs have to be administered through nasogastric feeding tubes (Pagliaro, 2002). One report stated that nurses considered the occlusion of nasogastric tubes to be a significant problem in using oral powders (Hepojoki, 2008). The type of the feeding tube (material, size of the bore, nasogastric or gastrostomy), placement (stomach, duodenum, jejunum), enteral nutrition and feeding schedule can affect drug administration, absorption and drug-nutrient interactions (Pagliaro, 2002). Feeding tubes made of polyurethane have a lower incidence of clogging compared to other materials. Tube occlusion can be prevented also with flushing before and after the administration of drugs and enteral feedings, and also between different drugs (Pagliaro, 2002; Paediatric Formulary Committee, 2007). In neonates sterile water must be used to rinse the medicine down via a nasogastric tube.

Liquid oral medicines have an advantage compared to solid dosage forms (Costello et al., 2007). An ideal delivery system is accurate, suits all the age groups, and has a minimal dosage frequency and a good palatability. It should also contain only few non-toxic excipients and be easy to administer. Finally, it has to be a stable formulation which is commercially available.

### 2.4.1 Active ingredient

The active ingredient of the extemporaneous formulation may be: 1) drug substance of pharmacopoeial standard, 2) from manipulated licensed formulation, including also excipients or, 3) though not recommended, a chemical without official standards which may have been purchased from a variety of sources and submitted to varying procedures to establish the quality. These chemicals are often not sold as ingredients for the preparation of medicines (Brion et al., 2003).

Ideally, extemporaneous products are prepared from pure drug substances, but more frequently, because of the easier availability, commercial dosage forms intended for adults are manipulated by crushing the tablet or opening the capsule and using the contents
The resulting powder may be dissolved or suspended with various excipients to produce an oral liquid medicine, or it may be redistributed in smaller strength capsules or powder papers, usually after dilution with lactose or some other inactive ingredient. It is important that the uniformity of dose distribution is checked according to appropriate pharmacopeial monographs (Costello et al., 2007; European Pharmacopoeia 6.1, 2007).

Active ingredient of this work, nifedipine is sensitive to light (European Pharmacopoeia 6.1, 2007; Thoma, 1996). Although UV-light in the energy-rich short-wavelength region is very often the cause of the degradation of drugs, a distinct spectral region of visible light seems to be responsible for the main photolysis of nifedipine (Figure 2). The graph shows that nifedipine solution is stable down to a wavelength of 475 nm, and that photolysis begins at 450 nm and increases considerably up to 400 nm. Nifedipine is converted to a pharmacologically inactive nitrosophenylpyridine derivative when exposed to daylight and artificial light of certain wavelengths, and to a nitrophenylpyridine derivative when exposed to ultraviolet light (Figure 3).

Figure 2. Influence of the wavelength of the irradiation light on the photostability of nifedipine; (●●●) dependence of the residual concentration on the wavelength of xenon radiation (left ordinate); (−−−) long wavelength section of the nifedipine adsorption spectrum (right ordinate) (adapted from Thoma, 1996)
2.4.2 Excipients

Excipients, inert ingredients, are added to increase the bulk, add desirable colour, mask the unpleasant taste and smell and facilitate a uniform mixture of the active ingredient in the final preparation (Pawar and Kumar, 2002). Very small amounts of active ingredients require a carrier to ensure their uniform distribution in the dispensed product, and to guarantee an accurate dose.

Bulk fillers contribute to the product’s uniformity, stability, flow characteristics and compressibility (Pawar and Kumar, 2002). Lactose is widely used as a filler or diluent in tablets and capsules, and to a more limited extent in infant formulas (Rowe et al., 2007). Lactose, a disaccharide of glucose and galactose is, however, absorbed after hydrolysis by the intestinal enzyme, lactase (Pawar and Kumar, 2002). Microcrystalline cellulose, which is derived from purified wood cellulose by acid hydrolysis is primarily used as a binder and diluent in oral tablet and capsule formulations (Pawar and Kumar, 2002; Rowe et al., 2007). Cellulose causes no systemic adverse effects, because it is not absorbed by
humans. Colloidal cellulose is used as a suspending agent for active ingredients in liquid preparations. Hypromellose, hydroxypropylmethylcellulose, is a purified form of cellulose, cotton lints or wood pulp. It is used both as tablet binder, in film-coating, as matrix in sustained-release tablet formulations and as a suspending and thickening agent in liquid formulations (Rowe et al., 2007). Hypromellose is regarded as a non-toxic and non-irritant material, although excessive oral consumption may have a laxative effect. Purified water is the most commonly used solvent in liquid preparations (Pawar and Kumar, 2002; Rowe et al., 2007). However, water may serve as a culture medium for bacteria and fungi (European Pharmacopoeia 6.1, 2007). Purified water is prepared by distillation, ion exchange, reverse osmosis or by some other suitable method.

Excipients have been considered to be almost inert in adults; however, rare adverse effects, particularly in children, have been reported (Table 2). They may lead to life threatening toxicity in paediatric patients when multiple doses of medications with the same preservative are employed (e.g. benzyl alcohol and benzoic acid) (Glass and Haywood, 2006). Dose-related adverse effects of excipients are of particular concern in the preterm newborn, low-birthweight neonates and infants, this being attributable to the immaturity of hepatic and renal function (Costello et al., 2007).
Table 2. Reported adverse effects caused by excipients especially in children

<table>
<thead>
<tr>
<th>Excipient</th>
<th>Adverse reaction</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bulk fillers:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactose</td>
<td>Diarrhoea, malabsorption, vomiting, flatulence (in patients with lactose-intolerance)</td>
<td>Kumar et al., 1996</td>
</tr>
<tr>
<td></td>
<td>Jaundice, hypoglycaemia, CNS symptoms, cataracts (in patients with galactosemia)</td>
<td></td>
</tr>
<tr>
<td>Sweeteners and flavouring agents:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspartame</td>
<td>Headache, grand mal seizures, memory loss, gastrointestinal symptoms, dermatological symptoms (large quantities) Potentially toxic metabolites methanol, aspartic acid and phenylalanine Phenylalanine is harmful in patients with phenylketonuria Aspartic acid is neurotoxic and epileptogenic</td>
<td>American Academy of Pediatrics, 1997 Pawar and Kumar, 2002 Rowe et al., 2007</td>
</tr>
<tr>
<td>Fructose</td>
<td>Hypoglycaemia (in patients with fructose intolerance)</td>
<td>Kumar et al., 1996</td>
</tr>
<tr>
<td>Menthol</td>
<td>Hypersensitivity reactions, systemic allergic reactions</td>
<td>Kumar et al., 1993</td>
</tr>
<tr>
<td>Peppermint oil</td>
<td>Atrial fibrillation, muscle pain, cooling or burning sensations</td>
<td>Kumar et al., 1993</td>
</tr>
<tr>
<td>Saccharin</td>
<td>Irritability, hypertonia, insomnia, opisthotonus and strabismus, cross-sensitivity with sulfonamides Approved for children &gt;3 years</td>
<td>Costello et al., 2007 Pawar and Kumar, 2002</td>
</tr>
<tr>
<td>Sodium cyclamate</td>
<td>Incidence of bladder cancer increased in rats Use is restricted in many countries</td>
<td>Costello et al., 2007</td>
</tr>
<tr>
<td>Sorbitol, mannitol, xylitol</td>
<td>Large amounts: osmotic diarrhoea</td>
<td>Pawar and Kumar, 2002</td>
</tr>
<tr>
<td>Sucrose</td>
<td>Tooth decay Cariogenicity, increased degradation of active drug, allergic reactions (very rare)</td>
<td>Costello et al., 2007 Kumar et al., 1996</td>
</tr>
<tr>
<td><strong>Colouring agents:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azo dyes</td>
<td>Anaphylactic reactions, angioedema, asthma, urticaria, hyperkinesis, cross-sensitivity with acetylsalicylic acid, sodium benzoate and indomethacin (tartrazine FD&amp;C yellow5 = E102, sunset yellow FD&amp;C 6 = E110)</td>
<td>Pawar and Kumar, 2002</td>
</tr>
<tr>
<td>Quinoline dyes</td>
<td>Contact dermatitis</td>
<td>Pawar and Kumar, 2002</td>
</tr>
<tr>
<td>Xanthine dyes</td>
<td>Photosensitizer (eosin: FD&amp;C red22), carcinogenicity (erythrosine: FD&amp;C 3 = E127)</td>
<td>Pawar and Kumar, 2002</td>
</tr>
<tr>
<td><strong>Preservatives and antibacterial agents:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzalkonium chloride</td>
<td>Dose-related bronchoconstriction, cough, burning sensation, occasionally facial flushing, pruritus</td>
<td>American Academy of Pediatrics, 1997 Costello et al., 2007</td>
</tr>
<tr>
<td>Benzoic acids and benzoates</td>
<td>Displacement of bile from albumin binding sites in premature neonates, 'gassing syndrome’</td>
<td>Costello et al., 2007 Kumar et al., 1993</td>
</tr>
<tr>
<td>Benzy] alcohol</td>
<td>A number of neonatal deaths and severe respiratory and metabolic complications (32–105 mg/kg/d), bronchitis, haemoptysis, hypersensitivity reactions (rare)</td>
<td>American Academy of Pediatrics, 1997</td>
</tr>
<tr>
<td>Boric acid</td>
<td>Is not used internally owing to its toxicity: death from ingestion of &lt;5g in young children</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td>Parabens</td>
<td>Skin sensitization and cross-sensitization with each other Concern has been expressed over the use of methylparaben in infants' parenteral products because bilirubin binding may be affected, which is potentially hazardous in hyperbilirubinemic neonates</td>
<td>Costello et al., 2007 Kumar et al., 1993 Rowe et al., 2007</td>
</tr>
<tr>
<td>Substance</td>
<td>Effect</td>
<td>Reference</td>
</tr>
<tr>
<td>-----------------------------------</td>
<td>------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Sodium benzoate</td>
<td>Nonimmunological contact urticaria, anaphylaxis&lt;br&gt;It has been recommended that sodium benzoate injection should not be used in neonates</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td>Sodium borate</td>
<td>Damaged skin, severe toxicity (vomiting, diarrhoea, erythema, CNS depression, kidney damage)&lt;br&gt;Lethal oral intake 5g in children</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td>Thiomersal</td>
<td>Hypersensitivity (at 0.1% concentration in children)</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td><strong>Surfactants and solubilising agents:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethanol</td>
<td>Accumulation of acetaldehyde&lt;br&gt;In the USA, the maximum quantity of alcohol included in OTC medicines is: 10% v/v for use by individuals of 12 years of age and older, 5% v/v for children aged 6–12 years of age, and 0.5% v/v for children under 6 years of age&lt;br&gt;In Europe there are no limits set</td>
<td>Costello et al., 2007, Rowe et al., 2007</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Renal failure (in 1937, children treated with sulphanilamide elixir developed renal failure traceable to the ethylene glycol which had been used as a solvent)&lt;br&gt;The WHO has set an estimated acceptable daily intake of polyethylene glycols at no more than 10 mg/kg</td>
<td>Pawar and Kumar, 2002, Rowe et al., 2007</td>
</tr>
<tr>
<td>Glycerol</td>
<td>&gt;40% in volume: mucositis, diarrhoea, electrolyte disturbances</td>
<td>Pawar and Kumar, 2002</td>
</tr>
<tr>
<td>Polysorbate</td>
<td>Hypersensitivity&lt;br&gt;Serious adverse effects (E-Ferol syndrome: thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis, including some deaths, in low-birthweight infants&lt;br&gt;The WHO has set an estimated acceptable daily intake at no more than 25 mg/kg</td>
<td>Costello et al., 2007, Rowe et al., 2007</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>One-third as intoxicating as ethanol&lt;br&gt;Effects on central nervous system&lt;br&gt;Ototoxicity, cardiac arrhythmias, seizures, osmotic laxative effects, contact dermatitis lactic acidosis (especially in neonates and children &lt;4 years of age)&lt;br&gt;Acceptable daily intake up to 25 mg/kg&lt;br&gt;Not recommended for children &lt;4 years (limited alcohol dehydrogenase)&lt;br&gt;Half-life 17h in neonates (5h in adults)</td>
<td>American Academy of Pediatrics, 1997, Costello et al., 2007, Rowe et al., 2007</td>
</tr>
<tr>
<td><strong>Miscellaneous groups, e.g. antioxidants, lubricants, etc:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liquid paraffin</td>
<td>Lipoid pneumonia caused by aspiration or use of ophthalmic preparations&lt;br&gt;Should not be used in very young children</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td>Potassium metabisulphite</td>
<td>Bronchospasm, anaphylaxis (especially in those with a history of asthma or atopic allergy)</td>
<td>Rowe et al., 2007</td>
</tr>
<tr>
<td>Povidone</td>
<td>Anaphylactic reaction</td>
<td>Costello et al., 2007</td>
</tr>
<tr>
<td>Sulphites</td>
<td>Wheezing, dyspnoea, chest tightness (in patients with known reactive airway disease)&lt;br&gt;Anaphylaxis, hives, itching</td>
<td>American Academy on Pediatrics, 1997, Pagliaro, 2002</td>
</tr>
<tr>
<td>Thymol</td>
<td>Respiratory arrest, nasal congestion edema (reported in newborn)&lt;br&gt;Not for children under 5 years</td>
<td>Rowe et al., 2007</td>
</tr>
</tbody>
</table>
2.4.3 Oral solid dosage forms

The main groups of oral solid dosage forms are: oral powders, granules, capsules, gastro-resistant capsules, prolonged-release capsules and tablets (National Agency for Medicines, 2008b). In this review, oral powders and capsules and in addition, splitting of tablets will be discussed.

2.4.3.1 Oral powders

Oral powders are preparations consisting of solid, loose, dry particles of varying degrees of fineness (European Pharmacopoeia 6.1, 2007). They contain one or more active substances, with or without excipients. Single-dose oral powders are individually weighed powders packed individually in folded powder papers (Allen, 2002; Brion et al., 2003; European Pharmacopoeia 6.1, 2007). Since powders are dry, they generally represent a stable dosage form as long as they are protected from moisture and heat (Allen 2002; Brion et al., 2003). Powders have a large surface area that is exposed to atmospheric conditions (Allen, 2002). Small particles are more reactive and can absorb larger quantities of gases, such as carbon dioxide.

Single-dose oral powders are more time consuming to prepare than capsules or oral liquids. Different strengths may be required to medicate children of different ages. The taste or caustic nature of the active drug may limit their use (Allen, 2002; Brion et al., 2003). Usually the powders are administered in water, milk, some other beverage or food if any incompatibilities are not present (Allen, 2002). Powders should never be ingested without first moistening them because of the possible aspiration or choking hazard (Pagliaro, 2002).

The first step in the bulk powder preparation is to ensure that all the components of the mixture are in the same particle size range (Allen, 2002). Size reduction or comminution of a tablet is carried out by a process of crack propagation, whereby localized stresses produce strains in the particles which are large enough to cause bond rupture (Staniforth and Aulton, 2007). In small scale preparation, comminution involves mainly manual methods, e.g. trituration, levigation and pulverization by hand (Allen, 2002). Gummy-type materials are best comminuted using pulverization, insoluble materials for suspension by levigation and hard fracturable powders by trituration. Once pulverized by trituration, the powder should be levigated with a levigating agent to form a smooth paste (Jew et al., 2003).
Whenever a product contains more than one component, a mixing or blending stage is required in the manufacturing process to ensure an even distribution of the active components (Twitchell, 2007). When mixing a small amount of a potent drug in a powder mix, the degree of mixing must be of a high order to ensure a consistent dose. The lower the proportion of active component present in the mixture, the more difficult it is to achieve an acceptably low deviation in the active content. Secondly, the more particles that are present in a unit dose, the lower the probable variation in content. Therefore, by decreasing the particle size, the variation may be reduced but on the other hand, increased cohesion and adhesion with smaller particles can lead to particle aggregation.

Particles larger than 250 µm are usually relatively free flowing but as the size falls below 100 µm, powders become cohesive and flow problems are likely to occur (Staniforth and Aulton, 2007b). If the particle size is less than 10 µm, powders are usually extremely cohesive and resist flow under gravity, except possibly as large agglomerates. A powder that is too fluffy can be compacted slightly by the addition of a few drops of alcohol, water, or liquid paraffin (Twitchell, 2007). Magnesium stearate, less than 1% of the total weight enhances the lubrication and flow characteristics. Electrostatic forces can be neutralized with sodium lauryl sulphate, up to 1%. It in turn may reduce the ease of mixing. On the other hand, a sufficiently small powder may become adsorbed onto ‘active sites’ on the surface of a larger ‘carrier’ particle. However, it is possible to estimate by calculation the particle size required to achieve a formulation with the desired specifications.

Pharmaceutical mixing is a process called geometric dilution (Allen, 2002). It is started with the ingredient in the smallest quantity, and then additional ingredients are added in order of quantity required by approximately “doubling” the portion being mixed with each addition. Mixing can be done in a mortar with a pestle. Mortars need to be nonporous so that no drug substance remains in the pores to decrease the dose or to contaminate the next product to be prepared. When handling hazardous drugs mixing powders in a plastic bag using a spatula can lessen the amount of powder suspended in the air around the preparation area.

Pharmaceutical mixes are likely to be partly ordered (particles are not independent of each other) and partly random, the extent of each amount depending on the component properties (Twitchell, 2007). Components of neutral mixtures like powders have no tendency to mix or segregate spontaneously once work has been done to mix them. However, powders of different particle size may become segregated during mixing or
storing and shipping (Allen, 2002). Segregation will cause an increase in content variation (Twitchell, 2007). Typically, powder mixes contain particles that differ in size, shape and density and thus will tend to behave differently. More dense large particles tend to settle more rapidly than small particles (Allen, 2002; Twitchell, 2007). However, smaller particles tend to fall through the voids between larger particles and thus move to the bottom of the mass (percolation segregation) (Twitchell, 2007). Larger particles will tend to have greater kinetic energy imparted to them during mixing and therefore move greater distances than smaller particles (trajectory segregation). These effects together lead to the fact that there is a tendency to find larger particles at the edge of the powder heap when they are poured out of the container. The use of excipients which have a density similar to the active component is one approach to minimize segregation.

2.4.3.2 Hard gelatine capsules

Hard capsules have shells consisting of two prefabricated, cylindrical sections, each of which has one rounded, closed and one open end (European Pharmacopoeia 6.1, 2007). The active substances are filled into one of the sections that is then closed by slipping the other section over it. Normally this dosage form is intended to be swallowed whole, but for some purposes such as administering for infants, the capsules are opened before administration and the contents gently mixed with a small amount of suitable liquid or soft food (Allen, 2002; Brion et al.; 2003, Pagliaro, 2002).

The primary ingredients of hard gelatine capsule shells are gelatine, sugar and water, but they may also contain a dye and/or an opacifying agent and about 0.15% sulphur dioxide to prevent decomposition (Allen, 2002). Hard gelatine capsules normally contain about 10–15% moisture, though gelatine can absorb up to 10 times its weight in water (Allen, 2002, Jones 2007).

The capsule size selected should be slightly larger than is needed to hold the drug substance, because excipients are needed to produce a full capsule (Allen, 2002). For children capsules number 1–5, that is capacities of 0.50–0.12 ml, are normally used. Manually operated capsule filling devices are suitable for small scale production (Allen, 2002; Brion et al., 2003).

The excipients in capsule formulation can have a significant effect on the rate of dissolution of poorly soluble and hydrophobic drugs (Ashford, 2007). Hydrophilic diluents like lactose often increase the rate of penetration of gastrointestinal fluids into the contents
of the capsule and thus promote the dispersion and dissolution of the drug. Increase in packing density of the encapsulated mass is believed to decrease liquid permeability and also the dissolution rate whereas the use of a surfactant may facilitate liquid penetration.

2.4.3.3 Splitting of tablets

Instead of extemporaneous preparation, tablets are sometimes cut into smaller segments in the pharmacy or on the ward to obtain appropriately-sized dosage units for children (Brion et al., 2003). These segments are defined as tablets cut into halves, quarters or smaller pieces. They are often crushed before administration in liquid or with food. The extent of ward-based segmenting of tablets is unknown, but it is believed to be extensive and might well occur if pharmacies have neither the time nor the information to provide other possibilities (Brion et al., 2003; Hepojoki, 2008).

Unequal breaking of tablets may result in dose variability (Teng et al., 2002; van Santen et al., 2002). Some tablets cannot be easily divided in half because of their size, a shallow score line, or thickness (van Santen et al., 2002; Sedrati et al., 1994). Even when commercial tablet cutters are used, the accuracy of splitting may be variable (Marriott and Nation, 2002; Sedrati et al., 1994; Teng et al., 2002). Uniformity of the drug content in different parts of the tablet may be unknown because content uniformity is tested only with undivided tablets. Splitting of tablets may also lead to loss of mass, due to powdering and fragmentation of the score line (Costello et al., 2007; van Santen et al., 2002; Teng et al., 2002). In one study, over 40% of manually split tablet portions (n = 1752) deviated from ideal weight by more than 10% and over 10% deviated by more than 20% (McDevitt et al., 1998). Greater than 15% variation of the intended mean half-tablet weight was found in certain products when they were split in half with a commercial splitter (Sedrati et al., 1994). Similar results have been found also by other investigators; the weight of a split tablet can range even from 50% to 150% of the actual half-tablet weight (Costello et al., 2007; van Santen et al., 2002). Teng et al (2002) found that of the 11 split tablet products (10 tablets for each product) evaluated, only three products passed the uniformity of dosage units test of the United States Pharmacopeia.

Uneven breaking of tablets may lead to significant fluctuations in the administered dose (Marriott and Nation, 2002). This may be clinically significant for drugs, which have a narrow therapeutic range. If the half-life of drug is long or the therapeutic range is wide, dose fluctuations are less likely to be clinically significant. The degree of inaccuracy seems to be associated with tablet size, shape and type of score line. Oval 10-mm tablets
with deep scores on both sides were most accurate in manual splitting (McDevitt et al., 1998). The tablet-splitting device was most accurate with larger (> 600 mg) tablets that were coated, and had an oblong shape and flat edges.

The tablet dissolution rate and absorption characteristics of coated and controlled-release tablets may be affected when tablets are split (Marriott and Nation, 2002). Splitting may also expose a drug’s taste, which has been masked in the coated tablet. A controlled-release tablet that has been split may produce overdose, which could lead to a number of adverse effects (Sam, 2002). Finally, enteric-coated tablets also should not be split.

2.4.4 Oral suspension

Main groups of oral liquid dosage forms are as follows: oral drops, oral liquids, oral solutions, oral suspensions, oral emulsions and syrups (National Agency for Medicines, 2008b). In this review, only oral suspensions will be discussed.

A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 \( \mu \)m are dispersed in a liquid (usually aqueous) medium (Attwood, 2007). Oral liquids are comparatively quick to prepare and allow versatility in dosage (Brion et al., 2003). For the extemporaneous preparation of suspensions on a small scale, the powdered drug can be mixed with the suspending agent and some of the vehicle using a mortar and pestle (Billany, 2007). The dosage can be measured from a single strength preparation by using an oral syringe (Brion et al., 2003). However, under these conditions it may be difficult to ensure palatability, as well as physical, chemical and microbiological stability. Preparations for oral administration should not include more than \( 10^3 \) bacteria and not more than \( 10^2 \) fungi per gram or per millilitre (European Pharmacopoeia, 6.1, 2007). New guidelines on the standards required for the preparation of non-sterile liquids in healthcare establishments recommend using closed systems for processing and transferring to protect the product from contamination (Pharmaceutical Inspection Convention, 2008).

It has been stated that an aqueous suspension is a useful dosage form for administering insoluble or poorly water-soluble drugs (Ashford, 2007). For poorly soluble drugs like nifedipine, dissolution is the limiting step in absorption (Costello et al, 2007). Based on Noyes-Whitney equation, it is known that if the dispersed drug in the suspension has a large surface area then this will enhance dissolution and hence absorption (Attwood,
In contrast to powder-filled hard gelatine capsules, dissolution of all drug particles begins immediately on dilution of the suspension in gastrointestinal fluids (Ashford, 2007).

Solutions and elixirs can be particularly irritating to the gastric mucosa and may be associated with adverse drug reactions like nausea and vomiting (Pagliaro, 2002). Gastric irritation and osmotic diarrhoea may result from administering drugs that increase the osmolality of the GI contents.

### 2.4.4.1 Sedimentation and redispersion

The product must remain sufficiently homogenous for at least the period between shaking the container and measuring the required amount (Billany, 2007; Marriott, 2007). In a suspension formulation where there is a dispersion of solids in a liquid of low viscosity, the components will tend to separate out and energy must be continuously supplied to keep the components adequately dispersed (Twitchell, 2007). The problems of the suspension include sedimentation, caking (close packing of the sedimented particles), flocculation and particle growth that occurs due to temperature fluctuations and these can all affect the solubility of the drug (Billany, 2007; Florence and Attwood, 2006). Adhesion of suspension particles to container walls has also been noted as a problem, particularly with low-dose drugs.

There has to be a balance between attractive and repulsive forces (Attwood, 2007). The electrical repulsive forces between the particles allow the particles to slip past one another to form a close packed arrangement at the bottom of the container, with the small particles filling the voids between the larger particles. Instead, a flocculated suspension will form loosely bonded sediments (Attwood, 2007; Billany 2007). A flocculate is a cluster of particles that do not settle as individual particles but are held together in a loose open structure (Florence and Attwood, 2006). The supernatant clears rapidly, but because of the random arrangement of the particles in the flocks, the sediment is not closely packed. The rapid clearance of the supernatant in a flocculated system produces the risk of an inaccurate dose being administered (Billany, 2007; Florence and Attwood, 2006). On the other hand, in a completely deflocculated system the particles are not associated. Pressure on the individual particles can lead to close packing of the particles to such an extent that the particles become irreversibly bound together. Thus, a suspension needs to be partially flocculated to enable easy redispersion and also it should be viscosity controlled to minimise the sedimentation rate.
Cake formation, the most serious physical stability problem of suspensions, may occur due to the formation of bridges between the particles (Attwood, 2007; Billany, 2007; Florence and Attwood, 2006). This cannot be totally prevented by reduction of particle size or by increasing the viscosity of the continuous phase. Fine particles can fill the voids between the larger ones and form more closely packed sediment which may be difficult to redisperse (Attwood, 2007; Florence and Attwood, 2006). Flocculating agents can prevent caking whereas deflocculating agents increase the tendency to cake (Florence and Attwood, 2006). The zeta potential of the particles can be measured to determine whether one should add flocculating or deflocculating agents. Thickeners produce a viscous medium and thus prevent the movement of the particles and sedimentation becomes delayed. In practice, the ease of redispersion in parallel with the uniformity of dose need to be tested (Costello et al., 2007).

For extemporaneous suspensions, it has been claimed that the ideal suspending agent should be readily dissolved or dispersed in water without resort to special techniques and should not influence the dissolution rate or absorption rate of the drug (Florence and Attwood, 2006). The hydrocolloids such as several non-Newtonian pseudoplastic cellulose derivatives used as suspending agents may produce a deflocculated system, particularly if used at low concentrations (Billany, 2007; Marriott, 2007). Hydrophilic colloids protect the solid hydrophobic particles with a multimolecular layer and thus impart a hydrophilic characteristic which promotes wetting. However, it is essential that the areas on each suspended particle remain free from absorbate, so that cross-linking can recur after the product is shared.
3 AIMS OF THE STUDY

The aim of this licentiate study was to evaluate the pharmaceutical quality of hospital pharmacy-prepared extemporaneous oral nifedipine dosage forms and their feasibility for use as paediatric medications.

Specific aims were:

1. to determine the content uniformity of nifedipine in oral powders and capsules prepared from crushed tablets with different amounts of lactose monohydrate or microcrystalline cellulose,

2. to determine the stability of nifedipine in oral powders for up to one year,

3. to formulate an oral liquid dosage form of nifedipine from both commercially available tablets and pure drug powder with a hypromellose solution for small-scale production and to determine the content uniformity of the suspension, and

4. to determine the short-term (1 month) chemical, microbiological and physical stability of an oral nifedipine suspension which was packaged in a capped unit-dose syringe.
4 MATERIALS AND METHODS

4.1 Materials

4.1.1 Nifedipine

The drug substance, nifedipine, was obtained either as the drug powder (Orion Corporation, Turku, Finland) or from crushed tablets (Adalat 10 mg retard, Bayer AG, Leverkusen, Germany). Nifedipine is practically insoluble in water (European Pharmacopoeia 6.1, 2007).

According to the manufacturer, the particle size of the nifedipine powder was less than 5 \( \mu m \) in at least 85% of particles, and all the particles were under 20 \( \mu m \). The manufacturer stated that the particle size of nifedipine in the tablet form was 7–13 \( \mu m \), with not more than 20% of particles over 25 \( \mu m \) and at most 2% of the particles over 30 \( \mu m \). Adalat 10 mg retard could be pulverized, because it does not contain any technological structure which is not allowed to be crushed; the retard effect is based on the particle size and the low water solubility of the drug.

4.1.2 Excipients

Lactose (Lactosum monohydricum Ph.Eur. parve granules, Pharmatose® 80 mesh, DMV International) and microcrystalline cellulose (Avicel® PH-102, FMC Corporation or Emcocel® 90M, Tamro, Finland) were used as excipients in the oral solid dosage forms. Hypromellose (Metocel E50LV, Ph.Eur. 50 mPa.s, University Pharmacy, Finland) was used as the suspending agent in sterile water, which was used as a vehicle in suspensions.

The solubility of lactose in 20°C water is 1 in 5.24 (Rowe et al., 2007). Lactose is not hygroscopic. The bulk density of Pharmatose® 80 mesh (DMV International) is 0.76 mg/cm\(^3\) and the tapped density is 0.91 mg/cm\(^3\). According to the supplier, 70–90% of the particles were under 250 \( \mu m \), <20% were under 100 \( \mu m \) and >95% were under 315 \( \mu m \).

Microcrystalline cellulose is practically insoluble in water (Rowe et al., 2007). The bulk density for microcrystalline cellulose is 0.29 g/cm\(^3\) for Emcocel® 90M and 0.32 g/cm\(^3\) for Avicel® PH-102. The tapped densities are 0.35 g/cm\(^3\) for Emcocel® 90M and 0.48 g/cm\(^3\) for Avicel® PH-102 (Allen, 2002; Rowe et al., 2007). Not more than 8% of the particles are retained in a mesh size of 250 \( \mu m \) and not less than 45% are retained in a mesh size of
74 µm (Rowe et al., 2007). Since it is a hygroscopic ingredient, it absorbs moisture from the air and thus has to be dispensed in tightly closed containers (Allen, 2002).

In Europe, grades of hypromellose are distinguished by appending a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20°C (Martindale, 2002). Hypromellose powder absorbs moisture from the atmosphere (Rowe et al., 2007). It is soluble in cold water, forming a viscous colloidal solution. The pH of 1% w/w aqueous solution is 5.5–5.8. Aqueous solutions may be sterilized by autoclaving, but on cooling must the coagulated polymer be redispersed by shaking.

Adalat® retard tablets contain microcrystalline cellulose as a lubricant and disintegrant, maize starch as a binder, filler and disintegrant, lactose monohydrate as a filler, polysorbate 80 as a wetting agent and non-ionic surfactant, and magnesium stearate as a lubricant (Pharmacca Fennica, 2007; Rowe et al., 2007). The filmcoating contains polyethylenglycol (macrogol) 4000 as a plasticizer in conjunction with film-forming hypromellose, white pigment titanium dioxide (E171) as a coating agent, opacifier and colouring pigment, and red ferrous oxide (E172) as colouring agent to increase the stability of light-sensitive active ingredient.

### 4.1.3 Packaging materials

Nifedipine powders were packed in waxed, sealed powder papers, which were sized at 47 x 30 mm (Paperityö, Helsinki, Finland).

Hard gelatine capsules, volumes of 0.50 ml (clear number 1, Tamro, Finland), 0.30 ml (clear number 3, Gallipot, USA), and 0.21 ml (white number 4, Gallipot, USA) were used as the packaging material in the capsules, whose contents were emptied for use.

Unit doses of nifedipine suspension were packed into 2 ml disposable syringes (Discardit, Becton Dickinson, Spain). Syringes were made of polyethylene (PE) and polypropylene (PP). The syringes were capped (Kombi-Stropfen, Clinico, Bad Hersfeld, Germany).

To protect the nifedipine from light all the dosage units were packed in black plastic bags (Amerplast, Ikaalinen, Finland). The containers and packing materials used in the study were the same as the actual packaging used for storage and distribution.
4.1.4 Standards for high performance liquid chromatography (HPLC)

Nifedipine stock solution, 1 mg/ml, was prepared from analytical grade nifedipine (nifedipine N-7634, Sigma Chemical Company, St. Louis, MO). HPLC-grade methanol (Lab-Scan, Dublin) was used to dilute the stock solution to standard concentrations of 5 µg/ml, 7 µg/ml (II, III, IV), 10 µg/ml (II, III, IV), 13 µg/ml (I) and 15 µg/ml (II, III, IV).

In studies II, III and IV, bupivacaine hydrochloride (Astra, Finland) was used as an internal standard.

4.2 Methods

4.2.1 Preparation of oral powders (I, IV) and capsules (IV)

Nifedipine oral powders and capsules were prepared by mixing five crushed and carefully ground 10-mg nifedipine tablets and the geometric amounts of either lactose or microcrystalline cellulose to achieve a final nifedipine concentration of 1.0 mg/unit. Nifedipine tablets were crushed in a mortar with a pestle. Crushed nifedipine tablets and nifedipine drug powder were examined in the scanning electron microscope (Jeol JSM-35 Scanning microscope, Tokyo, Japan). Nifedipine was always handled in a dimly lit room.

The resulting powder was divided into portions in powder papers or capsule shells. To prepare oral powders, the powder mixture was individually weighed into portions of 50 mg, 100 mg, 300 mg or 500 mg. The powders were packed in waxed powder papers. While preparing capsules, hard gelatine capsules of sizes 1 (0.50 ml), 3 (0.30 ml) and 4 (0.21 ml) were filled with the resulting powder using a hand operated capsule filler.

4.2.2 Testing of nifedipine at various hypromellose concentrations and preparation of suspension (II, III)

To find the optimal resuspendible and dose-accurate combination, different concentrations of hypromellose colloids were compounded with both nifedipine drug powder and crushed tablets. Hypromellose concentrations of 0.5%, 1.0%, 1.5%, 2.0%, 2.5% and 3.0% were used. The samples were taken with 2 ml disposable syringes, which are also used in practice.
The following tests were applied:

1. visual observation of sedimentation after one month of storage at room temperature (22–23°C, relative humidity (RH) of 60–72%),
2. measurement of the nifedipine concentration from the upper, middle and lower parts of the suspension vial 15 seconds after redispersion of the sediment by inverting the vial 10 times,
3. measurement of the nifedipine concentration from the middle part of the vial immediately, 1 min and 2 min after shaking, and
4. measurement of nifedipine concentration and resuspending properties after one month of storage in a unit dose syringe at room temperature (22–23°C, 60–72% RH).

Hypromellose powder was wetted with hot (80–90°C) water and cold (5°C) water was then added and the hypromellose solution was allowed to cool in ice water until it was thoroughly hydrated. Hypromellose solution was sterilized in a autoclave.

Nifedipine oral suspensions were prepared using nifedipine tablets or drug powder. The tablets were allowed to soak in hypromellose solution and then crushed. A small amount of hypromellose was ground into the drug powder. A uniform paste was prepared by adding geometric amounts of hypromellose solution. This was packed into a single unit syringes with a cap.

4.2.3 Content uniformity (I, II, IV)

The content uniformities of the nifedipine oral powders and suspensions were determined by a method described in the European Pharmacopoeia (European Pharmacopoeia 3rd ed, 1996; European Pharmacopoeia 5.5, 2006). The test for content uniformity is based on the assay of the individual contents of active substance of a number of dosage units to determine whether the individual contents are within the limits set. Ten dosage units were taken at random and individual contents of nifedipine were measured using high performance liquid chromatography. The preparation complied with the test if not more than one of the 10 individual contents was beyond ±15% of the average content, and if none were beyond ±25% of the average content.
4.2.3.1 HPLC-assay

Nifedipine amount was measured by a reproducible and validated stability-indicating HPLC method (Hagan, 1994). A forced photodegradation experiment on the nifedipine substance was performed in order to develop a validated HPLC-method. This was conducted by exposing nifedipine drug powder and crushed tablets to light of different wavelengths until significant degradation occurred. The stability-indicating capability of the HPLC method was verified by heating the nifedipine solution and a crushed tablet which were first mixed with either 1 M hydrochloric acid or 1 M sodium hydroxide (Mehta, 1993). The selectivity and specificity of the HPLC method were also confirmed by using liquid chromatography-mass spectrometry (Helin, 1995). The system precision of the HPLC method was examined and the correlation coefficients were determined (Hagan, 1994).

The concentrations of nifedipine formulations were estimated by peak height (I) or area (II, III, IV) relative to the drug substance using HPLC with UV detection at a wavelength of 238 nm. The HPLC system used in each of the studies is described in publications I, II and IV with a reverse phase C18 column being used. The mobile phase consisted of 68–70% methanol in 30–32% deionized distilled water which contained 0.1M ammonium acetate and 0.1% triethylamine. The pH was adjusted to 5.8. The flow rate was 1.0 ml/min. Bupivacaine was used as an internal standard (II, III, IV).

Each randomly selected sample of nifedipine oral powder, capsule or suspension was emptied carefully into a sample bottle. Methanol was added to a total volume of 10.0 ml. Ultrasound sonication (I, IV), centrifuging (II, III) and shaking (IV) were used to ensure dissolution of nifedipine in methanol. To prepare a sample solution, a 1000 µl of the resulting nifedipine solution was taken and diluted 1:10 with methanol. This solution as such (I) was assayed by HPLC, or a 750 µl the aliquot of solution was mixed with 250 µl of bupivacaine which acted as an internal standard solution (II, III, IV), and then assayed. All the samples were prepared in a dimly lit room and protected from light.

4.2.4 Chemical stability studies (I, III)

To study the stability the samples were stored under three controlled conditions: 1) at room temperature (21–23°C, 43–47% RH (I), 60–72% RH (III)) protected from light, 2) in a refrigerator (5–7°C, 60–66% RH (I), 67–77% RH (III)) protected from light, and 3) at room temperature (21–23°C, 60–72%RH (I), 58–62% RH (III)) exposed to artificial daylight.
Temperatures of the room and refrigerator were adjusted according to the European Pharmacopoeia (European Pharmacopoeia 3rd ed, 1996; European Pharmacopoeia 5.5, 2006).

It is difficult to establish the actual exposure of nifedipine products to light during practical usage. In tests simulating glass-filtered daylight, ‘artificial daylight’ fluorescent tubes were used. The spectrum of artificial full colour daylight was measured and it resembled the spectrum of mixed artificial light of the room and natural daylight coming through a window. Solid drug substances were spread across the folded powder paper. The samples from the powder papers and oral syringes were spread in a single layer to provide a maximum area of exposure to the light source. The spectral distribution of the light sources used was determined (III). The illumination of the sample area was measured with a lux meter and was found to be 400 lux at a distance of 60 cm from the lamp (I, III).

Nifedipine powder papers were stored for either 12 months protected from light or for 5 days when exposed to light. Nifedipine suspensions made in the optimal vehicle, 1% hypromellose, were stored after for 28 days protected from light or for 7 days when exposed to artificial daylight.

Samples were removed after the pre-determined period of storage and were analysed to assay the nifedipine concentration and to assess the degree of photodegradation. An HPLC-method was used to determine the nifedipine concentration as previously described. Drugs were considered stable if they retained ≥ 90% of the initial drug concentration (Mehta, 1993).

4.2.5 Physical stability studies (II, III)

Both nifedipine 1 mg/ml suspension and the optimal vehicle, hypromellose 1.0% solution, were tested for density (Mohr Westphal scale, Germany), pH (Mettler Toledo 320, Switzerland), osmolality (Osmostat Auto-Osmometer, Japan), viscosity (Falling Sphere Viscometer and Haake Rotovisco RV 2, Gebrüder Haake, Germany), surface tension (Krüss Interfacial Tensiometer, GWB, Germany) and organoleptic properties. Nifedipine suspensions were tested immediately after preparation and on days 14 and 28 of storage at either room temperature (22°C, 60–72% RH) or in a refrigerator (6°C, 67–77% RH). Hypromellose 1.0% solution was studied at the time of preparation, before and after steam sterilization and at 3, 6 and 12 months. The products were tested at 20°C, because
changes in temperature can affect viscosity and other physical characteristics. The equipment was calibrated at intervals as recommended by manufacturer.

4.2.6 Microbiological stability studies (II, III)

Although the European Pharmacopoeia does not require that an oral preparation should be microbe free, this is, of course, preferable for critically ill neonates. The microbiological stability of nifedipine suspensions and 1.0% hypromellose solution were investigated by using the European Pharmacopoeia method (European Pharmacopoeia 3\textsuperscript{rd} ed, 1996). Antimicrobial properties of the nifedipine solution were studied. The microbiological stability of nifedipine suspensions was determined immediately after preparation and on days 7, 14, 21 and 28 days after storage either protected from light at room temperature (22°C, 60–72% RH) or in a refrigerator (6°C, 67–77% RH) began. The sterility of the hypromellose 1.0% solution was tested after steam sterilization, and after 3, 6 and 12 months of storage at room temperature (22°C, 60–72% RH) using the method of direct inoculation (European Pharmacopoeia 3\textsuperscript{rd} ed, 1996). Fastidious anaerobe broths, tryptic soy broths and sabouraud broths were used as media.
5 RESULTS

5.1 Particle size characteristics of nifedipine drug powders and crushed tablets

The particle size of nifedipine drug powder and crushed Adalat® 10 mg retard tablet was characterized visually in a scanning electron microscope to obtain information about the properties of the powder mixture and suspensions. Nifedipine drug powder was relatively uniform in particle size whereas crushing of nifedipine tablets produced particles less than 100 µm that differed in size and shape (Figures 4 and 5). The particle size, which was less than 100 µm, was about the same particle size of the excipients and thus prevented stratification between large and small particles.

Figure 4. Nifedipine drug powder as viewed in a scanning electron microscope (II). Scale bar is 100 µm.
Figure 5. Nifedipine tablet crushed with a mortar and pestle and examined in a scanning electron microscope (II). Scale bar is 100 µm.

5.2 Testing of nifedipine at various hypromellose concentrations (II)

Nifedipine suspensions that were made from hypromellose concentrations of 0.5%, 1.0% and 1.5% were more flocculated and easier to redisperse than the other suspensions (II, Table 1). Suspensions made from nifedipine drug powder were more difficult to redisperse than the suspensions made from crushed tablets, but the concentrations after mixing were close to each other. As a result, hypromellose 1.0% was selected as a vehicle for suspensions with both drug powders and crushed tablets.

5.3 Content uniformity (I, II, IV)

The content uniformities of nifedipine powders, capsules and suspensions complied with the test specifications. The mean ± SD content of nifedipine theoretical content 1.0 mg was 0.92 ± 0.03 mg in powders (I), and 1.06 ± 0.05 mg and 1.09 ± 0.05 mg in nifedipine suspensions (II) made from crushed tablets and drug powders with 1.0% hypromellose,
respectively. The largest deviations from the mean content were 4.6% for powders, and 8.5% and 9.2% for suspensions. No remarkable differences were noted between hypromellose concentrations 0.5%, 1.0% and 1.5% or between nifedipine drug powders and crushed tablets.

Comparison between the different amounts of lactose monohydrate and microcrystalline cellulose as excipients in oral powders and capsules indicated that content uniformity remained acceptable although content was reduced down to about 85–90% of the theoretical value. In powders weighing 100 mg and 50 mg, the content was below 80% of the theoretical value both with lactose and microcrystalline cellulose (Figures 6 and 7). The nifedipine content was over 80% of the theoretical value in small capsules where the amount of the excipients were quite similar.

It was noticed that about 8% of the nifedipine amount of 1.0 mg was lost during the preparation and storage of powder papers (I). About 75% of that was found from the emptied powder papers. Minor amounts were found in the mortar and pestle and the other equipment used.
Figure 7. Nifedipine content in oral powders and emptied capsules number 1 (200 mg), 3 (130 mg) and 4 (80 mg) filled with cellulose microcrystalline. Theoretical amount of nifedipine was 1 mg. Mean values are shown (n = 10).

5.4 Chemical stability studies (I, III)

At least 92% of the initial concentration of nifedipine remained in the powders that were protected from light and stored at room temperature or in refrigerator for one year. In suspensions compounded from crushed tablets or drug powder, 95% and 93% of the mean nifedipine concentrations remained in the suspensions stored at room temperature, throughout the 28-day study period. When stored in the refrigerator, 91% and 92% remained, respectively. No evidence of the presence of degradation products was observed.

Significant degradation of nifedipine was observed in the powders exposed to light. Photodegradation of the nifedipine exceeded 20% within three hours and 40% within six hours and was essentially complete after three days. In suspensions made from tablets, photodegradation exceeded 26% within three hours and 40% within six hours, and was essentially complete after 7 days. Nifedipine powder in suspensions degraded more rapidly: 30% within three hours and nearly all of the active drug has disappeared after three days.
5.5 Physical stability studies (II, III)

At the end of the study intervals, the samples of drug-free hypromellose solution 1% and nifedipine suspensions (1 mg/ml) in 1% hypromellose solution protected from light were examined for any changes in their physical properties. Hypromellose solution 1% remained physically stable during the study period of 12 months (II, Table 5). The pH, viscosity, density, osmolality and surface tension of the nifedipine suspensions prepared both from tablets and drug powder, remained fairly stable over 28 days (III, Tables 3–4). Visual inspections revealed no change in colour during the study period. The colour of the nifedipine suspensions changed when they were exposed to light for 7 days.

5.6 Microbiological stability studies (II, III)

No microbiological contamination was observed in any samples of drug-free hypromellose 1% during a period of 6 months (22–23°C). Because of probable laboratory contamination, Propionebacterium was found in one of the samples at 12 months, but the duplicate test was sterile.

The antimicrobial properties of nifedipine suspension 1 mg/ml were examined. Nifedipine suspension did not inhibit the growth of microbes (Staphylococcus aureus, Bacteroides fragilis, Candida albicans). In the study of the microbiological stability of nifedipine suspension 1 mg/ml, no bacterial or fungal growth was observed in suspensions during the 28 day study period.
6 DISCUSSION

6.1 Nifedipine and excipients

Nifedipine is commonly used cardiovascular drug for which no licensed liquid is available. A nifedipine formulation obtained from crushed solid dosage form may not be bioequivalent with the same dosage form swallowed whole (Standing and Tuleu, 2005). It is known that when nifedipine retard tablets are crushed, drug release and dissolution rate increase (Tuleu et al., 2005). However, the usual recommendation in hypertension is to give a modified release preparation to avoid large swings in blood pressure (Standing and Tuleu, 2005). Licensing of nifedipine allows adults the benefit of once daily dosing, decreased risk of adverse drug reactions and formalised post-marketing surveillance. Children, who need to be treated with the same drug, have to take a dose three times a day, and are exposed to potentially increased risk of adverse drug reactions because no sustained release formulation is available.

To administer nifedipine orally to infants, one of the following methods may be used: 1) removal of nifedipine oily liquid from commercial soft capsules, 2) splitting of nifedipine retard tablets into segments, crushing the segment and administering it with food or beverages, 3) importing commercial drops of nifedipine 20 mg/ml, or 4) preparation of extemporaneous suspensions, powders or capsules from crushed retard tablets or drug powder (Tuleu et al., 2005). Unfortunately, nifedipine soft capsules of different brands contain different amounts of liquid and nifedipine drops are too concentrated. They both contain polyethylene glycols of low molecular weight as diluents, which might be harmful to infants. Splitting of tablets may lead to significant fluctuations in the administered dose. Thus, extemporaneous suspensions, powders or capsules are the choice to produce nifedipine drug products to infants.

The selection of the appropriate excipients for extemporaneous preparation is the responsibility of the pharmacist. Adverse toxic effects have been reported in paediatric patients due to the use of inappropriate excipients. Properties of the excipients may have also an influence on the uniformity of content and on loss of drug substance during its dispensing.

The ingredients in our nifedipine oral powder and capsule studies were selected because of their flow properties and particle size distribution. Both lactose and microcrystalline
cellulose are widely used and safe excipients in solid oral pharmaceutical formulations. The ingredient used in the suspension study, hypromellose, also known as hydroxypropylmethylcellulose, is nonreactive and pH-neutral, and thus assumed to be suitable for neonatal use. While it was appreciated that pure hypromellose as a suspending agent would not produce an ideal suspension but it was believed that the suspension would be accurate and safe to use also for neonates who have several restrictions on what excipients can be used. Hypromellose vehicle has also been reported to be suitable for administering nimodipine 60 mg via an oral syringe, in patients with acute subarachnoid haemorrhage (Soppi et al., 2007).

Lactose is broken down after hydrolysis by intestinal lactase and absorbed (Pawar and Kumar, 2002). Unabsorbed lactose is converted to lactic acid, carbon dioxide and hydrogen gas by the intestinal flora, and this can acidify the bowel, increase the osmotic load and irritate the colon. The safety of lactose during the neonatal phase is still being debated, as preterm infants have diminished levels of the enzyme lactase (Guandalini et al., 2006). Lactase activity increases progressively in the fetal intestine through the third trimester and approaches its maximum expression at term. Very few preterm neonates born at 28 weeks' gestation and approximately 40% of infants born at 34 weeks' gestation have significant intestinal lactase activity. Lactose is also contraindicated in infants with galactosemia, a rare congenital disorder that results in accumulation of galactose-1-phosphate, resulting in developmental delay, hepatic failure and cataracts (Pawar and Kumar, 2002).

6.2 Content uniformity

The content uniformity is a major factor if one wishes to assure repeatability of dosages and thus, the preparation of a safe and effective medication. Although the test of content uniformity is a requirement of European Pharmacopoeia (2007) and USP Pharmacists' Pharmacopeia (2008) for oral powders, capsules and suspensions, results can seldom be found in peer-reviewed journals.

Instead of the preparation of an extemporaneous product, tablet segments are sometimes used. According to our studies, better content uniformity is, however, achieved by extemporaneous preparation of oral solid or liquid dosage forms. Crushing of tablets is a critical point in the powder mass preparation. The grinding time and technique can influence the resulting homogeneity of the powder mixture by affecting the electrostatic
properties of the powder. It also has to be noted that particles may become segregated if they need to be stored before dispensing the doses. Thus, an awareness of this problem and professional skills are key factors in preparing extemporaneous medicines of good quality.

Our results indicated that the loss of nifedipine during the preparation process may be considerable. On the average, content uniformity testing revealed 0.92 mg of nifedipine in the 1.0 mg powders. Three quarters of the missing amount was located on the emptied powder papers. In the oral powder study of Hepojoki (2008) significant loss of drug substance, dipyridamole, was also found: on average 3% of the drug was found to be adhering to the equipment used during its preparation, 4–15% on the powder papers and 9–14% on the equipment used during administration. The amount of drug loss was dependent on the excipient used.

We found that preparation of small capsules, such as size numbers 3 or 4 was acceptable when considering the average nifedipine content. Thus, 80 mg of microcrystalline cellulose or 160 mg lactose was sufficient. Instead, the amount of excipient in oral powders has to be higher, since the amount of recovered nifedipine decreased as the total mass of the prepared oral powder was 50 mg or 100 mg. Nifedipine recovery was nearly the same in all emptied capsules compared with emptied oral powders weighing 300 mg or more. The reason for that might be smaller area of the capsule shells compared to the sealed powder papers.

A 1.0% solution of hypromellose was thick enough to reduce the rate of settling. Tötterman et al (1994) found that autoclaving decreased the viscosity of hypromellose-E50 1.5–4.0% solutions and the decrease in viscosity increased with the increase in the concentration of hypromellose. According to our study, the viscosity of the hypromellose 1.0% solution did not decrease remarkably during steam sterilisation, perhaps because of its low concentration.

Nifedipine suspension, formulated with hypromellose 1.0% solution, remained sufficiently homogenous to permit the removal of the accurate dose after shaking. Our impression was that suspensions made from crushed tablet were easier to redisperse than suspensions made from drug powder, which may be because of the differences in the particle size. The particle size in drug powder was smaller than in crushed tablet. That may result in more closely packed sediment. Prefilled oral syringes assure the uniformity of doses and also represent a medication that is ready to use. Only a small amount of air
needs to be drawn into the syringe before administration to ensure the resuspension of the settled particles. Unit-dose packaging of nifedipine suspensions prevents microbiological contamination, which was found by Ghulam et al. (2007) in multidose extemporaneous preparations.

6.3 Stability

These formulations provided adequate stability of extemporaneously prepared and light-protected nifedipine powders, capsules and suspensions for use in hospitalised patients. The investigated stability of the nifedipine formulations now means that the nifedipine preparations can be stored. The photodegradation of nifedipine was faster in suspensions made from drug powder than in those made from tablets because of light-protective effect of the excipients present in the tablets. Because these extemporaneously prepared nifedipine products are stable in the secondary package but unstable if it is not present, it is necessary to label products to prevent storage without secondary package. Tuleu et al. (2005) found that nifedipine in extemporaneous suspension (1 mg/ml) started to degrade after 15 min of exposure to light.

Nahata et al. (2002) investigated the stability of nifedipine in two oral suspensions and found them to be stable up to three months with refrigeration and at room temperature in amber plastic bottles. The vehicles used in that study were methylcellulose 1% : simple syrup NF (1:13) and Ora Plus® : Ora Sweet® (1:1). Dentinger et al. (2003) found extemporaneously prepared nifedipine 10 mg/ml oral solution to be stable for at least 35 days when stored in amber glass bottles at 22–25°C. The solution was prepared from nifedipine powder with polyethylene glycol 400, glycerol, and peppermint oil. According to Table 2, sucrose from simple syrup, and sucrose, glycerol and methylparaben of Ora-Sweet® and Ora-Plus®, and polyethylene glycol, glycerol and peppermint oil might cause some adverse effects. Thus, it is recommended that these excipients should not be used in neonates and infants.

One problem arising in stability testing of powder papers, capsules and dose syringes is that the analytical results tend to be more scattered because they are distinct dosage units rather than the true aliquots encountered with stability studies on drugs in solution. Thus, the uniformity of content has to be ensured.
6.4 Practical implications

In practice, extemporaneous preparation is an acute multidisciplinary process where decisions are made in co-operation with physicians, pharmacists and nurses. At present, there are no comprehensive published standards, and therefore decisions in different steps of preparation process have to be made by using professional pharmaceutical skills. During this study, a management flow chart and decision pathway was created for solving the issues encountered in the production of extemporaneous oral preparations (Figure 8). Roles and responsibilities in different stages of the preparation process are presented in Table 3.

In a ward setting, some problems may occur in administering the nifedipine powder through a nasogastric tube. However, the present studied nifedipine suspensions were found to flow easily through the small-bore nasogastric feeding tube, and no tube occlusion has been encountered.

In routine work, photodecomposition might occur not only during storage but also during preparation and use of the product. To prevent photodegradation, correct handling and storage procedures of nifedipine preparations needs to be taught to nurses, other health care providers, and parents. Extemporaneous nifedipine single-dose preparations are simple to use also at home, and the stability of the drug is relatively good.

Table 3. Model of roles and responsibilities in extemporaneous preparation in hospital pharmacy in Finland

<table>
<thead>
<tr>
<th>Handling state</th>
<th>Chief pharmacist (master degree)</th>
<th>Pharmacist (bachelor degree)</th>
<th>Accredited technician</th>
<th>Physician</th>
<th>Ward nurse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Order</td>
<td>R</td>
<td>RS</td>
<td>AC</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>Design of product</td>
<td>AC</td>
<td>R</td>
<td>RS</td>
<td>AC</td>
<td>Cl</td>
</tr>
<tr>
<td>Formulation</td>
<td>A</td>
<td>R</td>
<td>RS</td>
<td>AC</td>
<td>R</td>
</tr>
<tr>
<td>Preparation</td>
<td>A</td>
<td>R</td>
<td>I</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Packaging and labelling</td>
<td>AC</td>
<td>AC</td>
<td>R</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final check</td>
<td>A</td>
<td>RAC</td>
<td>R</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>Dispensing</td>
<td>AC</td>
<td>R</td>
<td>SI</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R = responsible person, A = person to whom R is accountable, S = can be supportive, C = could be consulted, I = should be informed
<table>
<thead>
<tr>
<th>Process</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design of product</strong></td>
<td>Suitable commercial product: - pharmacotherapeutical and biopharmaceutical aspects</td>
</tr>
<tr>
<td></td>
<td>Yes: Licensed and labeled for paediatric use</td>
</tr>
<tr>
<td></td>
<td>No: Commercial: 1) therapeutic alternative 2) dosage form alternative</td>
</tr>
<tr>
<td></td>
<td>Yes: Licensed and labeled for paediatric use</td>
</tr>
<tr>
<td></td>
<td>No: Extemporaneous preparation: - unlicensed use</td>
</tr>
<tr>
<td></td>
<td>No: Unlicensed or off-label use of commercial product</td>
</tr>
<tr>
<td><strong>Formulation</strong></td>
<td>Extemporaneous oral liquid preparation: - pharmacopoeial formula - stability-indicating formula</td>
</tr>
<tr>
<td></td>
<td>No: Extemporaneous oral solid preparation: - pharmacopoeial formula - stability-indicating formula</td>
</tr>
<tr>
<td></td>
<td>Yes: Active pharmaceutical ingredient: - pure drug substance - manipulation of commercial solid dosage form</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>Oral liquid: - single-dose - multiple-dose</td>
</tr>
<tr>
<td></td>
<td>Oral suspension: - single-dose - multiple-dose</td>
</tr>
<tr>
<td></td>
<td>Capsules: - emptied before use</td>
</tr>
<tr>
<td></td>
<td>Oral powders</td>
</tr>
<tr>
<td><strong>Packaging and labelling</strong></td>
<td>Packaging</td>
</tr>
<tr>
<td></td>
<td>Labelling</td>
</tr>
<tr>
<td></td>
<td>Double checking of calculations Quality control</td>
</tr>
<tr>
<td></td>
<td>Approval of the product</td>
</tr>
</tbody>
</table>

Figure 8. Process of preparing extemporaneous oral preparations and decision-making
7 CONCLUSIONS

According to these studies, the following conclusions are presented:

1. Nifedipine capsules, whose contents are emptied prior to use, provide an alternative to oral powders in preparing paediatric medications. The content uniformities of the nifedipine capsules and oral powders made from crushed tablets with different amounts of lactose monohydrate or microcrystalline cellulose met the established requirements. However, the nifedipine amount was less than 80% of the theoretical value in oral powders of total weight 100 mg and 50 mg.

2. Nifedipine 1.0 mg in 500 mg of a powder compounded extemporaneously from nifedipine tablets and lactose monohydrate was stable for up to one year when stored in waxed powder papers in black plastic bags at room temperature and in refrigerator.

3. A 1.0% hypromellose solution had the best properties as a suspending agent for 1 mg/ml nifedipine. Autoclaved drug-free hypromellose 1.0% solutions were microbiologically stable for at least 6 months.

4. The content uniformity of the nifedipine suspension made from both crushed tablets and drug powder met the established requirements.

5. Nifedipine unit-dose suspensions, packaged in capped syringes, were chemically, physically and microbiologically stable throughout the 4-week study period in oral syringes that were at room temperature or being refrigerated protected from light.

6. When exposed to light, nifedipine in the powder or suspension degraded rapidly at room temperature. In all, 20–30% photodegradation of the nifedipine occurred within three hours.
8 REFERENCES


European Pharmacopoeia, supplement 5.5 to the 5th edition. Council of Europe, Strasbourg, France, 2006

European Pharmacopoeia 3rd ed, Council of Europe, Strasbourg, France, 1996


Helin M: Vastasyntyneiden lääkitys sairaalafarmasian haasteena. Master’s thesis, Faculty of pharmacy, University of Kuopio, Kuopio 1995

Hepojoki T: Lastenlääkinnän ongelmat sairaalafarmasiassa ja dipyridamoliannosjauheiden annosvaihtelun tutkiminen. Master’s thesis, Faculty of pharmacy, University of Helsinki, Helsinki 2008


Pharmacca Fennica. Lääketietokeskus Oy, Helsinki 2007


