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Minna Helin-Tanninen

Compounding of Paediatric Oral Formulations

Extemporaneous Nifedipine Capsules, Powders and Suspensions in the Hospital Pharmacy

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ABSTRACT:

Despite efforts to improve the availability of commercial drug products for children, there is still a widespread need for compounded preparations. Age-appropriate dosage forms formulated at different strengths containing harmless excipients are routinely needed. Therefore, hospital pharmacies still compound a wide range of preparations although there are no appropriate and comprehensive published standards.

The present study examined the chemical and physical stabilities and content uniformities of one compounded, nifedipine in 1 mg oral dosage forms by using reproducible and validated stability-indicating high performance liquid chromatography (HPLC) methods. Individually weighed oral powders, hard gelatin capsules and unit-dose or multi-dose suspensions were compounded either by using a crushed commercial tablet or from nifedipine drug powder.

The results indicate that both solid and liquid oral dosage forms may provide suitable solutions to treat paediatric patients of different ages. The total mass of the nifedipine oral powder had to be 300 mg or more in order to ensure accurate dosage. When the mass was 100 mg or 50 mg, the nifedipine amount was less than 80% of the targeted amount. Most of the missing amount was located on the emptied powder papers. Nifedipine capsules, sizes 1–4 (0.21–0.50 ml), whose contents were emptied prior to use, do represent a good alternative to oral powders when comparing the recovery. Nifedipine 1 mg/ml unit-dose suspension in hypromellose 1% was chosen as the formulation for administration via nasogastric feeding tubes. Oral powders were chemically stable for the studied period of 12 months and unit-dose suspensions were chemically, physically and microbiologically stable for four weeks, at room temperature or in the refrigerator. Due to the light sensitivity of nifedipine, it required protection from light during handling and storage. When exposed to artificial daylight, 20–30% photodegradation occurred within three hours. The content uniformities of the nifedipine unit-dose suspensions, powders and capsules met the requirements of the European Pharmacopoeia. Vigorous agitation, i.e. inverting the bottle 10-15 times instead of three times, was critical for ensuring the content uniformity of nifedipine 1 mg/ml multi-dose suspensions compounded with extemporaneous vehicles. In contrast, nifedipine 1 mg/ml multidose suspensions passed the test if the bottle was inverted only three times when more sophisticated commercial suspension vehicles were used.

In conclusion, compounded nifedipine oral powders and unit-dose suspensions were stable and uniform throughout the study periods when protected from light. Emptying of capsules represents an alternative to oral powders. The agitation of suspension vehicle is important to ensure the quality of oral multi-dose suspensions. The individual needs of each child's in nifedipine medication can be satisfied with these age-appropriate dosage forms.

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Helin-Tanninen, Minna
Lasten ex tempore –lääkevalmisteet, sairaala-apteekissa valmistetut nifedipiinikapselit, -jauheet ja -oraalisuspensiot
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TIIVISTELMÄ:

Lasten lääkehoidon kehityksestä huolimatta kaupallinen lääkevalikoima ei kata kaikkia lapsipotilaiden lääkitystarpeita. Suurin osa valmisteista on suunniteltu ja tutkittu ainoastaan aikuisilla eikä niitä voida käyttää sellaisenaan lapsille, joille tarvittaisiin useita vahvuuksia, sopivia lääkemuotoja ja turvallisia, haitattomia apuaineita. Siksi sairaala-apteekeissa valmistetaan edelleen runsaasti ex tempore –lääkevalmisteita lapsille. Ne ovat myyntiluvattomia tuotteita, joita on tutkittu melko vähän.

Tässä työssä tutkittiin sairaala-apteekissa valmistettujen suun kautta annettavien nifedipiinivalmisteiden kemiallista ja fysikaalista säilyvyyttä ja annosvaihtelua. Analytiikassa käytettiin muun muassa korkean erotuskyvyn nestekromatografiaa (HPLC). Yksitellen punnitut jauheet, kovat liivatekapselit ja yksittäisannoksiksi tai pulloon pakatut suspensiot valmistettiin joko murskatuista tableteista tai nifedipiinipuhdasaineesta.

Sekä kiinteitä että nestemäisiä lääkevalmisteita voidaan käyttää eri ikäisten lasten hoitoon. Tutkimuksessa havaittiin, että nifedipiinijauheiden massan on oltava vähintään 300 mg, jotta saadaan riittävän tarkkoja annoksia. Kun jauheiden massa oli 100 tai 50 mg, nifedipiinin saanto oli alle 80% tavoitepitoisuudesta. Lääkeainetta jäi eniten tyhjennettyihin annosjauhekuoriin. Tyhjennettävät kapselit, koot 1–4 (0,21–0,50 ml), ovat varteenotettava vaihtoehto jauheille, sillä nifedipiinin saanto pysyy riittävänä. Vastasyntyneiden nenämahaletkulääkintää varten kehitettiin yksittäispakatut nifedipiiniannossuspensiot, joissa apuaineena käytettiin 1% hypromelloosia. Jauheet säilyivät kemiallisesti muuttumattomina 12 kuukauden tutkimuksen ajan ja yksittäispakatut suspensiot kemiallisesti, fysikaalisesti ja mikrobiologisesti neljä viikkoa sekä huoneenlämmössä että jääkaapissa. Valonarka nifedipiini on suojattava valolta käsittelyn ja säilytyksen aikana, sillä valolle altistettuna 20–30% lääkeaineesta hajoaa kolmessa tunnissa. Yksittäisannoksiksi pakattujen suspensioiden, jauheiden ja kapseleiden annosvaihtelu täytti Euroopan farmakopean vaatimukset. Ravistelun määrällä on suuri merkitys moniannossupensioiden annosvaihtelulle. Kun käytettiin apteekissa valmistettua suspensiopohjaa, tarvittiin 10–15 kääntelyn huolellinen ravistelu, kun sen sijaan kaupallisiin, teollisesti kehitettyihin suspensiopohjiin valmistetut nifedipiinisuspensiot sekoittuivat hyvin jo vähällä, 3 kääntelyn ravistelulla.

Tutkimuksen perusteella nifedipiinijauheet ja yksittäispakatut suspensiot säilyivät hyvin ja tasalaatuisina tutkimuksen ajan, kun ne suojattiin valolta. Tyhjennettävät kapselit ovat hyvä vaihtoehto suun kautta annettavaksi kiinteäksi lääkevalmisteeksi. Suspensiopohjan valinta vaikuttaa merkittävästi moniannossuspensioiden laatuun. Tutkituilla nifedipiinivalmisteilla on mahdollista täyttää lapsipotilaiden yksilölliset lääkitystarpeet.

Luokitus: QV 754, QV 779, QV 786, WX 179
Yleinen Suomalainen asiasanasto: farmasia; apteekit; sairaalat; lastentaudit; lääkkeet; lääkeaineet; kapselit; jauheet; stabiilius; homogeenisuus; nestekromatografia

The latin word Infant means speechless.

We have to speak on behalf of the speechless.

Acknowledgements

Writing is way to a live, but carrying out research is way to help. The focus of this work is a premature, neonate, infant, toddler or a child – a paediatric patient who needs medication. Unfortunately, these patients are not always able to receive industrially manufactured medicines for which the quality is assured. The starting point of this study was the need to produce a neonatal nifedipine medication in special health care in the situation where there are no suitable commercial products. The work expanded to testing different dosage forms so that a suitable option could be found for the many medication challenges posed by paediatric patients.

It is not possible to undertake a dissertation alone, without encouragement and guidance. Encouragement and guidance I have really received since my Master's Degree from my excellent supervisors. When they started this job, they surely did not envisage how long this project would last. My two supervisors, the principal supervisor of my work, Chief Pharmacist Toivo Naaranlahti, Ph.D., and Kirsi Kontra, Lic.Sc. (Pharm.), deserve my sincere gratitude for all their efforts, guidance and patience during these years, their fantastic senses of humour and ability to cooperate as a team and thus 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 received competent, prompt and relevant supervision from Professor Kristiina Järvinen, Ph.D., during the final years of the study. Thank you for your expert advice and valuable comments. I am also grateful to my supervisor during the first years, City Manager Petteri Paronen, Ph.D., for his broadmindedness and assistance in helping me to obtain the facilities that made this work possible.

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Suonenjoki, November 2013

Minna Helin-Tanninen

List of the original publications

This dissertation is based on the following original publications:

I Helin M, Kontra K, Naaranlahti T and Wallenius K. Content uniformity and stability of nifedipine in extemporaneously compounded oral powders. *American Journal of Health-System Pharmacy 55: 1299–1301, 1998.*

II Helin-Tanninen M, Naaranlahti T, Kontra K and Wallenius K. Enteral suspension of nifedipine for neonates. Part 1. Formulation of nifedipine suspension for hospital use. *Journal of Clinical Pharmacy and Therapeutics 26: 49–57, 2001.*

III Helin-Tanninen M, Naaranlahti T, Kontra K and Ojanen T. Enteral suspension of nifedipine for neonates. Part 2. Stability of an extemporaneously compounded nifedipine suspension. *Journal of Clinical Pharmacy and Therapeutics 26: 59–66, 2001.*

IV Helin-Tanninen M, Naaranlahti T, Kontra K and Savolainen K. Nifedipine capsules may provide a viable alternative to oral powders for paediatric patients. *Journal of Clinical Pharmacy and Therapeutics 32: 49–55, 2007.*

V Helin-Tanninen M, Autio K, Keski-Rahkonen P, Naaranlahti T and Järvinen K. Comparison of six different suspension vehicles in compounding of oral extemporaneous nifedipine suspension for paediatric patients. *European Journal of Hospital Pharmacy 19: 432-437, 2012.*

The publications were adapted with the permission of the copyright owners. In addition, some unpublished data are presented in chapter 5.

Contents

Abbreviations

ADR	Adverse drug reaction
APF	Australian Pharmacopoeia Formulae
API	Active pharmaceutical ingredient
AV	Acceptance value
BP	British Pharmacopoeia
BPD	Bronchopulmonary dysplasia
CCA	Calcium channel antagonist
CFU	Colony forming unit
EMA	European Medicines Agency
EU	European Union
FDA	U.S. Food and Drug Administration
GMP	Good manufacturing practices
HPLC	High performance liquid chromatography
MA	Marketing authorisation
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PDCO	Paediatric Committee
PIC/S	Pharmaceutical Inspection Convention
PIC/S GPP	Good preparation practices
PIP	Paediatric investigation plan
PUMA	Paediatric use marketing authorisation
RSD	Relative standard deviation
SD	Standard deviation
SEM	Scanning electron microscope
SmPC	Summary of product characteristics
USP	United States Pharmacopeia

Definitions

ADOLESCENT	From 12 years to less than 18 years.
CHILD	From 2 years to less than 12 years.
COMPOUNDING	The process undertaken by the individual pharmacist who creates a medicine from active drug substance and excipients or from an authorised dosage form and excipients when no suitable dosage form is commercially or locally available (Ernest *et al*. 2012). Also known as extemporaneous dispensing or preparation.
EXTEMPORANEOUS PREPARATION	A product, which is dispensed immediately after preparation and not kept in stock (Pharmaceutical Inspection Convention, 2008).
INFANT	From 1 month to less than 12 months.
MANIPULATION	Modification of marketed dosage form at time of administration, eg. segmenting or splitting tablet or mixing with food (Ernest *et al*. 2012).
NEWBORN (NEONATE)	From birth to 28 days of age.
OFF-LABEL USE OF MEDICINES	All uses of a marketed drug not detailed in the Summary of product characteristics including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration (Neubert *et al*., 2008).
PRETERM NEWBORN (PREMATURE)	Born before 37 weeks of gestation.
RECONSTITUTION	Manipulation to enable the use or application of a medicinal product with a marketing authorization in accordance with the instructions given in the summary of product characteristics or the patient information leaflet (*Council of Europe Resolution CM/ResAP(2011)1*).

SPECIALS	Extemporaneous preparations that are made in larger volumes by licensed manufacturers.
STABILITY	The extent to which a preparation retains, within specified limits, and throughout its period of storage and use, the same properties and characteristics that is possessed at the time of compounding (The United States Pharmacopeial Convention, 2008).
TODDLER	From 1 year to less than 2 years of age.
UNLICENCED USE OF MEDICINES	All uses of a drug, which have not received a European marketing authorisation as medicinal for human use in either adults or children (Neubert *et al*., 2008). The categories: medicines compounded extemporaneously, modifications to licensed product, particular formulation manufactured under a 'specials' licence ', unlicensed drug made by a licensed manufacturer, a chemical used as a medicine, drugs used prior to granting of a licence or under special manufacturing licence, and imported drugs which are licensed in the country of origin (Turner *et al*., 1998).

1 Introduction

Compounding has remained an integral part of pharmacy practice. Extemporaneous compounding in hospitals and community pharmacies is important since it allows the provision of age-appropriate dosage forms when suitable authorised medicines are not available (Giam and McLachlan, 2008; Nunn, Aindow and Woods, 2012). The compounding of customised medicines is needed in particular situations in which the proprietary medicines available do not meet the specific needs of the patients: need for particular strengths, alternative dosage forms, ingredients or organoleptic characteristics (Carvalho, Taylor and Tuleu, 2012).

The lack of appropriate manufactured paediatric formulations is a worldwide problem (Giacoia, Taylor-Zapata and Mattison, 2007a). Since many drugs are not licensed for use in paediatric populations, the manufacturer does not usually produce age-appropriate dosage forms for the market (Pai and Nahata, 2001). There are also situations where the medicines are not available from commercial suppliers: shortages of medicines, discontinued medicines, special combinations or orphan medicines (Carvalho, Taylor and Tuleu, 2012). A positive trend in the approval of safe and efficacious medicines for children seems to be in progress in Europe (Ceci *et al*., 2006). The European paediatric regulation (Regulation (EC) No 1901/2006) had a positive impact on achieving this goal.

This dissertation, where the extemporaneous compounding of oral paediatric formulations is examined, is in a field where rather limited amounts of research have been published. Without specific technical information, pharmacists are often forced to rely on their professional skills and general knowledge of pharmaceutical compounding science. This study is restricted mainly to extemporaneous oral formulations for use in preterm and term newborns, infants and toddlers. In these age groups, the range of doses and dosage forms used may be wide, because of the developmental changes that occur during the first years of life (Tuleu, 2007).

Nifedipine is one of the drugs which may need to be administered for all these age groups as an extemporaneous preparation because in Finland commercial nifedipine is available as either tablets or extended-release tablets (Pai and Nahata, 2001; Standing and Tuleu, 2005; Sahney, 2006). In Kuopio University Hospital, over 5600 nifedipine powders were compounded in 1994 and although less in 2012, still over 1100 oral unit-dose syringes were prepared. Extended-release nifedipine is one of the most commonly used oral calcium channel antagonists (CCA) in the treatment of chronic paediatric hypertension (Moncica *et al*., 1995; Sadowski and Falkner 1996; Sinaiko, 1996, Silverstein *et al*., 1999; Sahney, 2006; Seikaly, 2007; Meyers and Siu, 2011). Nifedipine is also one of the oldest agents in therapy of paediatric pulmonary arterial hypertension although today it is limited to selected patients who need to undergo a positive acute vasodilator challenge (Hawkins and Tulloh, 2009; Ivy, 2012). Nifedipine has also been indicated in bronchopulmonary dysplasia (BPD), a result of lung injury mostly encountered in low birth weight preterm infants requiring mechanical ventilation and supplemental oxygen (Kochanek, 1985; Brownlee, Beekman and Rosenthal, 1988; Johnson *et al*., 1991; Ali *et al*., 2013; Zysman-Colman *et al*., 2013).

The aim of this study was first to formulate, then to characterize in vitro and finally to compare different extemporaneous oral formulations of nifedipine intended for paediatric use from preterm newborns to children. The stability and uniformity of dosage units were a focus of special investigation. In this respect, nifedipine is an ideal model drug due to its undesirable physicochemical properties, such as insolubility in water and sensitivity to light.

2 Review of the Literature

2.1 AUTHORIZED MEDICINES

Of all the active substances that were authorized and issued with a Marketing Authorisation (MA) by the European Agency for the Evaluation of Medicinal Products in the period October 1995 to September 2005, only 33% were licensed for paediatric use, 23% for use in infants and only 9% were available for newborns (Ceci *et al*., 2006). During the last 14 years, the FDA has updated the labeling of 434 drugs for which studies have been completed in children, but only one is a product intended for premature infants (Davis, Connor and Wood, 2012). Since the introduction of antenatal corticosteroids and surfactant 15 to 20 years ago, no new medications appeared that would have substantially improved the outcome for preterm infants.

The paediatric market is comparatively small and segmented by age groups, necessitating different formulations and dosing for each age group (Leff and Roberts, 1987; Primovic, 1993; Nahata, 1999a; Steinbrook, 2002; Glass and Haywood, 2006; Ernest et al., 2007; Giacoia, Taylor-Zapata and Mattison, 2007b; Nahata and Allen, 2008). Drug testing is costly, time-consuming and could result in a poor return on investment. During recent years, there has been a trend in the pharmaceutical industry to decrease the variety and number of dosage forms being marketed (Allen, 2003). Therapeutic advances (e.g. modified-release forms) are rarely available for children. In the future, the paediatric drug formulation and adult formulations should be developed in tandem (Salunke et al., 2011).

The Regulation issued by the European Parliament and of the Council on Medicinal Product for Paediatric Use came into force in January 2007, nearly ten years later than the corresponding mandatory regulation in the USA. It obliges the pharmaceutical industry to undertake clinical trials in the paediatric population (*Regulation (EC) No 1901/2006 of the European Parliament and of the Council, 2006*; Breitkreutz, 2008). There are several goals of this regulation: to facilitate the development and accessibility of medicinal products for use in children, to ascertain that medicinal products used to treat the paediatric population are subject to ethical research of high quality, to ensure that medicinal products are appropriately authorised for use in the children, to improve the information available on the use of medicinal products in the various paediatric populations, to achieve these objectives without subjecting children to unnecessary clinical trials and to prevent any delay in the authorisation of medicinal products for other age groups.

Four key measures were introduced by the new European Union (EU) legislation: installing an expert committee on paediatric medicines (Paediatric Committee, PDCO) at the EMA, requesting a Paediatric Investigation Plan (PIP) at an early stage of clinical development for all new chemical entities, granting a Supplementary protection certificate and market exclusivity for a new drug which have been developed with adherence to the agreed PIP, and granting a Paediatric Use Marketing Authorisation (PUMA) for drug substances with expired patent protection (*Regulation (EC) No 1901/2006 of the European Parliament and of the Council, 2006*; Breitkreutz, 2008). In addition, EMA and PDCO have drawn up a priority list of off-patent medicinal products for which studies are required (*European Medicines Agency EMA/98717/2012, 2012*). As a result, various collaborative project groups have been established in the EU in recent years (Breitkreutz, 2008; Finney, 2011). Both European Medicines Agency and World Health Organization have published guidance on pharmaceutical development of paediatric medicines (*European Medicines Agency*, 2006; *European Medicines Agency EMA/CHMP/QWP/805880/2012 Rev. 2, 2013*; World Health Organization, 2012).

Over a period of five years, up to the end of 2011, the Paediatric Committee had evaluated PIPs for 683 medicines, of which 70% were in adherence to a PIP (*European Medicines Agency EMA/428172/2012, 2012*). The plans led to new paediatric indications in 24 medicines and to new pharmaceutical forms appropriate for children in 7 medicines, which is not as many as it was expected (Lindell-Osuagwu *et al.,* submitted). Ten new medicinal products out of 113 new active substances were centrally authorized and received a paediatric indication.

2.2 OFF-LABEL AND UNLICENSED MEDICINES

Off-label and unlicensed use of drugs in paediatric drug therapy occurs in all countries and specialty areas of practice (Conroy and McIntyre, 2005; Giam and McLachlan, 2008; Kimland and Odlind, 2012; Mason, Pirmohamed and Nunn 2012). Many medicines licensed for use in adults are not officially licensed for infants, even though their use may be considered as the current standard of care.

Prescription, dispensing and administration of unlicensed and off-label medicines are permitted according to the legislation in most countries, including EU countries; this procedure is not forbidden in Finnish legislation (Turner, Nunn and Choonara, 1997; Giam and McLachlan, 2008; Ministry of Social Affairs and Health, 2010). However, in some countries e.g. India, unlicensed and off-label prescribing is considered illegal (Mudur, 2004; Conroy and McIntyre, 2005).

2.2.1 Use

The off-label and unlicensed use of medicines in paediatrics is common in many countries. In hospital and neonatal care studies, the proportion of off-label use has ranged from 10% up to 65% of all prescriptions (Kimland and Odlind, 2012). In outpatient care, the proportion of off-label drug prescriptions has varied between 11% and 31% (McIntyre *et al*., 2000; Olsson *et al*., 2011; Kimland and Odlind, 2012). The lack of common definitions for off-label and unlicensed use of medicines complicates comparison between different countries (Neubert *et al*., 2008).

The unlicensed drug use in hospital wards accounted for 4.6% of prescriptions in Sweden, 6.9% in United Kingdom but as high as 48% in the Netherlands (Turner *et al*. 1998; 't Jong *et al*., 2001; Kimland *et al*., 2012). National differences are also apparent in the unlicensed drug use in outpatient care i.e. 0.3% in an English study but 16.6% of the total prescriptions in a Dutch study and if one considered the age group 0–1 year then the percentage rose to 34.7% (McIntyre *et al*., 2000; Schirm, Tobi and de Jong-van den Berg, 2003).

In a Finnish study conducted in 2001 in a neonatal intensive care unit (NICU), general paediatric ward and paediatric surgical ward in Kuopio University Hospital, 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*., 2009). The age groups most commonly receiving unlicensed drugs were neonates, infants and toddlers. However, in 2011 prescriptions for unlicensed medicines compounded by the hospital pharmacy were less common than in 2001 (Lindell-Osuagwu *et al.*, submitted). The overall proportion of prescriptions for unlicensed drugs (13%) was similar to that described in other studies (11–12%) in paediatric intensive care units in Australia and Italy (O'Donnell, Stone and Morley, 2002; Dell'Aera *et al*., 2007; Lindell-Osuagwu *et al*., 2009). The majority, from 67% to 80% of European and Australian infants, 93% of extremely low birth weigh infants in Australia and even all patients in Kuopio University Hospital need to receive at least one unlicensed or off-label medicine during their stay in the NICU (Conroy *et al*., 2000; O'Donnell, Stone and Morley, 2002; Lindell-Osuagwu *et al*., submitted).

In the European study it was noted that the majority, 60%, of those most important extemporaneous products were marketed as suitable licensed paediatric formulations in other European countries, North America or Australia (Brion, Nunn and Rieutord, 2003). Thus, regulatory authorities need to cooperate to ensure licensing approval in all European countries and to enable free movement of licensed medicines between European countries. Today special permission for compassionate use is needed from the Finnish Medicines Agency. Cost and transporting time may also prevent the willingness to import.

2.2.2 Risks

Knowledge of drug administration in children has lagged behind that of adults (Sinha and Cranswick, 2007). The skill and judgement of physicians and pharmacists are critical in ensuring that the patient receives the appropriate drug, the best dosage form and an optimal dosing regimen. In the absence of specific clinical trial-based data in children, clinicians are forced to rely on experience from adult patients, although children have different pharmacokinetics to adults and their response to many medicines can be unpredictable (Nahata, 1992; Pagliaro, 2002; Conroy and McIntyre, 2005; Costello, 2007; Williams, 2013). The decision to use a drug in neonates is often based on a number of factors such as the clinical experience of the prescribing physician, an expert opinion, studies in older children, or a pilot study in newborns (Sinha and Cranswick, 2007; Davis, Connor and Wood, 2012).

In 2010, out of an estimated 134.2 million livebirths worldwide, 11.1% were born preterm, ranging from about 5% in several European countries up to 18% in some African countries (Blencowe *et al*., 2012). Unlicensed and off-label medicine use is more likely to occur in newborn infants, who may be predisposed to suffer adverse drug reactions (ADRs) due to their physiological immaturity (Zenk, 1994; Conroy and McIntyre, 2005; Costello, 2007).

The lack of suitably adapted medicines and calculated individualized doses for children may increase the risk of ADRs and/or ineffective treatment: either under- or over-dosing (Costello, 2007; Pagliaro, 2002). According to a large review of 102 studies, the use of multiple drugs seems to be an important predictor of the appearance of ADRs in children (Smyth *et al*., 2012). Anti-infectives and anti-epileptics were the most frequently reported therapeutic classes associated with ADRs in hospitalized children and anti-infectives and non-steroidal anti-inflammatory drugs were frequently associated with ADRs in paediatric outpatients. Furthermore ADRs occurred in 3.9% of the licensed drug prescriptions and in 6% of the unlicensed or off-label precriptions in paediatric inpatients (Turner *et al*., 1999). Evaluation of the studies confirm the higher risk of ADRs when prescribing is unlicensed or off-label and also indicate that these ADRs can be serious but there is still lack of clarity and this is an area that needs further research (Conroy and McIntyre, 2005; Mason, Pirmohamed and Nunn, 2012).

When a drug is not approved for use in infants and children, it is usually not available in an appropriate dosage form, formulation, size or concentration for the paediatric population. Children are often unable to swallow capsules or tablets due to anatomy of their buccal cavity, and consequently some deaths has been reported associated with aspiration of solid dosage forms (Reilly and Walter, 1992; Tuleu, 2007; Ernest *et al*., 2007; Giacoia, Taylor-Zapata and Mattison, 2007a). Many pharmaceutical preparations contain ingredients that have been reported to cause ADRs for paediatric patients (Leff and Roberts, 1987; Ernest *et al*., 2007). The range of doses needed may be wide because there is such a wide variation in body mass and developmental biological and pharmacological features (Nahata, 1991; Wong, 2007; Ernest, et al., 2007).

Ampoules normally contain adult-sized doses and even ampoules or vials intended for children may contain much more than required for neonates (Choonara and Nunn, 2006). In addition, drug products intended for adults are not often available in a concentration

low enough to permit accurate and precise dispensing of small doses (Nahata, 1999a; Nahata, 1999b). At the point of administration 10% of doses required some kind of manipulation or measurement of a small volume, e.g. under 0.2 ml volume (Nunn *et al*., 2013). Trying to measure less than 0.1 ml or a dilution to permit a larger volume to be dispensed was needed in 25% of the manipulated drugs. Errors may occur in measuring doses under 0.1 ml and measurement errors with potent drugs like morphine and digoxin have been reported as sources of intoxication and deaths in paediatric patients (Nahata, 1999a; Nahata, 1999b; Wong, 2007). Dilutions of 1:10 or 1:100 are often required to accurately measure the required doses (Zenk, 1994).

The total blood volume of a 500 g preterm infant is 40 ml (Ernest *et al*., 2007). A 1 kg neonate may only receive a total of 150 ml of fluids each day, and this much include all nutritional requirements as well as therapy (*European Medicines Agency, 2006*). Seriously ill neonates are often fluid restricted, limiting the volume of medications that can be administered (Glass and Haywood, 2006). The delay in administration of intravenous drugs in paediatric patients may be as long as several hours (Roberts, 1994). In premature infants, intravenous flow rates of <10 ml/hour, even as low as 3 ml/hour, can require about 6 to 18 hours for drugs to be completely infused into the patient.

Concentrated and high-osmolality (>400-500mOsm/kg) oral dosage forms may be associated with irritating effects on the gastrointestinal tract, resulting in nausea, vomiting, diarrhoea or necrotizing enterocolitis (NEC) mainly in preterm newborns (Zenk and Huxtable, 1978; White and Harkavy, 1982; Leff and Roberts 1987; Pagliaro, 2002). NEC is characterized by damage to the intestinal mucosa, which can progress to necrosis, even intestinal perforation and is associated with high rates of morbidity and mortality (Willis *et al*., 1977; Polo *et al*., 2007). Prematurity is the most important risk factor associated with NEC and the frequency of NEC is 1–3/1000 live births (Polo *et al*., 2007).

The osmolality of the human milk is about 300 mOsm/kg (Tomarelli, 1976; Zenk and Huxtable, 1978). In several studies it has been observed that most of the oral liquids used in NICU and intensive care nursery were hyperosmolalic: in four published studies 100%, 96%, 75% and 96% of the analysed oral products were over 1000 mOsm/kg, respectively (White and Harkavy, 1982; Ernst *et al*. 1983; Mutz and Obladen, 1985; Polo *et al*., 2007). In many products, the high osmolality is not due to the active ingredient but to "inactive" excipients such as propylene glycol or sorbitol (Ernst *et al*., 1983; Mutz and Obladen, 1985).

2.3 COMPOUNDED PREPARATIONS

Compounded formulations can be considered as one subgroup of unlicensed drugs and it includes modifications to commercially manufactured products such as the preparation of a suspension or powders from tablets, or the preparation of a product from the individual raw materials (Giam and McLachan, 2008). The type of reconstitution where medicinal products are made ready for immediate administration (e.g. dissolution of a powder according to the appropriate instructions) is normally not considered as compounding (Pharmaceutical Inspection Convention, 2008). In addition, dividing or grinding solid dosage forms, dissolving tablets in water due to the inability of the patient to swallow the solid dosage form or administering fractions of a liquid, which nurses regularly do on the wards and at the bedside, is not extemporaneous preparation (Giam and McLachan, 2008; Nissen, Haywood and Steadman, 2009).

The basis for compounding medicine can be traced to the societies of Ancient Egypt, Greece, Rome and especially the Arabian cultures, where advanced levels of medical knowledge were developed (Marriot *et al*., 2010). It has been estimated that a broad knowledge of compounding was still essential for 80% of the prescriptions dispensed as late as in the 1920's (Sundberg, 1997; Allen, 2006; Trissel, 2009). The majority of

prescriptions were compounded by a pharmacist according to the order of a physician for each individual patient.

2.3.1 Frequency

In Sweden the proportion of prescriptions that require compounding decreased from 22% in 1956 to some 2.5% in 1986 (Kettis Lindblad, 1996). During the period 1987–1989 in relation to the total sales of drugs in Sweden, the proportion of extemporaneous preparations was about 1.5%; they were required most commonly for children. In Australia about 60% of the Victorian community pharmacies dispensed 1–5 extemporaneous prescriptions per week in 1998, i.e. for 75% of the pharmacies extemporaneous prescriptions made up <1% of total prescriptions (Pappas, 1999). Such a small percentage is not universal; in German community pharmacies about 25 million extemporaneous preparations are compounded every year (Zueck, 2008).

Giam and McLachlan (2008) reviewed 20 published studies to identify the relative extent of extemporaneous product use in the paediatric population. In the general medical and surgical wards, the frequency of extemporaneous or 'special' product use was reported to range from 2% to 26%. In the neonatal wards, extemporaneously prepared products or 'specials' were dispensed in 5–11% of all prescriptions. In the United Kingdom (UK), it was reported that almost half of the 45 (9.9%) extemporaneous products that were being prescribed had been compounded by the pharmacy with the rest being prepared by 'specials' manufacturers. The use of extemporaneous products and 'specials' was similar across all paediatric ages and conditions.

Extemporaneous products have been compounded most frequently in countries such as the Netherlands, where pharmacy preparation services are widely available and approximately 5% of the total prescription numbers are compounded (Schirm, Tobi and de Jong-van den Berg, 2003; Giam and McLachlan, 2008). However, the produced volume in the Netherlands has fallen dramatically due to the demands imposed by increased quality standards (Le Brun, 2011).

2.3.2 Dosage forms

Methods of extemporaneous preparation vary in different European countries (Brion, Nunn and Rieutord, 2003). Liquids are predominantly (> 60% of doses) compounded in Denmark, England, Ireland, Norway and Sweden, capsules in Belgium, Croatia, France and Switzerland and powders in Finland, Italy and Scotland. One common practice in Germany, Spain and Slovenia involves the preparation of a less well-defined combination of liquids, powders and capsules. In the Netherlands, extemporaneous preparation often means reformulating a solid dosage form into a liquid dosage form for infants, or conversion of tablets into capsules with an appropriate dose for children (Le Brun, 2011). Chloral hydrate, midazolam and caffeine oral liquids, and spironolactone, captopril, phenobarbital, hydrocortisone and ranitidine oral capsules are compounded in many hospitals throughout Europe (Brion, Nunn and Rieutord, 2003).

The types of compounded dosage forms have varied from time to time. In the late 1960s, mixtures and ointments were the most common extemporaneous preparations encountered in Sweden (Kettis Lindblad, 1996). In the years 1987–1989, dermatological preparations formed almost half of the total number of extemporaneous preparations, and mixtures, dental solutions, eye drops and capsules were the next most common in Sweden (Kettis Lindblad, 1996). On the other hand, in fifty English hospitals, a total of 256 different oral liquid formulations of 123 drugs were being prepared in the early 1980s (Purkiss and Kayes, 1981).

The American Society of Hospital Pharmacy conducted a survey in 1989 and found that oral rifampicin, spironolactone and caffeine were the most frequent extemporaneously compounded formulations for paediatric patients in USA (Crawford and Dombrowski,

1991). In the years 1998–1999, the most commonly prepared extemporaneous dosage form in USA was still a liquid formulation and the oral, gastric and nasogastric administration routes were most usual (Pai and Nahata, 2001).

In eight large hospitals in New Zealand in 2004, a total of about 250 extemporaneous products were compounded per month with suspensions being the most frequently compounded oral dosage form (Kairuz *et al*., 2007). The most common products were omeprazole suspension, phenobarbitone solution, midazolam solution, thyroxine suspension, ursodeoxycholic acid suspension and suspensions or solutions containing beta-blockers. In Australia, reconstituted products, ointments and creams were estimated as being the most common extemporaneous products in 1990s (Pappas, 1999). Subsequently, most of the preparations made in Queensland, Australia, were suspensions, eye drops and solutions (Cook, Ling and Lee, 2007). According to a questionnaire, a total of 95 different extemporaneous formulations were prepared by 28 hospital pharmacies.

2.3.3 Quality risks

Despite many improvements in quality, extemporaneous preparation is still confronted by a range of challenging issues especially quality issues when compared to off-label use of registered products or unlicensed use of commercially manufactured products (Table 1) (Leff and Roberts, 1987; Giam and McLachlan, 2008; Allen, 2010b). The same drug may be compounded in liquid, capsule or powder form according to different standards and monographs across Europe or even within the same European country. These differences reflect the different traditions of extemporaneous preparation (Brion, Nunn and Rieutord, 2003; Carvalho, Tuleu and Taylor, 2008). In addition, many different concentrations may be compounded for each dosage form (Brion, Nunn and Rieutord, 2003).

In a British survey of extemporaneous captopril formulations, it was discovered that 22 hospitals were using nine different liquid formulations of captopril while four hospitals crushed the tablets and dispersed the powder in water (Mulla *et al*., 2007). A Canadian study also found a wide variation in the types of captopril formulations used: four of the 14 centres were dispensing solid tablets, two dispensed solid tablets or liquid formulations and eight made different kinds of extemporaneously prepared liquid formulations (Bhatt, Thomas and Mondal, 2011). A British clinical study of 18 healthy adult volunteers provided evidence that unlicensed manufactured captopril liquid formulations were not bioequivalent to the licensed tablet form or to each other, and this could cause problems in the clinic (Mulla *et al*., 2011).

U.S. Food and Drug Administration (FDA) noted in its survey conducted in 2006, that there were problems with the quality of some compounded drugs (U.S. Food and Drug Administration, 2006). Potency ranged from 67.5% to 268.4% of the amount of drug declared on the product labelling, mainly in female hormone products and local anaesthetic products. From 1990 to 2005, the FDA had received reports of 240 serious illnesses, even deaths, associated with improperly compounded products. In the 2001 survey, the FDA stated that 34% of the 29 sampled products failed standard quality tests performed, mostly in potency testing (U.S. Food and Drug Administration, 2001). The wrong method of compounding was reported as a medication error on a total of 115 times (6% of all medication errors) during the period from 1999 to 2000 in United States (Cowley, Williams and Cousins, 2001). Chollet and Jozwiakowski (2012) found that 25% of thirty hydroxyprogesterone caproate injections prepared in compounding pharmacies failed to meet the potency requirements.

Table 1. Quality risks and areas of concern in extemporaneously compounded drug products.

Quality risk	**Reference**
Adverse drug reactions due to preparation error or instability or incompatibility of ingredients	Tuleu, 2007; Giam and McLachlan, 2008
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	Glass and Haywood 2006**;** Tuleu, 2007; Nunn, 2003
Bioavailability, **efficacy and safety** studies may not be available. Compounded formulations may not be **bioequivalent** to the licenced products or to each other.	Nahata, 1999c; Standing and Tuleu, 2005; Tuleu, 2007; Giam and McLachlan, 2008; Mulla *et al*., 2011; BMJ Group, 2012
Dilution of commercial formulations leading to dilution of co-solvents thus causing the precipitation of the drug and to dilution of preservatives resulting in microbial contamination	Nahata, 1999a; Nahata, 1999b; Glass and Haywood, 2006; Tuleu, 2007; Ghulam *et al*., 2007
Inaccuracy of dosing: dose uniformity and reproducibility	Standing and Tuleu, 2005; Tuleu, 2007; BMJ Group, 2012
Incompatibilities: excipients, manipulated solid dosage forms, food or beverages	Standing and Tuleu, 2005; Haywood and Glass, 2007; Tuleu, 2007; Giam and McLachlan, 2008; Nissen, Haywood and Steadman, 2009
Manipulation of adult dosage form of the available tablet, capsule or injection: lack of pure drug substances, harmful excipients, high osmolality, altered pharmacokinetics, cutting, crushing or dissolving of tablets/capsules that should not be modified	Nahata, 1999b; Pagliaro, 2002; Standing and Tuleu, 2005; Glass and Haywood, 2006; Tuleu, 2007; Nissen, Haywood and Steadman, 2009
Microbiological contamination of multidose preparations with insufficient preservation leading to potential risks, especially in the premature and newborn	Ghulam *et al*., 2007
Non-standard formulations: lack of published standards	Brion, Nunn and Rieutord, 2003; Tuleu, 2007; Giacoia, Taylor-Zapata and Mattison, 2007b; Ghulam *et al*. 2007**;** Jackson and Lowey, 2010
Preparation process: drug losses during the crushing and administration process, lack of information about validation and reproducibility	Tuleu, 2007; Nissen, Haywood and Steadman, 2009; BMJ Group, 2012
Skills of the pharmacist: variability in overall compounding practices and training	Treadway, Craddock and Leff, 2007
Stability data: chemical, physical or microbiological stability not studied, short shelf-life	Pai and Nahata, 2001; Brion, Nunn and Rieutord, 2003; Standing and Tuleu, 2005; Tuleu, 2007; Giam and McLachlan, 2008
Strengths: several different strengths compounded extemporaneously, 10-fold difference in available strengths, 10-fold dosing errors, strengths expressed per ml or per 5 ml	Standing and Tuleu, 2005; Jackson and Lowey, 2010
Taste of the drug or the preparation itself	Giacoia, Taylor-Zapata and Mattison, 2007b

Errors of dose calculations, problems with decimal points, e.g. omission or addition of zeroes were frequent, causing tenfold medication errors. These were reported at a mean rate of 0.062 per 100 patient days in the Hospital for Sick Children in Toronto, Canada (Doherty and Mc Donnell, 2012). Incorrect preparation was an error source in four medication errors out of 129 errors that reached patients. Kato *et al.* (2009) reported a case where a three-year-old boy received compounded thioridazine instead of erythromycin from a pharmacy owing to their similar commercial names. In another case, a measurement error by the compounding pharmacy resulted in a fatal colchinine concentration that was eight times greater than the recognized standard level (McKeown *et al*., 2007). Seifert and Jacobitz (2002) described three compounding errors out of a total of 40 pharmacy prescription dispensing errors. Compounding errors in liquids and capsules resulted in 12-fold overdosage; there was even a case of 500-fold overdosage.

There is North-American research from the years 1998-1999 stating that there were 103 drug formulations that had neither compounding nor stability information available compared to 76 extemporaneous formulations for which adequate stability data was available (Pai and Nahata, 2001). However, longer or better stability data had been requested 109 formulations, such as captopril, hydralazine, spironolactone, ursodiol and nifedipine. With respect to 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). In an unpublished UK survey, it was noted that 54% of 112 paediatric extemporaneous formulations displayed inadequate data about stability (Brion, Nunn and Rieutord, 2003). In Queensland, Australia stability data was available for 78% of preparations (Cook, Ling and Lee, 2007).

There are other risk factors associated with extemporaneous products, for example low concentration of a non-dissolved active ingredient, high susceptibility towards microbial growth, longer periods of storage or use, poor working technique and provision to a large number of patients (Pharmaceutical Inspection Convention, 2008). Due to the general lack of standards and peer-reviewed research in this field, it is recommended that a product should be dispensed extemporaneously only when no product with a MA is available and if there are no alternatives (Brion, Nunn and Rieutord, 2003; Nunn, 2003**;** BMJ Group, 2012; Jackson and Lowey, 2010).

2.3.4 Need for standards

Currently, there are neither appropriate nor comprehensive published standards about the process of extemporaneous preparation; in fact not all pharmacies compound according to published formulations (Brion, Nunn and Rieutord, 2003; Hurtado and Moffett, 2007; Giam and McLachlan, 2008; Nunn, Aindow and Woods, 2012). Standardised and verified methods of compounding with suitable instructions should be required (Ernest *et al*., 2012). The variability in the method of preparation should be minimised and there should be adherence to a method of quality assurance. In order to ensure product quality, it has been recommended that there should be harmonization of extemporaneous formulations and quality control procedures and collected data should be published as standards and uniformly implemented in all countries (Brion, Nunn and Rieutord, 2003; Nunn, 2003; Ghulam *et al*., 2007; Giacoia, Taylor-Zapata and Mattison, 2007b; Giam and McLachlan, 2008).

The European Pharmacopoeia contains a monograph about Pharmaceutical preparations, which allows the supply of unlicensed products to meet the special needs of individual patients with a suitable level of risk assessment being undertaken when considering this kind of the preparation (European Directorate for the Quality of Medicines & Health Care, 2013). USP26/NF21 Chapter <795> Pharmacy Compounding – Non-sterile preparations gives instructions including compounding process, stability, ingredients and quality control (Allen, 2011a; Allen, 2011b). The Australian government has also reviewed

the need for regulation of extemporaneous compounding in Australia (Australian government, 2005 and 2008; National coordinating committee on therapeutic goods (NCCTG), 2008). The relevant pharmacopoeial formularies are British Pharmacopoeia (BP), United States Pharmacopeia (USP), Australian Pharmacopoeia Formulae (APF) and Martindale (Allen, 2003; Glass and Haywood, 2006). In addition, many European states maintain complementary national pharmacopoeias, which may include some formulation or performance standards for compounded preparations.

The general quality instructions of the extemporaneous preparation in addition to national administrative regulations are presented in GMP, PIC/S GPP, other PIC/S guidance, ICH-guidelines and other national quality guidelines (Sharp, 2000; Pharmaceutical Inspection Convention, 2008 and 2013; Finnish Medicines Agency, 2007 and 2011; SHPA Manufacturing working party, 2010; European commission, 2012; ICH Guidelines, 2012). The Committee of Ministers published a resolution on quality and safety assurance requirements in order to avoid quality and safety gaps between medicinal products prepared in pharmacies and on an industry (Council of Europe Resolution CM/ResAP(2011)1). In this resolution, it is recommended that the GMP Guide be used as a reference for an appropriate quality system for high-risk preparations and the PIC/S GPP Guide be used for low-risk preparations.

Suitable sources of stability-indicating information include formularies such as Allen's compounded formulations, Nahata and Hipple's Pediatric drug formulations, Trissel's Stability of compounded formulations as well as peer-reviewed journals. In addition, some nations or individual hospitals like Calgary Health Region in Canada have created the formularies of their own to ensure that all practitioners use consistent formulas with confirmed stability information (Van Schijndel, 2002). The guidance contains usually the formula, conditions of storage and an estimate of shelf life based on chemical stability (Tuleu, 2007). However, there is often a lack of information about physical and microbiological stability and exact details of compounding.

Nowadays clinical practise is not always accurately represented in the SmPC, particularly for agents which are no longer under patent protection (Sinha and Cranswick, 2007). A reflection paper of EMA has encouraged manufacturers to provide relevant data of their products to practitioners, such as physicochemical data, excipients, pH, osmolality, dangers of manipulation, stabilities and compatibilities like compatible foods and drinks since this information would allow the pharmacist to dispense a satisfactory formulation (*European Medicines Agency, 2006*).

2.4 UNIFORMITY AND STABILITY OF EXTEMPORANEOUS PREPARATIONS

It has to be ensured that a formulation packaged in a specific container will remain within its physical, chemical and microbiological specifications during storage (Florence and Attwood, 2006). The main causes for limited stability are: 1) loss of drug (e.g. degradation), 2) loss of vehicle (e.g. evaporation), 3) loss of uniformity (e.g. caking of a suspension), 4) change of organoleptic characteristics (e.g. appearance), 5) change of bioavailability, 6) appearance of an irritant or toxic degradation product (Tuleu, 2007). Interactions between drug substance and excipients may also induce instability (Florence and Attwood, 2006; Glass and Haywood, 2006).

Extemporaneous preparations are often given arbitrary shelf lives or shelf lives based on published information (Tuleu, 2007). Compounders have to rely on drug-specific and general stability documentation and literature, but often have to estimate this information by considering the drug and its degradation mechanism, packaging container, the expected storage conditions, and the intended duration of therapy (The United States Pharmacopeial

Convention, 2008). Determination of the shelf life should be assessed conservatively, for example USP provides also maximum beyond-use dates for nonsterile solid and liquid formulations.

2.4.1 Uniformity of dosage units

Uniformity is tested in several ways in the European Pharmacopoeia (Table 2) (European Directorate for the Quality of Medicines & Health Care, 2013). The section on Uniformity of dosage units (2.9.40) contains the tests for content uniformity and mass variation, which are required to ensure the uniformity of dosage units: i.e. each unit in a batch should contain the labelled amount of the medicinal agent. Uniformity of content of single-dose preparations (2.9.6) is used to determine whether the individual contents of active substance are within the limits set with reference to the average content of the sample. Uniformity of mass of single-dose preparations (2.9.5) is required for capsules, powders and tablets. Oral liquid preparations supplied in multidose containers must comply with the test for Uniformity of mass of delivered doses from multidose containers (2.9.27).

The lower the proportion of active ingredient, the more difficult it is to achieve acceptable dose uniformity in a powder mixture (Twitchell, 2007). A lower amount of active ingredient in capsules showed a higher percentage of nonconformity when compared to higher dosage in a study that examined the amounts of morphine, ursodeoxycholic acid, hydrocortisone, captopril, and nicardipine capsules compounded in a hospital pharmacy over a period of three years (Mathaut et al., 2006).

The tablet dispersion method leads to wide variation of doses (Broadhurst et al., 2008). Dispersible aspirin tablets 75 mg were placed for three or five minutes in 10 ml of water and theoretical 7.5 mg (1 ml) or 15 mg (2 ml) doses were taken. However, all the doses withdrawn were less than required and never exceeded 76.5% of the intended dose. The white sediment on the bottom of the dispersion probably consisted of undissolved aspirin and excipients.

Deicke and Süverkrüp (2000) investigated dose uniformity and redispersibility of three commercial erythromycin ethyl succinate oral liquids. The required volume of water was added to powder or granules and then the suspension was shaken vigorously with the apparatus. The samples were taken three times a day for two weeks. One of the products performed satisfactorily, one showed moderate shortcomings while the dose uniformity of two samples of the third product was clearly deficient. The problems seemed to be associated with poor wetting behaviour of the solids. Orr and Hill (1980) studied variation in 120 mg/5 ml doses of paracetamol suspension and found variation ranging from 74 mg to 173 mg in doses taken from one bottle with spoon and from 81 mg to 390 mg in doses, which were taken from 25 nearly empty bottles.

The use of mass variation test to evaluate quality control of extemporaneously prepared microdose captopril capsules was claimed to be unreliable (Colucci *et al*., 1994). An analysis of captopril 1 mg capsules which had been compounded by triturating 25 mg tablets showed that capsules were within acceptable limits for weight variation test described in the USP but failed the test for content uniformity i.e. the amounts of captopril in capsules were 1.27 mg ± 0.31 mg. Instead, captopril 25 mg capsules compounded in the pharmacy passed the tests for uniformity of mass and uniformity of content (Marcatto *et al*., 2005).

Table 2. Uniformity tests of European Pharmacopoeia for hard capsules, oral powders (single-dose) and liquid preparations for oral use.

European Pharmacopoeia test	**Hard capsules**	**Oral powders (single-dose)**	**Liquid preparations for oral use**
Uniformity of dosage units (2.9.40)*	API ≥25 mg and ≥25%: Mass variation API <25 mg or <25%: Content uniformity	API ≥25 mg and ≥25%: Mass variation[1] Content uniformity[2] API <25 mg or <25%: Mass variation[1] Content uniformity[2]	Solutions in single-dose container: Mass variation Others: Content uniformity
Uniformity of content of single-dose preparations (2.9.6)**	API <2 mg or <2%	API <2 mg or <2%	Single-dose suspensions
Uniformity of mass of single dose preparations (2.9.5)**	Required if Uniformity of content is not tested	Required if Uniformity of content is not tested	Single-dose solutions (modified test)
Uniformity of mass of delivered doses from multidose containers (2.9.27)	Not required	Single dose container: Not required Required if supplied in multidose container	Solutions and suspensions supplied in multidose containers

*Primary test **Where justified or authorized [1]Single component [2]Multiple components

2.4.2 Chemical stability

Each active ingredient has to retain its chemical integrity and labelled potency within the specified limits (Allen, 2010a). A reduction of content down to 90% of theoretical value (with possible 95% confidence limits) is generally regarded as the maximum reduction acceptable (Mehta, 1993; Barnes, 2007).

Chemical degradation reactions can be sub-divided into hydrolysis, oxidation, isomerisation, polymerisation, and photodegradation (Barnes, 2007). These can all cause a loss of potency of the drug, often accompanied by changes in the appearance of the product (e.g. discoloration, formation of a precipitate). Most drugs exist in the reduced form and thus are susceptible to oxidation (Chan, 2001). A suspension formulation may often be more stable than the same drug in a solution because much of the drug is protected within the insoluble particles (Barnes, 2007).

The degradation of photolabile drugs depends on both the intensity and spectral distribution of the light source and is most common if they are exposed to ultraviolet light (Thoma, 1996; Florence and Attwood, 2006). Molecules that absorb wavelengths of sunlight or artificial light may become degraded (photolysis) (Florence and Attwood, 2006; Barnes, 2007). In addition, photodegradation may also occur as a consequence of absorption of radiation by excipients, which transfer the absorbed energy to the drug (photosensitisers) (Florence and Attwood, 2006).

Different numbers and structures of photodegradation products can be obtained by irradiating the drug in the solid state or in solution (Thoma, 1996). In the solid-state photodegradation only takes place at the surface and thus it happens more slowly than in solution (Thoma, 1996**;** Florence and Atwood, 2006). The rate of decomposition is influenced by the size and surface of particles, the colour and crystalline structure, and excipients. Different methods can be used to achieve protection from light, e.g. using coloured light-resistant containers, storage in the dark and coating tablets with a polymer

film containing ultraviolet absorbers or light protecting pigments. If the coating of the tablet is crushed, which is the case in extemporaneous preparation process, then photoprotection has to be assured with tinted packing materials.

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 storage or in a refrigerator and this will often require the use of an accurate, specific, reproducible and stability-indicating analytical method, e.g. high-performance liquid chromatographic technique should be used (Hagan, 1994; Chan, 1999; Nahata, 1999b; Barnes, 2007; ICH Harmonised Tripartite Guideline, 2012). A specific protocol for testing the photostability of new drugs and products has been described in the ICH Guideline (*European Medicines Agency CPMP/ICH/279/95, 1998*).

Lam (2011) described the lack of stability data in a study of 46 oral anticancer agents. He noted that only two of them were commercially available in an oral liquid dosage form and dispensing instructions for extemporaneous oral liquid formulation were available for 21 drugs, but only 14 of them had been tested for chemical stability and only three included physical stability data. Pharmacokinetic data on bioavailability could be found for seven agents. Chan (2001) reported that captopril 1% solution compounded from pure drug powder was more stable than one compounded from tablets because the copper and iron present in tablet excipients acted as catalysts for oxidation. An isoniazid mixture compounded from tablets exhibited over 10% degradation after three days because of an incompatibility between isoniazid and lactose (Haywood *et al*., 2005).

2.4.3 Physical stability

Physical stability means that the original physical properties, including appearance, palatability, uniformity, dissolution and suspendability, have been retained (Chan, 2001; Allen, 2002). In powders, the physical changes indicating instability include caking instead of free flowing, discoloration and release of pressure upon opening (Allen, 2002). In capsules, there can be changes in the physical appearance or consistency, softening or hardening of the shell, or discoloration, expansion or distortion of the gelatin capsule may occur. Physical instability in suspensions is expressed as caking of sediment or particle growth, which leads to inaccuracy of dose, poor appearance and grittiness (Florence and Attwood, 2006; Attwood, 2007; Barnes, 2007; Billany, 2007). The adhesion of suspension particles to container walls has also been noted as a problem, particularly with low-dose drugs (Florence and Attwood, 2006). Temperature fluctuations may cause crystal growth in suspensions and freezing of suspensions may result in a particle size redistribution and potential difficulties in resuspending (Billany, 2007; Allen, 2008). Particle growth can be prevented by the addition of polymers or surfactants (Sinko and Singh, 2011).

Physical stability of pharmaceutical suspensions is very important although it has been generally ignored in the area of extemporaneous preparations (Han *et al*., 2006). During the storage, the settled solid particles should not form a hard cake, but should be able to be readily dispersed into a uniform mixture with a moderate amount of agitation (Attwood, 2007; Tuleu, 2007; Sinko and Singh, 2011). In addition, the suspension must not be too viscous otherwise it will not flow freely out of bottle or pass through a syringe.

If the solid particles in the suspension are sufficiently small, i.e. surface area of the particles is large, they may be highly energetic and tend to regroup to reduce the surface free energy (Sinko and Singh, 2011). This type of flocculation creates light, fluffy conglomerates, which settle rapidly, form a large sedimentation volume and are easily resuspended (Florence and Attwood, 2006; Attwood, 2007; Billany, 2007; The United States Pharmacopeial Convention, 2008; Sinko and Singh, 2011). In flocculated systems, the liquid above the sediment is clear because all particles are associated with flocs. On the other hand, too rapid clearance of the supernatant in a flocculated system produces the risk of an inaccurate dose being administered (Florence and Attwood, 2006; Billany, 2007). Thus, for

this reason, it may be necessary to add suspending agents in order to retard sedimentation (Florence and Attwood, 2006; Billany, 2007; The United States Pharmacopeial Convention, 2008**;** Sinko and Singh, 2011).

In contrast, deflocculated particles settle slowly and form sediment and solid aggregates, and finally a cake that is difficult to resuspend (Sinko and Singh, 2011). Deflocculated suspensions have different sizes of particles and when the large ones settle, the small ones remain in a turbid supernatant and no clear boundary is formed. Controlled flocculation can be achieved with the desired surface charge, zeta potential, and can be produced with electrolytes, surfactants and hydrophilic polymers (coating of particles) or by adjusting the pH (Sinko and Singh, 2011).

Redispersion of the suspension can be influenced also by the particle size and changes in viscosity according to Stokes' equation:

$$v = \frac{d^2(p_1 - p_e)g}{18\eta} \qquad (1)$$

where v is the terminal velocity (cm/sec), d is the diameter of the particle (cm), ρ_1 is the density of the particle, ρ_e is the density of the medium, g is the gravitational constant, and η is the viscosity of the medium (poise) (Sinko and Singh, 2011).

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. Sotalol hydrochloride suspensions formulated with simple syrup/methylcellulose 1:2.4 vehicle displayed precipitation of particles and required more agitation than Ora-Plus/Ora-Sweet – formulations in order that they would be redispersed (Sidhom *et al*., 2005). Sedimentation in extemporaneously prepared spironolactone suspension appeared within 8–10 minutes in suspension vehicles methylcellulose 2%/dextrose 70%, carboxymethylcellulose 4%/cherry flavoured glycol, ethanol 10%/simple syrup and in methylcellulose1%/simple syrup. Simple syrup, syrup NF is a solution of 85% w/v sucrose in purified water (Asiri *et al*., 2001). Instead, in methylcellulose 2%/simple syrup, the sedimentation only started in 25 minutes. Even after vigorous vortexing, zonisamide in simple syrup or in methylcellulose 0.5% tended to separate into two phases, resulting in sampling variations (Abobo, Wei and Liang, 2009). When hypromellose and methylcellulose suspensions of hydrochlorothiazide were compounded with different proportions of glycerol as the wetting agent, it was found that as much as 20% of glycerol was needed to achieve the correct dose to be administered and to remain stable (Santoveña, Hernánder-Paiz and Fariña, 2012).

The range of stability testing should cover both organoleptic properties and physical properties and characteristics (Florence and Attwood, 2006). Firstly, the physical stability is assessed by visual inspection against a white and black background to rule out any changes in colour and appearance (Nahata, 1999b). In addition, suspension should be studied for uniformity of dose, ease of resuspending, settling, caking, crystal growth, viscosity, pH, odour and loss of volume (Allen, 2002; Tuleu, 2007). The rate of sedimentation, the final volume or height of the sediment, and the ease of redispersion of the product are assessed (Billany, 2007). Particle size of a suspension can be effectively characterized by the combination of widely available laser diffraction and microscopy techniques (Han *et al*., 2006). Since caking requires time to develop it has been recommended that a short beyond-use date should be considered for risky suspensions (Thompson, 2009c).

2.4.4 Microbiological stability

Pharmacopoeial requirements for microbiological quality of non-sterile oral preparations include: not more than 10^2 (maximum acceptable count is 200) aerobic microbes and not more than 10^1 (maximum acceptable count is 20) yeasts or moulds per gram or per millilitre in aqueous formulations, not more than 10^3 (maximum acceptable count is 2000) aerobic

microbes and not more than 10^2 (maximum acceptable count is 200) yeasts or moulds per gram or per millilitre in non-aqueous formulations and the absence of Escherichia coli in both types of dosage forms (European Directorate for the Quality of Medicines & Health Care, 2013).

Hygienic production, sterilization and suitable preservatives are used to prevent the presence or growth of microorganisms in the product (Hodges, 2007). The factors impacting on the hygienic preparation of medicines have been described: the provision of a clean and controlled work area, prevention of cross contamination, risk assessment, materials, quality of water, formulation, and health, hygiene, clothing and training of the personnel (Pharmaceutical Inspection Convention, 2008; *Finnisn Medicines Agency, 2007 and 2011*; *European commission, 2012*). Incorrect storage and unhygienic use of the product may also spoil the product (Ghulam *et al*., 2007).

Products containing sufficient water to permit bacteria or fungi growth are vulnerable to spoilage, in contrast, in dry conditions only spore-formers can survive well (Hodges, 2007). The presence of microorganisms and their metabolites can even impair the chemical or physical stability and the drug solubility by affecting the pH and efficacy of the preservative (Ghulam *et al*., 2007; Hodges, 2007; Tuleu, 2007). The occurrence of microbiological growth in aqueous medicines can affect the organoleptic characteristics of the product, produce turbidity, smell or taste, and can render the product unacceptable, harmful, or even toxic to the patient.

It has been reported that over 50 patients died and almost 700 were diagnosed with a fungal infection after receiving a methylprednisolone acetate injection produced by the compounding center (Thompson, 2013). A serious eye infection was diagnosed in 5 patients who received bevacizumab repackaged into single-use syringes.

Simple syrup can become contaminated with moulds although it is not susceptible to bacterial growth (Nahata, Pai and Hipple, 2003; Hodges, 2007). Methylcellulose 1%, with or without a preservative added to simple syrup BP in a ratio of 1:4 failed the BP quality assurance criteria (Ghulam *et al*., 2007). Multiple use of dosing devices may also be the source of contamination (Dockhorn *et al*., 2010). In English hospitals, a total 151 formulations out of 256 different oral liquid formulations contained tragacanth as the suspending agent (Purkiss and Kayes, 1981). Alternatives had to be evaluated when it was found that there was a high incidence of microbial contamination by coliforms and, occasionally, by even salmonella species (Farley and Lund, 1976).

The microbiological quality of the extemporaneous preparations can be tested in accordance with the European Pharmacopoeia although there are demands for an improved pharmacopoeia monograph when testing non-sterile extemporaneous formulations (Long *et al*., 2006; European Directorate for the Quality of Medicines & Health Care, 2013). In published studies microbiological examination is only sometimes performed with different techniques (Sidhom *et al*., 2005; Long *et al*., 2006; Brustugun *et al*., 2009).

2.5 EXTEMPORANEOUS ORAL DOSAGE FORMS FOR PAEDIATRIC PATIENTS

Medication with extemporaneous preparations in hospital is an acute multidisciplinary process where decisions need the input and co-operation between physicians, pharmacists and nurses, i.e. all of the professionals involved have a duty of care to the patient within their area of responsibilities (European Directorate for the Quality of Medicines & Health Care, 2013). Pharmacists are the only healthcare professionals formally trained in the art of compounding, thus the skills of the compounding pharmacists are needed to satisfy the individualized needs (McElhiney, 2003; Allen, 2006; Giam and McLachan, 2008). The pharmacist needs to take responsibility for ensuring that the extemporaneous medicine is of suitable quality, safe, stable and effective (Allen, 2006; Giacoia, Taylor-Zapata and Mattison,

2007b; Giam and McLachlan, 2008; Treadway, Craddock and Leff, 2007; Jackson and Lowey, 2010). The roles and responsibilities in different stages of the preparation process are presented in Table 3.

Table 3. Model of roles and responsibilities in compounding process in hospital pharmacy in Finland (Helin-Tanninen, 2008).

Handling state	**Chief pharmacist**	**Pharmacist (master's degree)**	**Pharmacist (bachelor's degree)**	**Accredited technician**	**Physi-cian**	**Nurse / pharmacist (bachelor's degree) on ward**
Order					R	S
Design of product		R	RS		AC	CI
Formulation	A	R	RS			
Compounding		AC	R	I		
Packaging and labelling		AC	AC	R		
Final check	A	RAC	R	I		
Dispensing		AC	R	SI		
Storage on the ward		C	C		A	R
Administration to patient		C			AR	RSC

R = responsible person, A = person to whom R is accountable, S = can be supportive, C = could be consulted, I = should be informed

Nunn, Aindow and Woods (2012) wrote that "the process of compounding is not without danger and there may be alternative strategies such as dose-rounding, therapeutic substitution or manipulation of adult dosage forms so that compounding is a last resort". When there are no comprehensive published standards for compounding, decisions in the different steps of preparation process have to be made by using professional pharmaceutical skills and risk analysis (Figure 1) (Glass and Haywood, 2006; Tuleu, 2007; Helin-Tanninen, 2008).

A risk assessment must be performed before deciding to extemporaneously prepare a medicine: to compound or not (Jackson and Lowey, 2010). Non-validated formula, narrow therapeutic index, long-term use and altered bioavailability are well-known serious risk factors when the use of a manufactured therapeutic alternative may be preferred (Glass and Haywood, 2006; Jackson and Lowey, 2010). The compounder is responsible for ensuring that the quality is built into the prepared product (Kastango, Trissel and Bradshaw, 2003; The United States Pharmacopeial Convention, 2008). The existence of standards, standardisation and rationalisation of products would help to improve product quality (Jackson and Lowey, 2010).

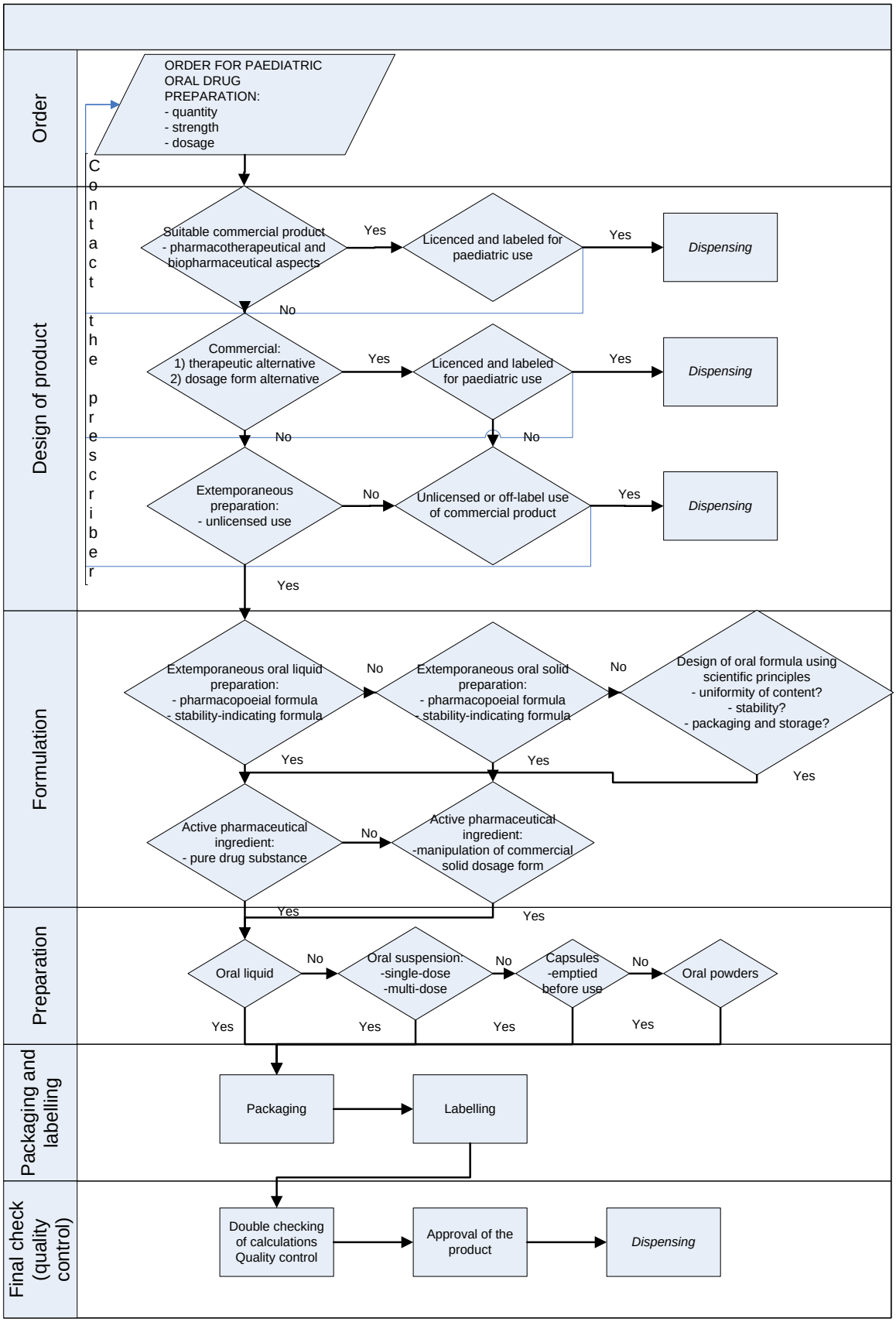

Figure 1. A management flow chart and decision pathway of compounding process for oral preparations (Helin-Tanninen, 2008).

Extemporaneous preparations can be compounded by a pharmacist from the authorised dosage form from industry-generated information, information from a pharmacopoeia or a peer-reviewed journal or national/hospital/published formulary, or, if not available, 'ad hoc' compounding from the authorised dosage form using the pharmacist's knowledge and skill (Ernest et al. 2012). The formulations should be kept as simple as possible to minimize risks associated with the preparation process and possible incompatibilities (Jackson and Lowey, 2010; Sam *et al*., 2012; Santoveña, Hernánder-Paiz and Fariña, 2012).

Correct calculations, accurate and precise measurements, appropriate formulation procedures and documentation are needed (Glass and Haywood, 2006). Documented preformulation studies include for example physical description, particle size, solubility, pKa, pH, stability, excipient toxicity, and other important characteristics (Nahata and Allen, 2008; Allen, 2008). The formulator may have a difficult choice: to use excipients for which toxicity is known and thus predictable, or excipients, about which there is no safety data for children (Standing and Tuleu, 2005). Critical control points should be set into a preparation process at those steps at which a control measure is applied to eliminate a hazard or at least to reduce it to an acceptable level (Nahata and Allen, 2008; Allen, 2008). Batch sizes should be consistent with the volume of drug orders and the stability of the compounded product (ASHP reports, 1993). The pharmacist is responsible for defining a beyond-use date for the prepared product (Glass and Haywood, 2006). The finished compounded preparations should be analysed at an appropriate level in-house or this task can be outsourced to a contract laboratory (Nahata and Allen, 2008).

Accurate measurement of the dose, acceptable taste and smell, and convenient administration are requirements in order to achieve patient compliance (Nunn and Williams, 2005; Tuleu, 2007; Allen, 2008; Sam et al., 2012). The objective of all of the quality assurance should be the assurance of the safety, protection and well being of the patient (Sharp, 2000).

2.5.1 Active pharmaceutical ingredient

The active pharmaceutical ingredient (API) of the extemporaneous formulation may be a drug substance of pharmacopoeial standard or it can be manipulated from a licensed formulation, including also its excipients (Brion, Nunn and Rietord, 2003; Tuleu, 2007; Nissen, Haywood and Steadman, 2009). Ideally, extemporaneous products should be compounded from pure drug substances, but access to suitable amounts of APIs is not always possible and can be cost-prohibitive and time-consuming for pharmacies even when the compounds are available (Cook, Ling and Lee, 2007). In order to reduce the need for high-risk manipulations of adult products, pharmaceutical manufacturers should make available their pure qualified active substances (*European Medicines Agency, 2006*). The reliability of supplies needs to be ensured. Chollet and Jozwiakowski (2012) found that eight of the ten API (hydroxyprogesterone caproate) samples did not meet the purity specifications required by FDA. One of the API samples was found to actually be glucose.

More frequently, commercial dosage forms intended for adults are manipulated: tablets are crushed or capsules are opened and the contents are used (Allen, 2002; Brion, Nunn and Rieutord, 2003; Tuleu, 2007). Some manufacturers do not provide any information on their product for use in extemporaneous formulations, either because of potential legal issues or because the data are too complex to be made available (Nahata and Allen, 2008). The best ways to manipulate industrial dosage forms could be evaluated by the pharmaceutical industry e.g. recommendations given in a MA (Salunke *et al*., 2011). It has also been claimed that industry-verified extemporaneous preparations and extemporaneous formulations compounded by dispensing pharmacists to their own formula with limited quality assurance need to be differentiated. The position of industry-verified extemporaneous preparations could be the same as for other industrial products, which are reconstituted according to MA.

If the starting material is neither licensed nor of pharmacopoeial standard then a risk assessment must be undertaken (Jackson and Lowey, 2010). Crushing of sustained-release tablet or capsule may increase toxicity or increase the risk of ADRs, since it involves breaking of enteric coat, film coat or delayed release coat which protects an acid-labile or light-sensitive active ingredient or controls the release of active ingredient, and thus can decrease efficacy or alter drug absorption (Birdsall and Uretsky, 1984; Mitchell and Pawlicki, 1992; Haywood and Glass, 2007; Nissen, Haywood and Steadman, 2009). The coating or film on an oral solid dosage form may also offer protection against local irritation, mask an unacceptable taste or prevent a potential hazard from a cytotoxic or teratogenic drug (Nissen, Haywood and Steadman, 2009; Jackson and Lowey, 2010).

The resulting powder may be dissolved or suspended with various excipients in order to produce an oral liquid medicine, or it may be redistributed into smaller strength capsules or powder papers after dilution with some inactive ingredient (Brion, Nunn and Rieutord, 2003; Tuleu, 2007). USP standards for pharmaceutical preparation require that the amount of API has to be equal to 90% to 110% of the intended dose (The United States Pharmacopeial Convention, 2008; Allen, 2010a). If there is wide variability of actual allowable range of the API (i.e. between 90% and 110%) in the manufactured product as the source of the drug, the compounded preparation could fail to meet specifications (Nahata and Allen, 2008; Allen, 2010a).

2.5.2 Excipients

Thousands of different excipients are used in different medicines (Haywood and Glass, 2011). Excipients may be added for various reasons, to increase the bulk, add desirable colour, mask the unpleasant taste and smell, protect, support or enhance stability and facilitate creating a uniform mixture of the active ingredient in the final preparation (Pawar and Kumar, 2002; Haywood and Glass, 2011).

In recent years, excipients have proved to be anything but inert (Table 4) (Noerr, 2000; Haywood and Glass, 2011). Maximum tolerated doses for excipients have often determined by animal safety testing but then extrapolated for use in adults (Ernest *et al*., 2007). Preterm or term newborns, and children may well be exposed to a variety of excipients present in the medicines that are essential for the treatment of illnesses, especially if they are critically ill infants receiving continuous infusions of medicines (Nahata, 2009). In an Estonian study Lass (2012) found that almost all (97%) treated hospitalised neonates received medicines with at least one potentially harmful excipient. The daily intake of some excipients may exceed the proposed maximum acceptable daily intake per kilogram of body weight for adults (Nahata, 2009). 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 (Tuleu, 2007). It has been recommended that the ideal preparations for neonates and particularly premature babies should be free of preservatives and flavouring and colouring agents (Lund, 1994). In addition, European and United States Paediatric Formulation Initiatives (PFI)s have started to create the STEP (Safety and Toxicity of Excipients for Paediatrics) database (Salunke, Giacoia and Tuleu, 2012).

Very small amounts of active ingredients often require a carrier to ensure their uniform distribution in the dispensed product, and to guarantee an accurate dose (Pawar and Kumar, 2002; Haywood and Glass, 2011). Bulk fillers contribute to the product's uniformity, stability, flow characteristics and compressibility (Pawar and Kumar, 2002). Lactose is often used as a filler or diluent in tablets and capsules, and to a more limited extent in infant formulas (Rowe *et al*., 2012). However, lactose, a disaccharide of glucose and galactose is absorbed after hydrolysis by the intestinal enzyme, lactase (Pawar and Kumar, 2002). Microcrystalline cellulose, which is derived from purified wood cellulose, is primarily used as a binder and diluent in oral tablet and capsule formulations (Pawar and Kumar, 2002;

Rowe *et al*., 2012). It is generally believed that microcrystalline cellulose is safe and is not absorbed into the systemic circulation after peroral administration (Kotkoskie *et al*., 1996; Rowe *et al*., 2012). However, some studies from 1970's, using rats, dogs and pigs, have indicated that persorption of microcrystalline cellulose may occur after per oral administration (Pahlke and Friedrich, 1974 and 1975; Seidemann, 1976).

Colloidal celluloses like hypromellose and methylcellulose are used as suspending agents in liquid preparations (Pawar and Kumar, 2002). Both are regarded as non-toxic and non-irritant materials, although excessive consumption orally may have a laxative effect. Purified water is the most commonly used solvent in liquid preparations (Pawar and Kumar, 2002; Rowe *et al*., 2010). It should be remembered that water may serve as a culture medium for bacteria and fungi (European Directorate for the Quality of Medicines & Health Care, 2013).

The antimicrobial preservative needs to be selected so that it will inhibit the growth of the likely microorganisms, and it should be in an undissociated form for penetration into microorganisms (Nahata and Allen, 2008). Furthermore, it should dissolve sufficiently in water, be nonirritating and nonsensiting, and have adequately stability and compatibility. The use of preservatives like benzyl alcohol and benzoic acid may lead to life threatening toxicity in paediatric patients when multiple doses of preserved medications are administered (Glass and Haywood, 2006).

It may be difficult to mask the taste of compounds with high solubility in liquid preparations (Allen, 2002; Davies and Tuleu, 2008; Cram *et al*., 2009). Even a small amount of solubilized drug in a suspension can trigger poor palatability. The age-related differences in the taste and smell have to be taken into account when designing good palatability: acceptable initial taste, after-taste, smell and texture for oral drug preparation (Nahata 1999d; Pawar and Kumar, 2002; Davies and Tuleu, 2008). For example viscous vehicles enhance the mouth feel and improve the perceived flavour of oral liquids by reducing the contact of the drug with the taste buds (de Villiers, 2009a). Flavours are not elaborated further in this review.

Table 4. Examples of reported adverse effects caused by excipients especially in children.

Excipient	Adverse effect	Reference
Antimicrobial preservatives:		
Benzalkonium chloride	Dose-related bronchoconstriction, cough, burning sensation, occasionally facial flushing, pruritus	American Academy of Pediatrics, 1997; Tuleu, 2007
Benzoic acids and benzoates	Displacement of bile from albumin binding sites in premature neonates, "gasping syndrome"	Kumar, Rawlings and Beaman, 1993; Tuleu, 2007
Benzyl alcohol	A number of neonatal deaths and severe respiratory and metabolic complications, neurologic symptoms, bronchitis, haemoptysis, kernicterus, hypersensitivity reactions (rare) Accumulation, leading to neonatal cardiovascular collapse, "gasping syndrome" and 20 deaths in low-birth-weight neonates with dose of 99-234 mg/kg/day	Gershanik *et al*., 1982; American Academy of Pediatrics, Committee on Fetus and Newborn and Committee on Drugs, 1983; American Academy of Pediatrics 1997; Noerr, 2000
Boric acid	Is not used internally owing to its toxicity: death from ingestion of <5g in young children	Rowe *et al*., 2012

Chloroform	Carcinogenic In UK: previously usual preservative in paediatric formulations, now maximum content 0.5%. The use as a preservative has been prohibited in USA since 1976.	Purkiss and Kayes, 1981; Hanson, 2003; Tuleu, 2007
Parabens	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 The WHO has set an estimated total acceptable daily intake for methyl-, ethyl-, and propylparabens at no more than 10 mg/kg	Kumar, Rawlings and Beaman, 1993**;** Tuleu, 2007; Rowe *et al*., 2012
Sodium benzoate	Nonimmunological contact urticaria It has been recommended that sodium benzoate injection should not be used in neonates The WHO acceptable daily intake of total benzoates, calculated as benzoic acid, has been estimated up to 5 mg/kg	Rowe *et al*., 2012
Sodium borate	Damaged skin, severe toxicity (vomiting, diarrhoea, erythema, CNS depression, kidney damage) especially in children Lethal oral intake 5g in children	Rowe *et al*., 2012
Thiomersal	Hypersensitivity (at 0.1% concentration in children). Ten out of 13 children died as a result of treatment with topical tincture containing thiomersal	Rowe *et al*., 2012
Antioxidants		
Propyl gallate	Methaemoglobinaemia in neonates, sensitizing in animals	Nitzan, Volovitz and Topper, 1979; Ernest *et al*., 2007
Sulphites	Wheezing, dyspnoea, bronchospasm (especially in those with a history of asthma or atopic allergy), anaphylaxis, urticaria, itching In Europe, the acceptable daily intake of sodium metabisulphite and other sulphites used in foodstuffs has been set at no more than 3.5 mg/kg, calculated as sulphur dioxide	American Academy on Pediatrics, 1997; Rowe *et al*., 2012
Thymol	Respiratory arrest, nasal congestion and edema (reported in newborn) Not for children under 5 years	Rowe *et al*., 2012
Bulk fillers:		
Lactose	Diarrhoea, malabsorption, vomiting, flatulence (in patients with lactose-intolerance) Jaundice, hypoglycaemia, CNS symptoms, cataracts (in patients with galactosemia)	Kumar, Rawlings and Beaman, 1993; Kumar *et al*., 1996; American Academy on Pediatrics, 1997; Tuleu, 2007
Mannitol	Anaphylactic reactions	Kumar *et al*., 1996

Colouring agents:		
Azo dyes	Anaphylactic reactions, angioedema, asthma, urticaria, contact dermatitis, rhinitis, hyperkinesis in hyperactive patients, cross-sensitivity with acetylsalicylic acid, sodium benzoate and indomethacin (tartrazine FD&C yellow5 = E102, sunset yellow FD&Cyellow6 = E110), bronchoconstriction (FD&C4 Ponceau Sx), contact dermatitis (FD&CRed36, FD&C17)	Kumar, Rawlings and Beaman, 1993; Kumar *et al*., 1996; American Academy on Pediatrics, 1997; Pawar and Kumar, 2002
Carmine	Allergic cheilitis, asthma	Kumar, Rawlings and Beaman, 1993
Quinoline yellow	Contact dermatitis	Kumar, Rawlings and Beaman, 1993; Pawar and Kumar, 2002
Triphenyl-methane dyes	Bronchoconstriction in asthmatic patients (FD&C blue1 = E133), erythema multiforme-like skin rash (fast green FCF: FD&C green3)	Kumar, Rawlings and Beaman, 1993; Kumar *et al*., 1996; Pawar and Kumar, 2002
Xanthine dyes	Potent photosensitizer (eosin: FD&C red22), potent photosensitizer, carcinogenicity (erythrosine: FD&C3 = E127), urticaria, syncopy, anaphylaxis, angioedema (fluorescein FD&C yellow7)	Kumar, Rawlings and Beaman, 1993; Pawar and Kumar, 2002
Surfactants, suspending and solubilizing agents and solvents:		
Carrageenan	Induces inflammatory responses in animals	Ernest *et al*., 2007
Ethanol	Accumulation of acetaldehyde, lethal dose 3 g/kg In the USA, the maximum quantity of alcohol included in over-the-counter 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 In Europe, there are no limits set	American Academy of Pediatrics, Committee on Drugs, 1984; Tuleu, 2007; Pawar and Kumar, 2002; Rowe *et al*., 2012
Glycerol	>40% in volume: mucositis, diarrhoea, electrolyte disturbances	Pawar and Kumar, 2002
Liquid paraffin	Lipoid pneumonia caused by aspiration Should not be used in very young children	Rowe *et al*., 2012
Polyethylene glycol	Renal failure (in 1937, children treated with sulphanilamide elixir developed renal failure traceable to ethylene glycol which had been used as a solvent), poisoning where 107 patients died The WHO has set an estimated acceptable daily intake of polyethylene glycols at no more than 10 mg/kg	Ernest *et al*., 2007; Rowe *et al*., 2012
Polysorbate	Hypersensitivity Serious adverse effects (E-Ferol syndrome: thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension and metabolic acidosis, including 38 deaths in low-birthweight infants) The WHO has set an estimated acceptable daily intake at no more than 25 mg/kg	Alade, Brown and Paquet, 1986; Balisteri, Farrell and Bove, 1986; Tuleu, 2007**;** Ernest *et al*., 2007; Rowe *et al*., 2012

Povidone	Anaphylactic reaction	Tuleu, 2007
Propylene glycol	One-third as intoxicating as ethanol Accumulation: hyperosmolality, effects on central nervous system, ototoxicity, cardiac arrhythmias, seizures, osmotic laxative effects, contact dermatitis, lactic acidosis (especially in neonates and children <4 years of age) Acceptable daily intake up to 25 mg/kg Not recommended for children <4 years (limited alcohol dehydrogenase). Half-life 17h in neonates (5h in adults).	Glasgow *et al*., 1983; American Academy of Pediatrics, 1997; Noerr, 2000; Tuleu, 2007; Kulo, de Hoon and Allegaert, 2012; Rowe *et al*., 2012
Sweetening and flavouring agents:		
Aspartame	Headache, grand mal seizures, memory loss, gastrointestinal symptoms, angioedema, pruritus, urticaria, granulomatous panniculitis, cross reactivity with sulphonamides, renal tubular acidosis (large quantities) Potentially toxic metabolites methanol, aspartic acid and phenylalanine; aspartic acid is neurotoxic and epileptogenic Phenylalanine is harmful in patients with phenylketonuria	Kumar, Rawlings and Beaman, 1993; Kumar *et al*., 1996; American Academy of Pediatrics, 1997; Pawar and Kumar, 2002; Rowe *et al*., 2012; Tuleu, 2007
Fructose	Hypoglycaemia (in patients with fructose intolerance)	Kumar *et al*., 1996
Menthol	Hypersensitivity reactions, systemic allergic reactions	Kumar, Rawlings and Beaman, 1993
Peppermint oil	Atrial fibrillation, muscle pain, cooling or burning sensations	Kumar, Rawlings and Beaman, 1993
Saccharin, saccharine sodium	Irritability, hypertonia, insomnia, opisthotonus and strabismus, urticaria, pruritus, nausea, diarrhea, tachycardia, papular skin eruptions, wheezing, cross reactivity with sulphonamides Approved for children >3 years	American Academy of Pediatrics, 1997; Kumar, Rawlings and Beaman, 1993, Pawar and Kumar, 2002; Tuleu, 2007
Sodium cyclamate	Photosensitization, eczema, dermatitis, pruritus, incidence of bladder cancer increased in rats Use is restricted in many countries	Kumar, Rawlings and Beaman, 1993
Sorbitol	Abdominal pain, decreased absorption of active drug, flatulence, osmotic diarrhoea (large amounts)	Kumar, Rawlings and Beaman, 1993; Kumar *et al*., 1996; Tuleu, 2007
Sucrose	Tooth decay Cariogenicity, hyperglycaemia, increased degradation of active drug, allergic reactions (very rare)	Kumar, Rawlings and Beaman, 1993, Kumar *et al.,* 1996; Pawar and Kumar, 2002, Tuleu, 2007
Xylitol	Osmotic diarrhea (large amounts)	Kumar *et al*., 1996

2.5.3 Manipulation of oral solid dosage forms

Instead of compounding, tablets are sometimes manipulated: cut into halves, quarters or smaller segments on the ward to obtain appropriately sized dosage units for children or cost savings (McDevitt, Gurst and Chen, 1998; Brion, Nunn and Rieutord, 2003; Hill *et al*., 2009; Navarro, 2009). 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 capability to provide other options (Brion, Nunn and Rieutord, 2003).

A tablet dispersion method is normally used on the wards (Haywood and Glass, 2007). The tablet, tablet segments or contents of capsule are placed in a cup of water or oral syringe and stirred by swirling a device until the contents have dispersed, and this is administered immediately to the patient (Dupuis and Armstrong, 1998; Haywood and Glass, 2007). An aliquot of the dispersion can be used only if the medication is soluble: for insoluble drugs, this method provides highly variable doses without the use of suspending agents (Standing and Tuleu, 2005).

Subdivision of tablets should be assessed and authorised by the competent authority (European Directorate for the Quality of Medicines & Health Care, 2013). Tablets comply with the test if not more than one individual mass of halves from 30 tablets is outside the limits of ±15% of the average mass and if no individual mass is outside the limits ±25% of the average mass. Unequal breaking of tablets may result in significant dose variability (Horn, Kuhn and Kanga, 1999; Marriott and Nation, 2002; Teng *et al*., 2002; van Santen, Barends and Frijlink, 2002). This may be clinically significant for drugs, which have a narrow therapeutic range or short half-life (Marriott and Nation, 2002; Hill *et al*., 2009).

The degree of inaccuracy seems to be associated with tablet size, thickness, shape, coating and type of score line (Sedrati *et al*., 1994; Marriott and Nation, 2002, van Santen, Barends and Frijlink, 2002). It has been reported that oval 10-mm tablets with deep scores on both sides were most accurate in manual splitting (McDevitt, Gurst and Chen, 1998). Even when commercial tablet cutters are used, the accuracy of splitting may be variable (Sedrati *et al*., 1994; Horn, Kuhn and Kanga, 1999; Marriott and Nation, 2002; Teng *et al*., 2002). The tablet-splitting device was most accurate with larger (> 600 mg) tablets that were coated, and had an oblong shape and flat edges (McDevitt, Gurst and Chen, 1998). Powdering and fragmentation during splitting of tablets can also be a source of loss of mass, from 1.1% to 14% when breaking tablets into halves and up to 27% when breaking them into quarters (van Santen, Barends and Frijlink, 2002).

Fewer than 50% of the splitted clonidine 0.1 mg and captopril 12.5 mg tablet quarters were within ±15% acceptance limits in the mass variation test (Horn, Kuhn and Kanga, 1999). In another study, over 40% of manually split tablet halves (n = 1752) deviated from ideal weight by more than 10% and over 10% deviated by more than 20% (McDevitt, Gurst and Chen, 1998). When a commercial splitter was used, nearly 40% of the portions (n=102) deviated by over 10%. 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). Teng *et al*. (2002) found that of the 11 tablet products splitted with single-edged razor blade (10 tablets for each product), only three products passed the uniformity of dosage units test of the United States Pharmacopeia. Finally, all three hand-split tablets failed the test.

In a study performed with 30 tablets of warfarin sodium 5 mg, metoprolol succinate 200 mg, lisinopril 40 mg, metoprolol tartrate 25 mg, simvastatin 80 mg and citalopram 40 mg it was found that dose variation exceeded USP specification for more than 30% of sampled half-tablets for the warfarin sodium, metoprolol succinate and lisinopril, and from 10% to 17% for metoprolol tartrate, simvastatin and citalopram (Hill *et al*., 2009). The drug content variation in half-tablets was greater for nonscored tablets as compared with scored tablets, but the loss of mass after splitting was only about 1%. The results also appeared to indicate that the drug had been uniformly dispersed within tablet.

The tablet dissolution rate and absorption characteristics of coated, enteric-coated and controlled-release tablets may be affected when tablets are split (Marriott and Nation, 2002; Sam, 2002). A controlled-release tablet that has been split may produce overdose: this has been suspected of causing to a number of adverse effects (Sam, 2002). Splitting may also expose the taste of the drug, which had originally been masked in the coated tablet (Marriott and Nation, 2002).

2.5.4 Compounding of oral powders

Oral solid dosage forms that are compounded for paediatric medication are mainly oral powders and capsules (Thompson, 2009a and 2009b). Oral powders (i.e. single-dose powders, divided powders, powder papers, sachets, chartulae), one of the oldest dosage forms, are preparations consisting of solid, loose, dry particles of varying degrees of fineness (Gennaro, 1990; Thompson, 2009a; European Directorate for the Quality of Medicines & Health Care, 2013). They contain one or more active substances, with or without excipients such as lactose or microcrystalline cellulose. Different strengths may be required to medicate children of different ages (Nahata, 1999a; Nunn, 2003).

Each dose of powder is weighed separately to a small folded waxed powder paper and thus oral powders are more time consuming to be compounded than capsules or oral liquids (Sandell, 1983; Nahata, 1999a; Allen, 2001; Allen, 2002; Thompson, 2009a). In the pharmaceutical industry, modern packaging materials of foil and plastic laminates had replaced paper wrappings because of their superior protective qualities (Summers, 2007). Oral powders generally represent a stable dosage form only for as long as they are protected from moisture and heat in tight containers (Gennaro, 1990; Allen, 2001; Allen, 2002; Thompson, 2009a).

The properties of a solid must be understood and evaluated to allow proper handling and manipulation of the material (Thompson, 2009a). The properties of powders are related to the size and surface area of the particles (Allen, 2002). Particles larger than 250 μm are usually relatively free flowing but as the size falls below 100 μm, powders become more cohesive and if the particle size is less than 10 μm, then powders are usually extremely cohesive and they resist flow (Staniforth and Aulton, 2007). Small particles present a greater surface area to the atmosphere and are thus more reactive to absorb gases like carbon dioxide (Allen, 2001).

A drug powder or a powder from commercially available crushed tablets or opened capsules may be diluted with excipient and redistributed into smaller strength powder papers (Nunn, 2003; Glass and Haywood, 2006). The first step in the powder preparation is to ensure that all the components of the mixture are in the same particle size range to prevent stratification of large and small particles (Gennaro, 1990; Allen, 2001; Allen, 2002; Thompson, 2009a). If one decreases the particle size, then more particles will be present in a unit dose and the probable variation in content may be reduced (Twitchell, 2007). Small particles dissolve faster due to their large surface area, and thus these kinds of powders tend to have a rapid onset of action (Allen, 2002; Thompson, 2009a).

In small-scale preparation, comminution involves mainly manual methods, e.g. trituration, levigation and pulverization by hand (Allen, 2002). Trituration refers to the process of rubbing substances down into fine particles in a mortar with a pestle or intimately mixing of fine powders in a mortar (Gennaro, 1990). In levigation, a paste is first created in a mortar by the addition of a suitable nonsolvent to the solid. Pulverization is the process of reducing the state of gummy (e.g. camphor) or it can consist of reagglomerating or grinding-resist solids with the aid of small amount of alcohol or some other volatile solvent.

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 (Twitchell, 2007). In order to conduct trituration in a mortar, the pestle is held firmly and downward pressure is

exerted with it while the pestle is moved in larger concentric circles (Thompson, 2009a). This is done by starting at the center of the mortar, moving outward to the sides of the mortar and then back to the center. If the powder has become compacted onto the sides of the mortar, it is continually removed by scraping it with a spatula.

Geometric dilution is used to ensure that small quantities of ingredients are uniformly distributed throughout the powder mixture (Gennaro, 1990; Allen, 2002; Thompson, 2009a). This is started with the ingredient in the smallest quantity. The volume of powder equal to the volume of powder mixture in the mortar is added and triturated with a pestle to a uniform mixture until all the powder ingredients have been added (Allen, 2002; Thompson, 2009a). If the powder is too fluffy, it can be compacted slightly by the addition of a few drops of alcohol, water or liquid paraffin (Allen, 2002). 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 compounded (Allen, 2002). Some powder will always be lost during the blending process (Thompson, 2009a).

Typically, the powder mixes contain particles that differ in size, shape and density and thus they may become segregated during mixing or storing and shipping (Allen, 2002; Twitchell, 2007). Larger particles separate at the edge of the powder heap while smaller particles tend to fall through the voids between larger particles and move to the bottom of the mass (Twitchell, 2007). Even in cases where particle sizes are similar, the more dense particles will move downwards and segregation will cause an increase in content variation (Allen, 2001; Twitchell, 2007). The use of excipients that have a similar density to the active component is one approach to minimize the risk of segregation.

Single-dose powders are weighed individually with a balance which is appropriate and accurate for the intended purpose (Thompson, 2009a). An intermediate amount of powder of 200 mg to 500 mg per packet is desirable. In addition, minimum weights of 120 mg and maximum of 500 mg of dose powder have been described (Sandell, 1983; Lund, 1994). The weight of 200 mg is recommended because this amount can be weighed and calculated easily (Marriott *et al*., 2010).

Powders should never be ingested without first moistening them because of the possible risk of aspiration or choking (Pagliaro, 2002). Usually the powders are administered in a liquid such as water or milk, in some other beverage or soft food if no incompatibilities are present (Allen, 2002; Glass and Haywood, 2006). The taste or caustic nature of the active drug may limit their use (Allen, 2002).

2.5.5 Compounding of hard gelatin capsules

While oral powders are standardized by mass, capsules are standardized by volume. The active substances are filled into one of the sections of the hard capsule shell that is then closed by slipping the other section over it (European Directorate for the Quality of Medicines & Health Care, 2013). Normally hard capsules are swallowed as a whole, but when they need to be administered to infants, the compounded capsules may be opened before administration (Allen, 1999; Allen, 2002; Pagliaro, 2002). The contents are gently and adequately mixed with a small amount of suitable liquid or soft food to avoid inhaling the powder into the lungs (Pagliaro, 2002).

The capsule size selected should be slightly larger than needed to hold the drug substance and sufficient excipients are added to fill the capsule shell (Allen, 2002). For children, the capsules with numbers 1–5, i.e. capacities of 0.48–0.13 ml, are normally used (Allen, 2002, Thompson, 2009b). Hard gelatin capsule shells normally contain about 12–16% water and thus they do not protect hygroscopic materials from atmospheric water vapour since moisture can diffuse through the gelatin wall (Allen, 2002; Rudnic and Schwartz, 2006**;** Jones, 2007, Thompson, 2009b). The excipients present in capsule formulation can have a significant effect on the rate of dissolution of poorly soluble and hydrophobic drugs

(Ashford, 2007). An increase in packing density of the encapsulated mass is believed to decrease liquid permeability and also to reduce the dissolution rate.

Manually operated capsule filling devices are suitable for small-scale production (Allen, 2002). Feton® from Belgium, Labocaps® from Denmark or Torpac® from USA consist of sets of plates which have predrilled holes to take 30–100 capsules (Jones, 2007). Smaller quantities can be prepared by blocking off unused holes (Allen, 1999). Empty capsules are fed into the holes, the bodies are locked by means of a screw and the caps are removed (Jones, 2007). The powder that should have good flow properties is spread with spatula so that it fills the bodies evenly. Then the capsules are closed.

2.5.6 Compounding of oral liquids

Liquid preparations for oral use include oral solutions and oral suspensions (European Directorate for the Quality of Medicines & Health Care, 2013). For infants and children under 5 years old, pharmaceutical liquids are traditionally preferred for oral administration (Allen, 2008). Multidose oral liquids provide a range of doses but they require a validated amount of preservatives and may be inaccurate in measuring of required dose (Sam *et al*., 2012). Instead, a single-unit oral liquid needs no measuring of dose but it provides only limited dose flexibility.

Liquid preparations have advantages of ease of administration compared to solid dosage forms, but usually dissolved drugs are more susceptible to degradation than when they are in the solid state (Tuleu, 2007; Jackson and Lowey, 2010). Solutions and elixirs can be irritating to the gastric mucosa and may be associated with some ADRs like nausea and vomiting (Pagliaro, 2002). Gastric irritation and osmotic diarrhoea may result from administering medicines that increase the osmolality of the gastrointestinal contents. An osmolality of 330–350 mOsm/kg is considered as most appropriate for enteral administration (Polo *et al*., 2007).

Oral liquids are comparatively quick to compound (Brion, Nunn and Rieutord, 2003). A small-scale preparation of an extemporaneous liquid dosage form from a tablet or capsule generally involves grinding of the tablets or emptying the contents of the capsules into a mortar (Nahata and Allen, 2008; The United States Pharmacopeial Convention, 2008; Jew, Soo-Hoo and Erush, 2010). To ensure uniformity of dose, it is recommended to add suspending agents to the vehicle whether or not the API in the tablet is soluble, because of the possible absorption of the drug to insoluble excipients in the tablets (Jackson and Lowey, 2010). In addition, a pharmaceutical suspension is an appropriate dosage form for administering insoluble or poorly water-soluble drugs (Ashford, 2007; The United States Pharmacopeial Convention, 2008). The suspension consists of two phases where finely divided insoluble particles, generally greater than 1μm, are uniformly dispersed throughout the liquid, usually an aqueous vehicle (Attwood, 2007; The United States Pharmacopeial Convention, 2008). The product must remain sufficiently homogenous for at least the period between shaking the container and measuring the required amount (Billany, 2007).

The particle size of the powder may first need to be reduced using a mortar and pestle in order to obtain small, uniform drug particles (The United States Pharmacopeial Convention, 2008). Many suspensions have particle sizes ranging from 1 to 100 μm, in better suspensions from 1 to 50 μm. Fine particles are more easily dispersed throughout the vehicle, settle more slowly and are less likely to cake.

The initial dispersion and proper wetting of an insoluble powder in a vehicle is an important step (Thompson, 2009c; Sinko and Singh, 2011). Hydrophilic materials can be first wetted with water-miscible liquids and hydrophobic substances with nonpolar liquids or surfactant (The United States Pharmacopeial Convention, 2008; Thompson, 2009c; Sinko and Singh, 2011). The incorporation of hydrophilic colloids like cellulose derivatives, xanthan gum and tragacanth will both increase the viscosity and protect the solid

hydrophobic particles with a multimolecular layer and thus impart a hydrophilic characteristic, which promotes wetting (Billany, 2007). A small quantity of selected vehicle is then added to form a paste (The United States Pharmacopeial Convention, 2008). Then additional vehicle is added in geometric portions and mixed to the desired volume. Small quantities of the added vehicle and good mixing are important to avoid the formation of lumps (van Schijndel, 2002). Formulating a stable suspension often requires more excipient content as compared with solid dosage forms (Standing and Tuleu, 2005). Friendly, the ease of redispersion in parallel with the uniformity of dose needs to be tested (Tuleu, 2007).

For poorly soluble drugs like nifedipine, dissolution is often the limiting step in absorption (Tuleu, Grangé and Seurin, 2005). A large surface of the dispersed drug in the suspension will enhance dissolution (Attwood, 2007). In contrast to the equivalent solid dosage forms like powder-filled hard gelatin capsules, dissolution of all drug particles begins immediately on dilution of the suspension in gastrointestinal fluids (Ashford, 2007; Marriott *et al*., 2010).

The dosage can be measured from a single strength preparation by using an oral syringe (Brion, Nunn and Rieutord, 2003). Since stability data in pharmacy-prepared prefilled plastic syringes is limited, the storage of drugs needs to be minimized (Tucro, 1994). New guidelines on the standards required for the preparation of non-sterile liquids in healthcare establishments have recommended the use of closed systems for processing and transfer to the wards to protect the product from contamination (Pharmaceutical Inspection Convention, 2008).

Oral syringes provided much higher dosing accuracy in comparison with the specifically designed measuring spoons when the volumes of 1.25, 2.5 and 5 ml were withdrawn corresponding to ¼, ½ and full spoon (Dockhorn *et al*., 2010). Errors may also occur in measuring doses less than 0.1 ml (Nahata, 1999b). Measuring devices such as syringes and needles may be used inappropriately: the dead space in the hub of the syringe and needle may contain a large volume in relation to the dose which, if rinsed can introduce a substantial error (Leff and Roberts, 1987; Nunn *et al*., 2013).

Only liquid preparations for oral use should be administered through small-bore nasogastric feeding tubes and if liquid forms are not available, an alternative administration route needs to be considered (Engle and Hannawa, 1999; Pagliaro, 2002; Dandeles and Lodolce, 2011). When available, it is recommended to use suspensions rather than syrups, particularly if the pH of the syrup is very low and it may form clumps with enteral nutritional formulas (Williams, 1989). In patients with nasogastric tubes, the taste of the product is not relevant. Feeding tubes made of polyurethane seem to have a lower incidence of clogging compared to other materials (Pagliaro, 2002). Enteral feeding tubes should be flushed with sterile water after every bolus feed and before and after medication administration and every four hours if they are providing continuous feeds (Gora, Tschampel and Visconti, 1989; Beckwith, Barton and Graves, 1997; Engle and Hannawa, 1999; Pagliaro, 2002; Dandeles and Lodolce, 2011; BMJ Group, 2012).

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). Infants should be spoken to softly, they should be handled gently and should be held and cuddled before and after administration. In the newborn, oral liquids may be dispensed via a plastic nipple to take advantage of their strong sucking reflex. If the infant refuses the nipple, a plastic oral drug syringe can be used. Small amounts of the drug (≤0.5 ml) should be placed between the cheek and gum toward the back of the mouth. Subsequently, the infant's throat can be gently stroked outside in a downward motion to facilitate swallowing.

Administration of an unsuitable formulation to paediatric patients can be stressful, traumatic and sub-therapeutic (Tuleu, 2007). Thus, in the present study, appropriate drug formulations and dosage forms for different age groups were considered.

3 Aims of the Study

The aim of this study was to evaluate the pharmaceutical properties of hospital pharmacy compounded age-appropriate oral dosage forms intended for paediatric patients by using nifedipine 1 mg/dose as the model drug.

Specific aims were:

1. to determine the content uniformity of nifedipine in powders and capsules prepared from crushed tablets,

2. to determine the chemical stability of nifedipine in powders,

3. to formulate a nifedipine suspension for newborns using hypromellose as an excipient and to determine its chemical, microbiological and physical stability, and

4. to compare six different nifedipine multi-dose suspensions by evaluating the effect of agitation on the content uniformity, and the sedimentation volume.

4 Materials and Methods

4.1 MATERIALS

4.1.1 Nifedipine (I–V)

The drug substance, nifedipine (C_{17}-H_{18}-N_2-O_6; Mol. Wt. 346.3), was obtained either as the drug powder (II–III) (Orion Corporation, Turku, Finland) or from manually crushed tablets (I–V) (Adalat® 10 mg retard, Bayer AG, Leverkusen, Germany). Crushed nifedipine tablets and nifedipine drug powder were scanned with an electron microscope (SEM) (II) (Jeol JSM-35 Scanning microscope, Tokyo, Japan).

According to the manufacturer, the particle size of the nifedipine powder was less than 5 μm in at least 85% of particles, and all the particles were under 20 μm. The manufacturer stated that the particle size of nifedipine in the tablet form was 7–13 μm, with not more than 20% of particles over 25 μm and at most 2% of the particles over 30 μm.

Adalat® 10 mg retard can be crushed, because it does not contain any special technological structure. The retard effect is based on the particle size and the low water solubility of the drug. Adalat® retard tablets contain microcrystalline cellulose and lactose as a filler, maize starch as a binder, filler and disintegrant, polysorbate 80 as a wetting agent and non-ionic surfactant, and magnesium stearate as a lubricant (Finnish Medicines Agency, 2013; Rowe *et al*., 2012). 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 the light-sensitive active ingredient.

Nifedipine is practically insoluble in water and sensitive to light (European Directorate for the Quality of Medicines & Health Care, 2013). In order to prevent photodegradation of nifedipine, it was always handled in a dimly lit room, illuminated with a yellow light with a wavelength over 450 nm, if needed.

The photostability of nifedipine is influenced by the wavelength and intensity of light exposure, concentration of solution, solvent effects and quality of vials (Thoma and Klimek, 1985b; Thoma and Klimek, 1991a). When exposed to light, nifedipine undergoes rapid photochemical degradation accompanied by a significant reduction in its pharmacological activity (Thoma and Klimek, 1985a; Al-Turk *et al*., 1988; Matsuda, Teraoka and Sugimoto, 1989; Logan and Patrick, 1990). Although UV-light is very often the cause of the degradation of drugs, a distinct spectral region of visible light seems to be responsible for most of the photolysis of nifedipine. Thus, nifedipine solution is stable in daylight down to a wavelength of 475 nm, but photolysis begins at 450 nm and increases considerably at wavelengths around 400 nm. Nifedipine is converted to a nitrosophenylpyridine derivative when exposed to daylight and artificial light of certain wavelengths, and to a nitrophenylpyridine derivative when exposed to ultraviolet light (Matsuda, Teraoka and Sugimoto, 1989; Thoma and Kerker, 1992; Thoma, 1996; European Directorate for the Quality of Medicines & Health Care, 2013).

As many as six photodegradation products have been found when pulverized tablets have been exposed to normal room light at room temperature for 30 days while the colour of the powder changed from yellow to brown (Hayase *et al*., 1994). Photodegradation products have thought to be inactive but it was reported recently that nitrosonifedipine may possess some antioxidant effects (Grundy, Kherani and Foster, 1994; Horinouchi *et al*., 2011).

4.1.2 Excipients (I–V)

Lactose (I, IV) (Lactosum monohydricum Ph.Eur. parve granules, Pharmatose® 80 mesh, DMV International, Veghel, The Netherlands) was used as filler and diluent in the oral solid dosage forms. The bulk density of Pharmatose® 80 mesh is 0.75 mg/cm^3 and the tapped density is 0.92 mg/cm^3 (Rowe *et al*., 2012). According to the supplier, 70–90% of the particles were under 250 μm, <20% were under 100 μm and >95% were under 315 μm. The solubility of lactose in 20°C water is 1 in 5.24 (Rowe *et al*., 2012). Lactose is not hygroscopic (Allen, 2002).

Microcrystalline cellulose (IV) (Avicel® PH-102, FMC Corporation or Emcocel® 90M, Tamro, Vantaa, Finland) was used as a diluent in the oral solid dosage forms. 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 (Rowe, et al., 2012). The tapped densities are 0.35 g/cm^3 for Emcocel® 90M and 0.48 g/cm^3 for Avicel® PH-102 (Doelker *et al*., 1995; Allen, 2002; Rowe *et al*., 2012). The nominal mean particle sizes are 100 μm and 91 μm for Avicel® PH-102 and Emcocel® 90M, respectively, and not more than 8% of the particles are retained in a mesh size of 60 μm and at least 45% are retained in a mesh size of 200 μm (Rowe *et al*., 2012). Microcrystalline cellulose is hygroscopic and practically insoluble in water.

Hypromellose (II, III, V), formerly hydroxypropylmethylcellulose, (Methocel® E50 Premium LV, Ph.Eur., University Pharmacy, Helsinki, Finland and Hypromellose 50 mPa.s, Colorcon, Kent, England) was used as a suspending and thickening agent in liquid formulations (Rowe *et al*., 2012). It has a nominal viscosity of 50 mPa.s for 2% (w/v) aqueous solution at 20°C. Hypromellose is practically insoluble in hot water and is soluble in cold water forming a viscous colloidal solution. Aqueous solutions may be sterilized by autoclaving.

Methylcellulose (V) (Methylcellulose USP 1500 mPa.s, Sigma-Aldrich, St. Louis, Missouri, USA) was used as viscosity-increasing agent in oral suspensions. Methylcellulose swells and disperses slowly in cold water, forming a clear to opalescent, viscous, colloidal dispersion (Rowe *et al*., 2012). Cellulose derivatives are liable to microbial spoilage and antimicrobial preservatives should be used.

Sodium benzoate (V) (Ph.Eur., Oriola, Espoo, Finland) was used to preserve Methylcellulose 1% vehicle. Sodium benzoate, which is used as preservative in oral medicines at concentrations around 0.02–0.5%, dissolves in water 1 in 1.8 and in boiling water 1 in 1.4 (Rowe *et al*., 2012). It has both bacteriostatic and antifungal properties in acidic solutions (pH 2–5), but in alkaline solutions it is almost without effect.

Sucrose (V) (Ph.Eur., Tamro, Vantaa, Finland) was used as a sweetening and viscosity-increasing agent to prepare Syrup NF (Rowe *et al*., 2012). Sucrose is soluble in water at 1 part in 0.5 parts at 20°C and 1 part in 0.2 parts at 100°C. Dilute sucrose solutions are liable to contamination by microorganisms but resist contamination at higher concentrations (e.g. above 60% w/w).

Commercial suspension vehicles (V) Suspension Diluent A® (Nova Laboratories, Leicester, UK), SyrSpend SF® Cherry (Gallipot, St. Paul, Minnesota, USA), Ora-Plus® (Paddock Laboratories, Minneapolis, Minnesota, USA), Ora-Sweet® (Paddock Laboratories) and Ora-Sweet SF® (Paddock Laboratories) were used in the study of multi-dose suspensions.

The excipients used in this study are illustrated in Table 5.

Table 5. Excipients of the extemporaneous nifedipine preparations (I–V). All suspensions contained purified water (II, III, V).

Dosage form	**Vehicle or filler**	**Suspending agents**	**Taste** **Flavors**	**Preserva-tives**	**Buffers** **Antifoaming agents** **pH adjustment**
Oral powder	Lactose	-	-	-	-
Capsule	Lactose	-	-	-	-
Capsule	Microcrystalline cellulose	-	-	-	-
Unit-dose suspension	Hypromellose 1%	Hypromellose	-	-	-
Multi-dose suspension	Hypromellose 1%	Hypromellose	-	-	-
Multi-dose suspension	Methylcellulose 1%–Syrup NF	Methylcellulose	Sucrose	Sodium benzoate	-
Multi-dose suspension	Suspension Diluent A®	Xanthan gum	-	Methylparaben Propylparaben	-
Multi-dose suspension	Ora-Plus®	Microcrystalline cellulose Sodium carboxymethyl-cellulose Xanthan gum Carrageenan	-	Potassium sorbate Methylparaben	Sodium phosphate Citric acid Simethicone
Multi-dose suspension	Ora-Sweet®	-	Sucrose Glycerin Sorbitol Citrus-berry	Methylparaben Potassium sorbate	Citric acid Sodium phosphate
Multi-dose suspension	Ora-Sweet SF®	Xanthan gum	Glycerin Sorbitol Sodium saccharin Citrus-berry	Methylparaben Propylparaben Potassium sorbate	Citric acid Sodium citrate
Multi-dose suspension	SyrSpend SF® Cherry	Modified food starch	Sucralose Artificial cherry-flavor Malic acid	Sodium benzoate	Sodium citrate Citric acid Simethicone

4.1.3 Packaging materials (I–V)

Waxed, sealed powder papers (I, IV), which were sized at 47 x 30 mm (Paperityö, Helsinki, Finland), were used as the primary package for nifedipine powders.

Hard gelatin capsules (IV), volumes of 0.50 ml (clear number 1, Tamro, Vantaa, Finland), 0.30 ml (clear number 3, Gallipot, St. Paul, Minnesota, USA), and 0.21 ml (white number 4, Gallipot, St. Paul, Minnesota, USA) were used as the primary package in the capsules, whose contents were emptied for use.

Disposable syringes (II, III) of 2 ml (Discardit®, Becton Dickinson, Madrid, Spain) were used as primary packages for unit doses of nifedipine suspensions. The syringes were made of polyethylene (PE) and polypropylene (PP). The syringes were capped (Kombi-Stropfen®, Clinico, Bad Hersfeld, Germany).

Black plastic bags (I–IV) (Amerplast, Ikaalinen, Finland) were used as secondary packages for all units to protect the nifedipine from light.

Coloured class bottles of 100 ml (V) (Ardagh Glass, Obernkirchen, Germany) were used as the packaging material for multi-dose suspensions.

4.1.4 Chemicals (I–V)

Analytical grade nifedipine (N7634, Sigma Chemical Company, St. Louis, MO and N7634, Sigma-Aldrich Chemie, Steinheim, Germany) and HPLC-grade methanol (Lab-Scan, Dublin, Ireland and Mallinckrodt Baker, Deventer, The Netherlands) were used to prepare nifedipine stock solution.

Bupivacaine hydrochloride (II–IV) (Astra, Finland) was used as an internal standard in the HPLC assay of nifedipine. The HPLC's mobile phase consisted of ammonium acetate (I–IV), triethylamine (I–IV), acetic acid (I–IV) and phosphate buffer (V) (Phosphoric acid 6024, Mallinckrodt Baker). Sodium hydroxide (I, V), hydrochloric acid (I, V) and hydrogen peroxide (V) were used in degradation studies.

Staphylococcus aureus (II–III) (ATCC 25923), *Bacteroides fragilis* (III) (ATCC 25285) and *Candica albicans* (III) (isolated from clinical specimen) were used for method suitability test (II) and for study of antimicrobial properties. Fastidious anaerobe broths (II) (Lab M, UK), tryptic soy broths (II) (Difco, USA), sabouraud broths (II) (Oxoid, UK), nutrient agar (III) (Oxoid, UK), blood agar (III) (Columbia-agar, BBL, USA, with 5% sheep blood), cled (III) (BBL, USA), malassezil (III) (Microbiological laboratory, Kuopio University Hospital) and sabouraud (III) (BBL, USA) were used as culture media.

4.2 METHODS

4.2.1 Compounding procedures (I–V)

The following written procedures for compounding were followed:

Nifedipine 1 mg oral powders (I, IV)

1. Work in a dimly lit room. You may use a yellow light, which has a wavelength of over 450 nm.
2. Place 5 nifedipine 10-mg tablets in a zero-tared metallic mortar.
3. Grind tablets with a pestle into a fine powder.
4. By geometric dilution, add the lactose or microcrystalline cellulose to the ground tablets to make a sufficient amount of powder.
5. Mix the resulting powder for 5 minutes.

6. Weigh each portion (50 mg, 100 mg, 300 mg or 500 mg) and transfer individually to waxed powder papers.
7. Pack the sealed powder papers in a black plastic bag.

Nifedipine 1 mg capsules (IV)

1. Work in a dimly lit room. You may use a yellow light, which has a wavelength of over 450 nm.
2. Place 5 nifedipine 10-mg tablets in a zero-tared metallic mortar.
3. Grind tablets with a pestle into a fine powder.
4. By geometric dilution, add the lactose or microcrystalline cellulose to the ground tablets to make a sufficient amount of powder.
5. Mix the resulting powder for 5 minutes.
6. Fill the resulting powder into hard gelatin capsules of sizes 1 (0.50 ml), 3 (0.30 ml) or 4 (0.21 ml) by using a hand operated capsule filler.

Nifedipine 1 mg/ml oral unit-dose suspension (II, III)

1. Work in a dimly lit room. You may use a yellow light, which has a wavelength of over 450 nm.
2. Use sterilized equipment under aseptic conditions in a laminar flow hood.
3. Count out 5 nifedipine 10-mg tablets, or measure the required amount of nifedipine drug powder.
4. Measure out 50 ml of hypromellose 1% m/v vehicle.
5. Put the tablets and a small amount of hypromellose 10 mg/ml in a mortar (not ceramic because of porosity) and allow soaking for 5 min. The filmcoating of the tablet will dissolve in the liquid.
6. Crush the tablets and mix to a uniform paste with the mortar and pestle.
7. Add geometric amounts of vehicle to the desired volume while mixing.
8. Draw the required amount of suspension into a single unit (oral) syringe and close the syringe with the cap. Mix the suspension. Draw as many syringes as needed.
9. Label the syringe for peroral use with a note to shake well before using. Never use a needle, in order to reduce the possibility of medication error.
10. Put the syringe into a black plastic bag for storage; this will protect the nifedipine from light. Label the plastic bag.
11. Before administration, draw a little amount of air into the syringe and resuspend the solid sedimented particles by shaking.

Nifedipine 1 mg/ml oral suspension 100 ml (V)

1. Work in a dimly lit room. You may use a yellow light, which has a wavelength of over 450 nm.
2. Use sterilized equipment under aseptic conditions in a laminar flow hood.
3. Count out 7 nifedipine 10-mg tablets.
4. Grind the tablets with a pestle in a stainless steel (or melamine) mortar to a uniform fine powder.
5. Suspend the powder with 2 ml of suspension vehicle.
6. Add suspension vehicle via geometric dilution to the volume of 70 ml while mixing.
7. Store in a coloured 100 ml glass bottle.
8. Label the bottle “Shake well before use”.

Hypromellose 1% m/v vehicle 1000 ml (II, III, V)

1. Measure 10.0 g hypromellose 50 mPa.s into a bottle of sufficient size to accommodate the total volume of the required solution.
2. Place one-third of the total water volume in a container, and heat to 80–90 °C with vigorous stirring until agglomerates disappear and particles are thoroughly wetted.
3. Add cold water (≈ 5 °C) to a volume of 1000 ml. Continue stirring gently until the mixture is homogenous.
4. Allow the solution to cool in ice-cold water until thoroughly hydrated, and then allow it to gradually warm to ambient temperature.
5. Divide the solution into usable portions, as in vials, which may then be sterilized by autoclave.
6. Autoclave at 121 °C for 20 min.
7. Allow cooling to room temperature.

Methylcellulose 1% m/v solution H.S.C. 100g (V) (Rappaport, 1983)

1. Dissolve 0.2 g sodium benzoate in 20 ml of boiling distilled water.
2. Add 1.0 g methylcellulose 1500 mPa.s powder and stir well in a blender for 2–3 minutes.
3. Add 80 ml ice-cold water (cautiously but quickly) and stir or blend well for 5–10 minutes.
4. Transfer to a 100 ml bottle.
5. Refrigerate for at least 4 hours until the creamy thick white liquid is converted to a clear gel. Mix contents occasionally by rolling gently.

Syrup NF (Simple Syrup) 100 ml (V) (de Villiers, 2009b)

1. Weigh 85 g sucrose and a sufficient quantity of purified water to make 100 ml of solution.
2. Heat up until the sucrose dissolves.
3. Store in a 100 ml glass bottle.

Suspension Vehicle H.S.C. (Methylcellulose 1%/Syrup NF) 100 ml (V) (Rappaport, 1983)

1. Add 70 ml of Methylcellulose 1% H.S.C. in 30 ml of Syrup NF.
2. Stir well using a rod or blender if available. The liquid foams easily.
3. Store in a 100 ml glass bottle.
4. Mix by rolling gently.
5. Store at room temperature overnight or for a minimum of 4 hours before use.

4.2.2 High performance liquid chromatography (I–V)

Nifedipine amount was measured in studies I–V by a reproducible and validated stability-indicating HPLC method (Mehta, 1993; Hagan, 1994; ICH Harmonised Tripartite Guideline, 2012). A forced photodegradation experiment on the nifedipine compound was performed in order to verify the stability-indicating capability of the HPLC method (Anderson, 1996). Specificity was evaluated by exposing nifedipine drug powder and crushed nifedipine 10 mg tablet to wavelengths of visible and UV-light until significant degradation occurred (I, II). In a preliminary study, nifedipine powder papers were removed from their outer carton and left on a windowsill for six days. In study V, nifedipine sample suspensions were exposed to window light for 1 hour. All suspensions were also allowed to stand at room temperature and protected from light for 1 month.

Specificity was verified by heating 1 ml of nifedipine standard solution 1 mg/ml and a crushed nifedipine 10 mg tablet, which were first mixed with either 1 M hydrochloric acid or 1 M sodium hydroxide to a volume of 10 ml (II). The solutions were heated at 60°C for 2

days. Both the nifedipine drug powder and crushed tablet were heated at 120°C for 2 hours. In study V, all nifedipine sample suspensions were treated with either sodium hydroxide, hydrochloric acid and hydrogen peroxide, and heated in a water bath at 70°C. The chromatograms of the nifedipine standard were compared to the degraded sample in order to ensure that no interfering peaks exist. The identity of nifedipine was also confirmed by liquid chromatography-mass spectrometry (I).

The system precision of the HPLC method was examined with 10–15 injections of nifedipine standard solutions in intra-day and interday variation assays (I–IV). In study V, the system suitability, inter-day and intra-day variations were assayed by six injections from six samples per day during three days. The correlation coefficients were determined in all studies to assure linearity.

The concentrations of nifedipine formulations were estimated by peak height (I) or area (II–V) relative to the drug substance using HPLC with UV detection at a wavelength of 238 nm (I–V) and 332 nm (V). The HPLC system used in each of the studies has been described in publications I, II, IV and V with a reversed 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 (I–IV). 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). In study V, the mobile phase consisted of 60% methanol in 40% phosphate buffer (30 mM, pH 7.0). The column temperature was maintained at 35°C and the mobile phase flow rate at 0.8 ml/min.

Each randomly selected 1 mg 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), shaking (IV) and vortex mixer followed by blending by hand once an hour for 3 hours (V) were used to ensure dissolution of nifedipine.

In order to prepare a sample solution, a 1000 µl of the resulting nifedipine solution was diluted 1:10 with methanol (I–IV) or a 500-µl sample was taken (V). This solution as such (I, V) was assayed by HPLC, or a 750-µl aliquot of solution was mixed with 250 µl of bupivacaine solution, which acted as an internal standard (II–IV) prior to HPLC analysis. All the samples were prepared in a dimly lit room (I–IV) or in a dark room illuminated with a yellow light with a wavelength over 450 nm (V) and then protected from light.

4.2.3 Uniformity of dosage units (I, II, IV, V)

The content uniformities of the nifedipine oral powders (I, IV), capsules (IV) and suspensions (II, V) were determined by methods described in the European Pharmacopoeia (Council of Europe, 1996; Council of Europe, 2006; Council of Europe, 2008). Nifedipine oral powders and unit-dose suspensions were studied immediately after preparation (I, II, IV). The content uniformity of multidose suspensions was tested after preparation and after 1, 2 and 4 weeks of storage at room temperature (23±2°C) protected from light (V). At each time point, the sample bottle was mixed either by inverting the bottle 10–15 times or only 3 times to mimic the shaking likely to take place in daily practice.

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 set limits. Ten dosage units were taken at random and individual contents of nifedipine were determined using HPLC.

Nifedipine oral powders, capsules and single-dose suspensions complied with the test Uniformity of content of single-dose preparations (2.9.6) if not more than one of the 10 individual contents was outside the limits of ±15% of the average content, and if none were outside the limits of ±25% of the average content (I, II, IV) (Council of Europe, 1996; Council of Europe, 2006).

Nifedipine multidose suspensions complied with the test Uniformity of dosage units (2.9.40) if the Acceptance value (AV) of the first 10 dosage units is at maximum 15.0 (Council of Europe, 2008). This new formula takes into account the target content of the product. The AV was calculated by using the formula:

$$|M - \overline{X}| + ks \quad (2)$$

where reference value (M) is defined by the mean of the individual contents ($\overline{X}$) expressed as a percentage of the label claim, when the target content (T) is ≤ 101.5. The k is the acceptability constant, which is 2.4 for ten samples, and s is the sample standard deviation.

4.2.4 Uniformity of mass (V)

Uniformity of mass of delivered doses from multidose containers (2.9.27) was investigated by using the method described in the European Pharmacopoeia (V) (Council of Europe, 2008). Twenty samples were taken from the freshly prepared and inverted nifedipine suspensions and weighed individually. The suspension complied with the test if not more than two of the 20 individual masses deviated from the average mass by more than 10% and none deviated by more than 20%.

4.2.5 Hypromellose concentration (II)

To find the optimal resuspendible and dose-accurate combination, different concentrations of hypromellose colloids were compounded with both nifedipine drug powder and crushed tablets and doses of 50 ml were packaged in clear glass vials, which were stored at room temperature protected from light (II).

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-cold water until it was thoroughly hydrated. Hypromellose solution was sterilized in an autoclave. The hypromellose concentrations of 0%, 0.5%, 1.0%, 1.5%, 2.0%, 2.5% and 3.0% were used.

The following tests were applied to the nifedipine suspensions compounded with different hypromellose vehicles:

- visual observation of sedimentation after one month of storage at room temperature (22–23°C, relative humidity (RH) of 60–72%),
- 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,
- measurement of the nifedipine concentration from the middle part of the vial immediately, 1 min and 2 min after shaking, and
- measurement of the nifedipine concentration and evaluating its resuspending properties after one month of storage in a unit dose syringe at room temperature (22–23°C, 60–72% RH).

4.2.6 Chemical stability studies (I, III)

In the tests of 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 in primary packaging material (400 lux at a distance of 60 cm from the fluorescent lamp) (TLD 36W/965, natural daylight 6500, Philips, Roosendaal, Holland) or to natural daylight. The temperatures of the room and refrigerator were adjusted according to the European Pharmacopoeia (Council of Europe, 1996; Council of Europe, 2006).

If one wishes to test photostability of a drug product, it is desirable to use a greater exposure to light than is likely to occur under practical conditions (Anderson *et al*. 1991). 'Artificial daylight' fluorescent tubes simulating glass-filtered daylight were used in studies I and III. The spectral distribution of the light sources used was determined (III). The illumination of the sample area was measured with a lux meter (I, III).

When being exposed to light, 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.

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

Samples were removed after the pre-determined period of storage and were analysed by HPLC to assay the nifedipine concentration and to assess the degree of photodegradation. Drugs were considered stable if they retained ≥ 90% of the initial drug concentration.

4.2.7 Physical stability studies (II, III, V)

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 (II, III).

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 being kept in a refrigerator (6°C, 67–77% RH) (III). Hypromellose 1.0% solution was studied at 20°C at the time of preparation, before and after steam sterilization and then at 3, 6 and 12 months (II). All equipment was calibrated at regular intervals as recommended by the manufacturers.

The sedimentation volume of the nifedipine suspensions was observed visually over 4 weeks (V). Suspensions were stored in cylindrical graduated flasks in the dark at room temperature (22±2°C) so that the settled powder sediment on the bottom and the clear supernatant phase on the top of the suspension could be easily observed.

4.2.8 Microbiological stability studies (II, III, V)

Although the European Pharmacopoeia does not require that an oral preparation should be microbe-free, this is, of course, preferable for critically ill neonates (European Directorate for the Quality of Medicines & Health Care, 2013). According to the European Pharmacopoeia, the acceptance criteria for non-sterile aqueous preparations for oral use are total aerobic microbial count of 10^2 CFU/ml (maximum acceptable count is 200) and total combined yeasts/molds count of 10^1 CFU/ml (maximum acceptable count is 20) and the complete abcence of Escherichia coli.

The microbiological stability of nifedipine suspensions and hypromellose 1.0% solution were investigated by using the European Pharmacopoeia method (II, III) (Council of Europe, 1998). The antimicrobial properties of the nifedipine solution were studied.

The microbiological quality of nifedipine suspensions was determined immediately after preparation and on days 7, 14, 21 and 28 days after storage began either protected from light at room temperature (22°C, 60–72% RH) or in a refrigerator (6°C, 67–77% RH).

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 (Council of Europe, 1998). Fastidious anaerobe broths, tryptic soy broths and sabouraud broths were used as culture media. Inspection of cultures was conducted after 14 days of incubation at 22°C and 35°C.

The microbiological quality of the nifedipine multi-dose suspensions (V) was studied preliminary by inoculating 0.5-ml sample of the suspension to the blood agar and nutrient agar both after the preparation and at the end of the 1-month storage period. The agars were incubated at 35°C for 2 days and then at 22°C for 3 days.

5 Results

5.1 MORPHOLOGY OF NIFEDIPINE POWDER AND CRUSHED TABLETS

The morphologies of nifedipine drug powder and crushed Adalat® 10 mg retard tablets were characterized in SEM (II). Crushing of nifedipine tablets produced particles that differed in size and shape whereas nifedipine drug powder was relatively uniform (Figures 2–4).

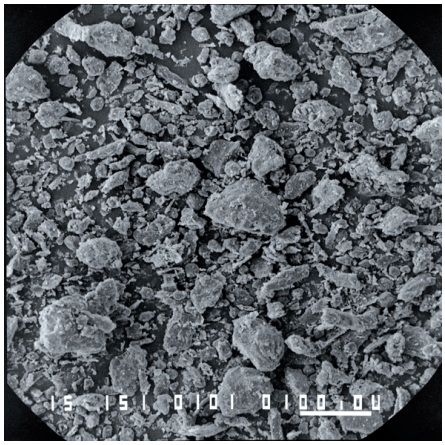

Figure 2. Nifedipine tablet crushed manually with a mortar and pestle and examined in a SEM. Scale bar is 100 µm. (I–V)

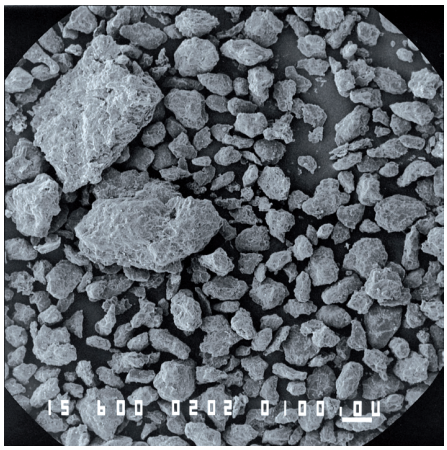

Figure 3. Nifedipine tablet crushed with an electronic crusher (Bamix®) for about 1 minute and examined in a SEM (unpublished data). Scale bar is 100 µm.

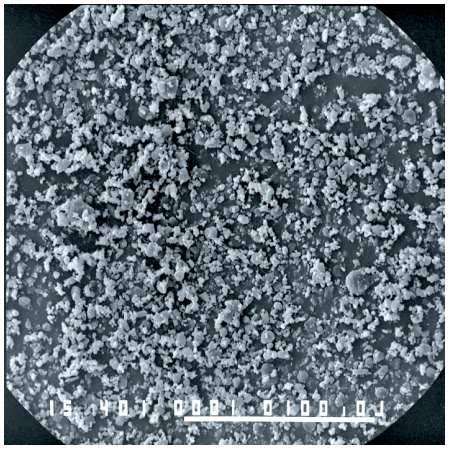

Figure 4. Nifedipine drug powder as viewed in a SEM. Scale bar is 100 µm. (II, III)

5.2 UNIFORMITY OF DOSAGE UNITS AND UNIFORMITY OF MASS (I, II, IV, V)

The content uniformities of nifedipine oral powders (I, IV), capsules (IV) and unit-dose suspensions (II) complied with the test specifications although some loss of nifedipine was observed (Table 6). The maximum deviations of the 10 individual contents were below ±15% of the average content (Table 7). No major differences in content uniformity were noted between hypromellose concentrations 0.5%, 1.0% and 1.5% or between nifedipine drug powders and crushed tablets in nifedipine suspensions that were packaged in vial.

A comparison between the different amounts of lactose and microcrystalline cellulose as excipients in nifedipine 1 mg oral powders of 500 mg and 300 mg and capsules of sizes 1, 3 and 4 indicated that content uniformity remained acceptable in both cases although the content was reduced to about 85–90% of the theoretical value (Table 7) (IV). In nifedipine 1 mg powders weighing 100 mg and 50 mg, the content was below 80% of the theoretical value both with lactose and microcrystalline cellulose (Figures 5 and 6). The nifedipine content was over 80% of the theoretical value in small capsules where the amount of the excipients were quite similar. Thus, 80 mg of microcrystalline cellulose or 160 mg of lactose was sufficient when compounding capsules. Instead, the amount of excipient in oral powders would need to be higher, since the amount of recovered nifedipine decreased as the total mass decreased. Nifedipine recovery was nearly the same in all emptied capsules compared with emptied oral powders weighing 300 mg or more.

It was noted that about 8% of the nifedipine amount of 1.0 mg was lost during the preparation and storage of powder papers and about 75% of that was identified to be present on the emptied powder papers (Table 6)(I). Minor amounts were found in the mortar and pestle and the other equipment used.

The multidose suspensions compounded with six different suspension vehicles complied with the test at each time point (AV≤15) when the suspension was mixed by inverting the bottle 10–15 times (Table 7)(V). Instead, when the suspension bottles were inverted only three times before sampling, the nifedipine suspensions compounded either with Methylcellulose 1%/Syrup NF or Hypromellose 1% vehicle did not comply with the test after 1 week of storage at room temperature while protected from light (Tables 8–10). In contrast, the four commercial suspensions complied with the test at each time point, even when they were mixed only by inverting the bottles three times.

The uniformity of mass of all freshly compounded nifedipine suspensions complied with the test specified in the European Pharmacopoeia (Table 11) (V).

Table 6. Loss of nifedipine during compounding process of 50 nifedipine 1.0 mg oral powders (n=1) (unpublished data).

Material	**Amount of nifedipine (mg)**
Total content of 50 oral powders	46
Mortar	0.5
Pestle	0.2
Tablet crusher	0.2
Other equipment (spatula, spoon etc.)	0.1
Emptied 50 powder papers	3.0
Total amount of nifedipine	50

Table 7. Content uniformities of nifedipine 1.0 mg in oral powders (I, IV), capsules (IV), unit-dose suspensions (II) and multidose suspensions (V) measured immediately after preparation complied with the requirements of European Pharmacopoeia (unpublished data of multi-dose suspensions).

Product	**Nifedipine***	**Excipient**	**Mean±SD (mg)**	**Maximum deviation from the mean(%)**
Oral powders 500 mg	Crushed tablet	Lactose	0.92 ± 0.03 (I)	+4.6 (I)
			0.87 ± 0.02 (IV)	+3.3 (IV)
Oral powders 500 mg	Crushed tablet	Cellulose microcrystalline	0.91 ± 0.04	-8.0
Oral powders 300 mg	Crushed tablet	Lactose	0.85 ± 0.03	+6.7
Oral powders 300 mg	Crushed tablet	Cellulose microcrystalline	0.88 ± 0.02	+2.6
Oral powders 100 mg	Crushed tablet	Lactose	0.77 ± 0.05	+14.9
Oral powders 100 mg	Crushed tablet	Cellulose microcrystalline	0.70 ± 0.03	+7.3
Oral powders 50 mg	Crushed tablet	Lactose	0.71 ± 0.04	-13.4
Oral powders 50 mg	Crushed tablet	Cellulose microcrystalline	0.62 ± 0.02	-5.9
Capsules n:o 1	Crushed tablet	Lactose	0.85 ± 0.02	+8.4
Capsules n:o 1	Crushed tablet	Cellulose microcrystalline	0.86 ± 0.04	+10.6
Capsules n:o 3	Crushed tablet	Lactose	0.87 ± 0.02	+3.8
Capsules n:o 3	Crushed tablet	Cellulose microcrystalline	0.83 ± 0.03	+5.8
Capsules n:o 4	Crushed tablet	Lactose	0.87 ± 0.01	-3.1
Capsules n:o 4	Crushed tablet	Cellulose microcrystalline	0.83 ± 0.05	-10.9
Unit-dose suspension	Crushed tablet	Hypromellose 1%	1.06 ± 0.05	+8.5
Unit-dose suspension	Crushed tablet	Hypromellose 1.5%	1.06 ± 0.04	+5.7
Unit-dose suspension	Drug powder	Hypromellose 0.5%	1.07 ± 0.05	+6.5
Unit-dose suspension	Drug powder	Hypromellose 1%	1.09 ± 0.05	+9.2
Multi-dose suspension	Crushed tablet	Suspension Diluent A®	0.99 ± 0.02	-3.5
Multi-dose suspension	Crushed tablet	Ora-Plus®/Ora-Sweet®	1.04 ± 0.01	+5.2
Multi-dose suspension	Crushed tablet	Ora-Plus®/Ora-Sweet SF®	0.94 ± 0.01	-8.4
Multi-dose suspension	Crushed tablet	SyrSpend SF® Cherry	0.99 ± 0.01	-2.7
Multi-dose suspension	Crushed tablet	Methylcellulose 1%/Syrup NF	0.93 ± 0.09	-15.6
Multi-dose suspension	Crushed tablet	Hypromellose 1%	1.00 ± 0.02	+3.7

*Crushed tablet is Adalat® 10 mg retard (Bayer AG)

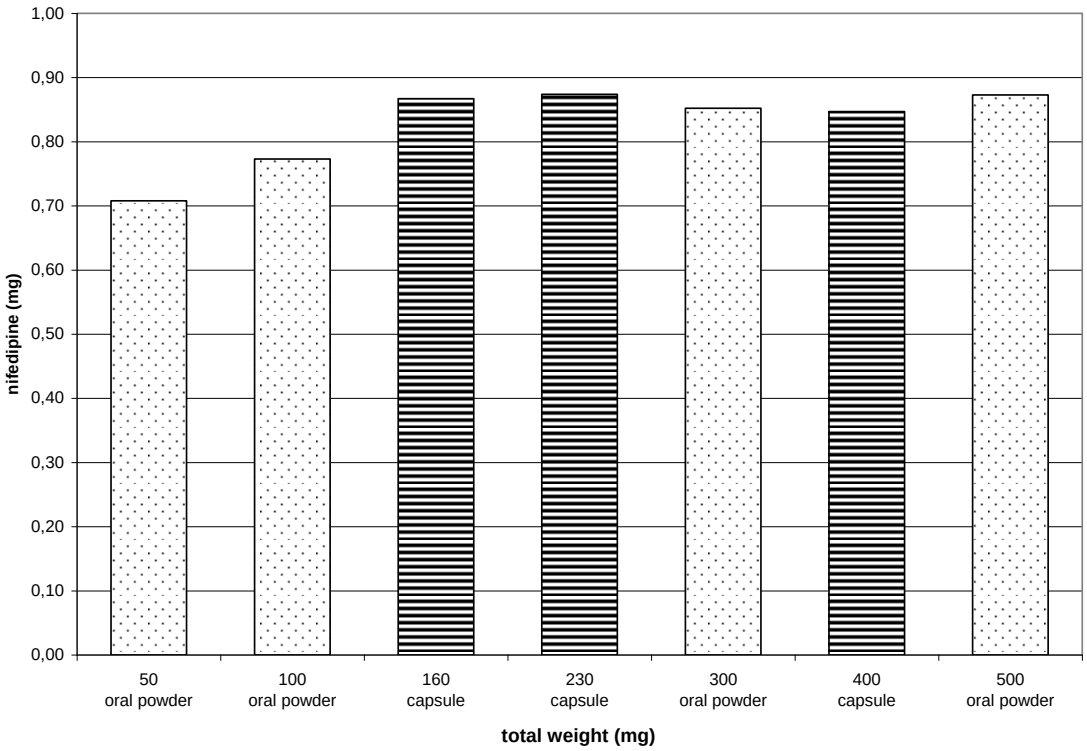

Figure 5. Nifedipine content in oral powders and emptied capsules number 1 (400 mg), 3 (230 mg) and 4 (160 mg) filled with lactose (IV). Theoretical amount of nifedipine was 1 mg. Mean values are shown (n = 10).

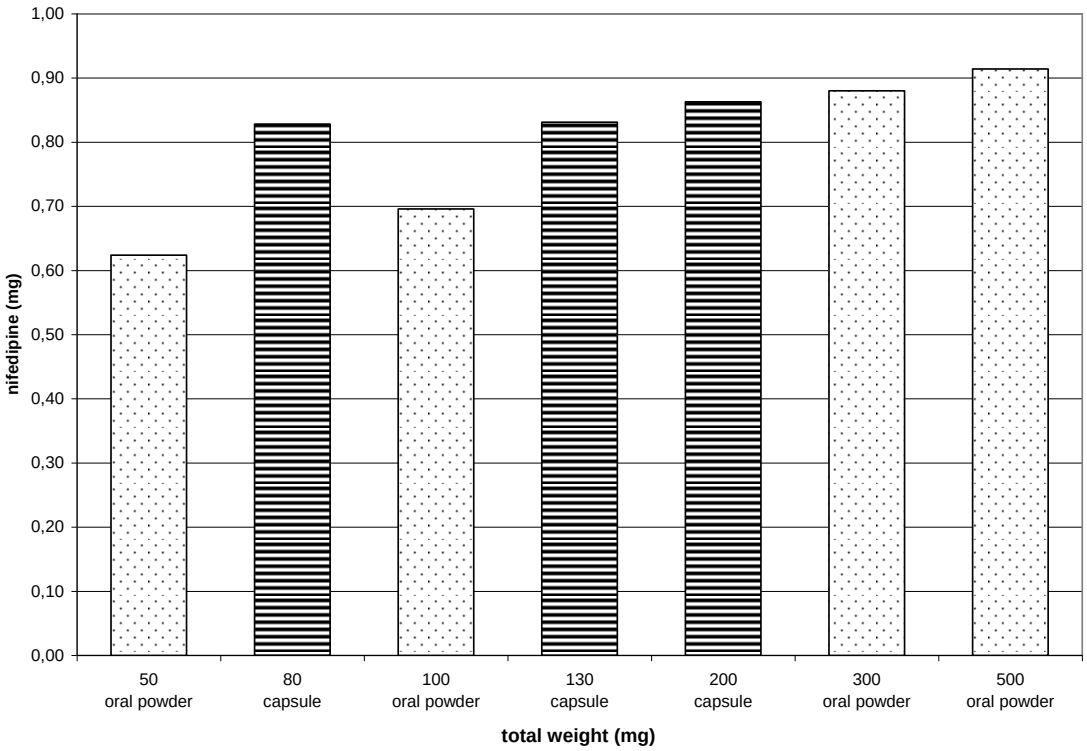

Figure 6. Nifedipine content in oral powders and emptied capsules number 1 (200 mg), 3 (130 mg) and 4 (80 mg) filled with cellulose microcrystalline (IV). Theoretical amount of nifedipine was 1 mg. Mean values are shown (n = 10).

Table 8. The uniformity of dosage units of nifedipine 1 mg/ml oral suspensions compounded with the six different vehicles and mixed by inverting the bottles either 10–15 times or 3 times before sampling (V). Suspensions were stored at room temperature. The preparation complies with the test if the AV is at maximum 15.0.

Suspension vehicle	**Acceptance value ± standard deviation (AV±SD, n=10)**			
Mixing protocol	**Initial**	**1 week**	**2 weeks**	**4 weeks**
Suspension Diluent A®				
10–15 times	0.04 ± 0.02	3.61 ± 0.02	1.19 ± 0.01	3.71 ± 0.03
3 times	2.18 ± 0.01	3.85 ± 0.04	0.05 ± 0.02	1.67 ± 0.02
Ora-Plus®/Ora-Sweet®				
10–15 times	2.61 ± 0.01	0.02 ± 0.01	0.03 ± 0.01	0.02 ± 0.01
3 times	0.03 ± 0.01	0.03 ± 0.01	0.04 ± 0.02	0.76 ± 0.01
Ora-Plus®/Ora-Sweet SF®				
10–15 times	4.85 ± 0.01	3.74 ± 0.02	1.41 ± 0.01	5.90 ± 0.01
3 times	0.01 ± 0.01	0.03 ± 0.01	2.03 ± 0.01	1.06 ± 0.01
SyrSpend SF® Cherry				
10–15 times	0.03 ± 0.01	4.39 ± 0.03	1.77 ± 0.01	3.57 ± 0.01
3 times	0.74 ± 0.01	1.76 ± 0.02	0.04 ± 0.02	0.70 ± 0.01
Methylcellulose 1%/Syrup NF				
10–15 times	5.31 ± 0.09	0.03 ± 0.01	1.09 ± 0.01	1.02 ± 0.02
3 times	2.58 ± 0.02	70.52 ± 0.04	-	-
3 times	18.41* ± 0.22	69.92 ± 0.00	-	-
Hypromellose 1%				
10–15 times	0.05 ± 0.02	2.69 ± 0.02	1.23 ± 0.07	0.03 ± 0.01
3 times	0.32 ± 0.03	26.27 ± 0.08	-	-
3 times	1.04 ± 0.01	21.86 ± 0.15	-	-

*exception to study protocol (AV>15), one week measurement was done to confirm the result

Table 9. The measured concentration of nifedipine in Methylcellulose 1%/Syrup NF -suspension mixed by inverting the bottle three times initially and after one week of storage at room temperature protected from light, the deviation from the theoretical concentration (1 mg/ml) and the calculated acceptance value (AV) (V). The preparation complies with the test if the AV is at maximum 15.0.

Sample	**Initial**		**1 week**		**Initial**		**1 week**	
	Conc. (mg/ml)	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**
1	0.95	-4.87	0.26	-73.56	0.65	-35.03	0.29	-71.44
2	0.94	-5.99	0.25	-74.88	0.65	-35.38	0.29	-70.98
3	0.96	-3.65	0.25	-74.84	0.64	-35.97	0.29	-70.99
4	0.93	-7.23	0.25	-75.12	0.64	-36.21	0.28	-71.52
5	0.95	-4.85	0.25	-74.63	0.67	-33.25	0.29	-71.49
6	0.95	-4.69	0.28	-72.48	0.68	-32.12	0.29	-71.48
7	0.99	-1.37	0.27	-72.50	0.82	-18.16	0.28	-71.53
8	0.98	-2.03	0.28	-71.83	1.02	1.94	0.28	-72.19
9	0.99	-0.60	0.33	-67.11	1.17	16.51	0.29	-71.33
10	0.95	-5.01	0.38	-62.24	1.14	13.78	0.29	-71.17
$\overline{X}$ (mg/ml)	0.96		0.28		0.81		0.29	
SD	0.02		0.04		0.22		0.00	
$\overline{X}$ (%)	95.97		28.08		80.61		28.59	
AV	**2.58**		**70.52**		**18.41**		**69.92**	

Table 10. The measured concentration of nifedipine in Hypromellose 1% -suspension mixed by inverting the bottle three times initially and after one week of storage at room temperature protected from light, the deviation from the theoretical concentration (1 mg/ml) and the calculated acceptance value (AV) (V). The preparation complies with the test if the AV is at maximum 15.0.

	Initial		**1 week**		**Initial**		**1 week**	
Sample	**Conc. (mg/ml)**	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**	**Conc. (mg/ml)**	**Deviation (%)**
1	1.01	1.47	0.91	-9.24	1.00	-0.14	0.52	-48.21
2	0.98	-1.80	0.67	-32.90	0.97	-3.02	0.60	-39.88
3	0.97	-3.35	0.67	-33.43	0.98	-1.76	0.63	-37.18
4	1.03	3.39	0.66	-33.78	0.97	-3.13	0.74	-25.94
5	0.97	-3.35	0.68	-31.82	0.97	-3.20	0.76	-23.79
6	0.95	-5.48	0.66	-34.32	0.97	-2.87	0.81	-18.73
7	0.96	-3.83	0.71	-28.79	0.97	-2.68	0.86	-14.02
8	0.98	-2.28	0.75	-24.72	0.97	-3.12	0.85	-14.84
9	0.98	-1.83	0.81	-18.79	0.97	-3.03	0.96	-4.38
10	1.00	-0.44	0.72	-28.01	0.98	-2.21	0.97	-3.00
$\overline{X}$ (mg/ml)	0.98		0.72		0.97		0.77	
SD	0.03		0.08		0.01		0.15	
$\overline{X}$ (%)	98.25		72.42		97.48		77.00	
AV	**0.32**		**26.27**		**1.04**		**21.86**	

Table 11. Uniformity of mass and maximum deviation from the mean of the mass of nifedipine 1 mg/ml suspensions in six different suspension vehicles (unpublished data).

Uniformity of mass	**Suspension Diluent A®**	**OraPlus® /Ora-Sweet®**	**OraPlus® /Ora-Sweet SF®**	**SyrSpend SF® Cherry**	**Methylcellulose 1%/Syrup NF**	**Hypromellose 1%**
Mean (mg)*	982.41	1172.98	1020.47	1011.80	1088.29	1005.18
Maximum deviation (%)	-1.2	±1.4	-9.8	-10.4	+1.5	-12.7

* Mean of twenty 1.0 ml samples

5.3 HYPROMELLOSE CONCENTRATION (II)

Nifedipine suspensions that were made from hypromellose concentrations of 0.5%, 1.0% and 1.5% were easier to redisperse than the other suspensions, which had hypromellose concentrations of 0%, 2.0%, 2.5% or 3.0% (Table 12) (II). No significant differences in the nifedipine concentrations were observed at hypromellose suspensions of 0.5, 1.0 and 1.5% measured immediately, 1 min and 2 min after shaking the vial. The suspensions made from nifedipine drug powder were more difficult to redisperse than the suspensions made from crushed nifedipine tablets, but the concentrations after mixing were close to each other. As a result, hypromellose 1.0% was selected as a vehicle for use in further suspensions with both drug powders and crushed tablets.

Table 12. Nifedipine 1 mg/ml suspension concentration measured from upper, middle and lower part of the vial 15 seconds after shaking (II).

Hypromellose concentration (%)	**Nifedipine***	**Nifedipine concentration (mg/ml)**			
		Upper	**Middle**	**Lower**	**Mean±RSD**
0	Crushed tablet	0.79	0.70	0.68	0.72 ± 0.06[a]
0.5	Crushed tablet	0.94	0.88	0.91	0.91± 0.03[a]
1.0	Crushed tablet	0.99	1.00	1.04	1.01 ± 0.03[a]
1.5	Crushed tablet	0.98	0.91	0.81	0.90 ± 0.09[a]
2.0	Crushed tablet	0.76	0.75	0.83	0.78 ± 0.04[a]
2.5	Crushed tablet	0.80	0.80	0.80	0.79 ± 0.01[a]
3.0	Crushed tablet	0.67	0.80	0.84	0.77 ± 0.09[a]
0	Drug powder	0.69	0.76	0.61	0.69 ± 0.08[b]
0.5	Drug powder	1.04	1.07	1.06	1.06 ± 0.02[b]
1.0	Drug powder	0.96	0.92	0.88	0.92 ± 0.04[b]
1.5	Drug powder	1.00	1.02	0.99	1.00 ± 0.02[b]
2.0	Drug powder	1.02	1.04	0.99	1.02 ± 0.03[b]
2.5	Drug powder	0.97	1.00	1.00	0.99 ± 0.02[b]
3.0	Drug powder	0.81	0.99	1.09	0.96 ± 0.14[b]

*Crushed tablet is Adalat® 10 mg retard (Bayer AG)
[a]Reported as mean concentration of duplicate determinations for two samples.
[b]Reported as mean concentration of duplicate determinations for four samples.

5.4 CHEMICAL STABILITY OF NIFEDIPINE (I, III)

At least 94% of the initial concentration of nifedipine remained in the powders that were protected from light and stored at room temperature or kept in a refrigerator for one year (Table 13) (I). In the suspensions compounded from crushed tablets 95% of the mean nifedipine concentrations remained, and from drug powder the corresponding value was 93% in the suspensions stored at room temperature protected from light, throughout the 28-day study period (Table 14) (III). When stored in a refrigerator protected from light, the corresponding values were 91% and 92% remaining. No evidence for the presence of degradation products was observed in the HPLC assay.

Significant degradation of nifedipine was observed in the powders and suspensions exposed to artificial daylight (Table 15) or natural daylight through a window (Figure 7). The spectrum of artificial full colour daylight resembled the spectrum of mixed artificial light of the room and natural daylight coming through a window (I, III) (Figures 8–9). The illumination of the sample area was found to be 400 lux at a distance of 60 cm from the lamp.

Photodegradation of the nifedipine exceeded 20% within three hours and 40% within six hours and was essentially complete after three days (Table 15). In suspensions made from crushed 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 the entire active drug has disappeared after three days. The photodegradation products of nifedipine were not specified in these studies but mainly one photodegradation product seemed to be present based on the mass spectrometry analysis (unpublished data).

Table 13. Chemical stability of nifedipine 1mg oral powders, stored at room temperature (22°C) and in a refrigerator (6°C) protected from light (I).

	% Initial nifedipine concentration remaining[a]	
Storage Time	**At room temperature[b]**	**In refregerator[c]**
7 days	105.6 ± 6.3	104.5 ± 5.4
14 days	103.7 ± 7.2	94.3 ± 5.5
21 days	100.7 ± 6.3	103.9 ± 3.5
28 days	102.1 ± 5.1	103.7 ± 5.6
2 months	108.5 ± 4.0	97.8 ± 5.8
3 months	104.2 ± 5.9	97.5 ± 2.9
4 months	110.1 ± 4.2	102.3 ± 5.1
6 months	101.5 ± 2.7	109.3 ± 4.7
8 months	103.4 ± 2.4	101.4 ± 3.3
10 months	96.2 ± 3.1	96.5 ± 4.8
1 year	98.2 ± 1.8	101.6 ± 4.1

[a]*Reported as mean-%±SD of triplicate determinations for six samples.*
[b]*Initial nifedipine concentrations per dose were 0.93±0.05 mg, 0.96±0.05 mg and 0.94±0.05 mg.*
[c]*Initial nifedipine concentrations per dose were 0.93±0.05 mg, 0.95±0.04 mg and 0.91±0.05 mg.*

Table 14. Chemical stability of nifedipine 1 mg unit-dose suspensions compounded both with crushed tablets or drug powder, stored either at room temperature (22–23°C) or in a refrigerator (5–7°C) and protected from light (III).

	% Initial nifedipine concentration remaining[a]			
Storage Time	**At room temperature**		**In refrigerator**	
	Tablet*[b]	**Powder[c]**	**Tablet*[d]**	**Powder[e]**
1 days	95.3 ± 5.9	93.0 ± 6.6	98.6 ± 3.8	92.2 ± 3.9
3 days	102.6 ± 5.1	94.4 ± 7.0	102.5 ± 1.6	96.2 ± 3.4
5 days	104.0 ± 3.5	96.7 ± 2.5	99.3 ± 6.2	95.6 ± 7.4
7 days	104.1 ± 8.6	95.2 ± 1.9	104.3 ± 4.9	94.0 ± 4.7
14 days	107.8 ± 4.9	104.1 ± 6.6	103.9 ± 3.1	103.9 ± 4.8
21 days	94.9 ± 6.4	96.4 ± 2.5	95.2 ± 2.1	93.6 ± 3.0
28 days	99.1 ± 6.8	95.0 ± 4.7	90.7 ± 6.0	92.0 ± 5.2

**Crushed tablet is Adalat® 10 mg retard (Bayer AG)*
[a]Reported as mean-%±SD of duplicate determinations for six samples. Initial nifedipine concentrations per dose were [b]0.95±0.05 mg, [c]1.00±0.05 mg, [d]0.96±0.02 mg and [e]1.03±0.02 mg in 1 ml of suspension.

Table 15. Chemical stability of nifedipine 1 mg oral powders and nifedipine 1 mg/ml unit-dose suspensions, compounded either with crushed tablets or drug powder, stored at room temperature (21–23°C) exposed to artificial daylight (unpublished data of oral powders).

	% Initial nifedipine concentration remaining		
Storage Time	**Oral powder [a]**	**Unit-dose suspension [b]**	
	Tablet*	**Tablet* [c]**	**Powder [d]**
3 hours	77.9 ± 4.6	73.5 ± 5.6	68.8 ± 11.3
6 hours	56.2 ± 1.3	57.0 ± 4.8	46.3 ± 9.7
18 hours	20.5 ± 2.0	23.4 ± 12.8	16.4 ± 26.3
1 day	25.7 ± 3.0	19.5 ± 16.3	11.5 ± 22.2
2 days	7.1 ± 1.0	14.8 ± 17.7	6.2 ± 48.2
3 days	4.2 ± 1.7	11.7 ± 17.9	0.5 ± 155.3
4 days	not detected	not detected	not detected
5 days	not detected	3.1 ± 47.4	not detected
7 days	not detected	0.7 ± 165.1	not detected

**Crushed tablet is Adalat® 10 mg retard (Bayer AG)*
[a]Reported as mean-%±SD of triplicate determinations for six samples. Initial nifedipine concentration per 1.0 mg dose was 0.91±0.03 mg.
[b]Reported as mean-%±SD of duplicate determinations for six samples.
Initial nifedipine concentrations were [c]0.98±0.03 mg/ml and [d]1.03±0.04 mg/ml.

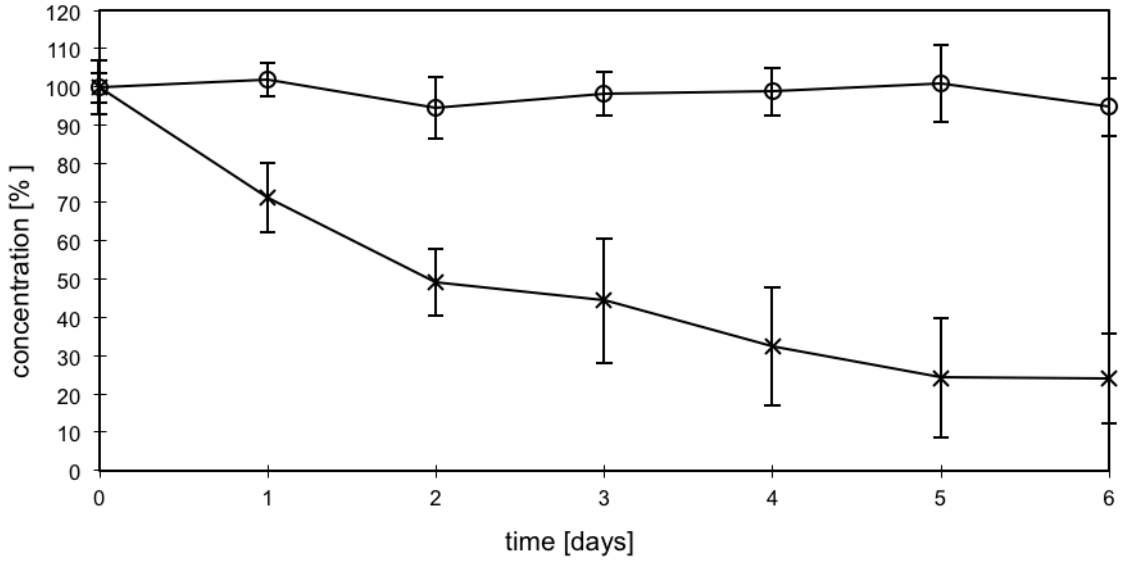

Figure 7. Chemical stability of nifedipine 1 mg oral powders stored at room temperature (24ºC) protected from light (—o—) and exposed to natural daylight at maximum 150 lux through the window in November in Finland (—x—) (preliminary study, unpublished data). The data is reported as mean-%±SD of triplicate determinations for six samples. An initial nifedipine dose was 0.92±0.03 mg.

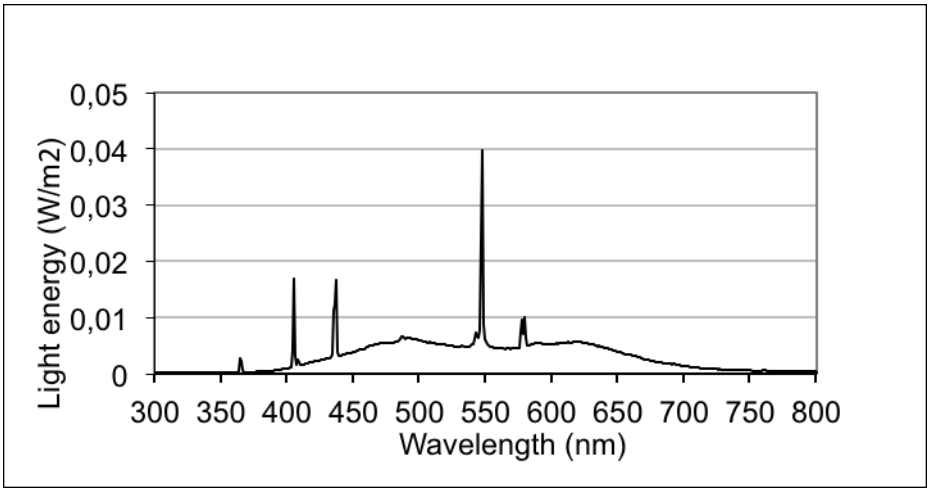

Figure 8. Spectrum of artificial full-colour daylight (300–800 nm) used in the photodegradation study (III).

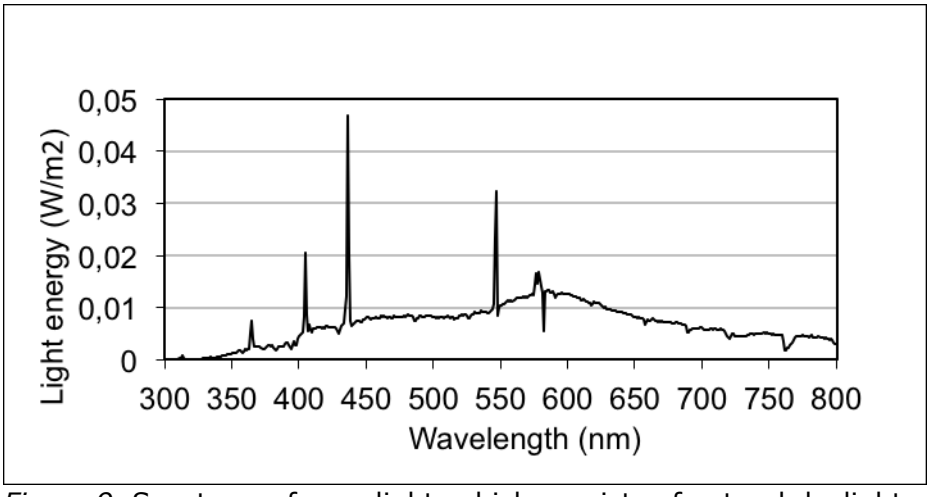

Figure 9. Spectrum of roomlight, which consists of natural daylight coming through a window and artificial light (300–800 nm) (III).

5.5 PHYSICAL STABILITY OF FORMULATIONS (II, III, V)

At the end of the study intervals, the samples of drug-free hypromellose 1% solution and nifedipine suspensions (1 mg/ml) in 1% hypromellose vehicle protected from light were examined for any changes in their physical properties: pH, viscosity, density, osmolality and surface tension (II, III, V). The drug-free hypromellose 1% solution remained physically stable during the study period of 12 months at room temperature (Table 16) (II).

The nifedipine unit-dose suspensions compounded either from tablets or drug powder also remained physically rather stable over 28 days either at room temperature or in a refrigerator protected from light and only minor changes in viscosity were detected (Tables 17–18)(III). Suspensions made from crushed tablets were easier to redisperse than suspensions made from drug powder. Visual inspections revealed that no change in colour had occurred during the study period. The colour of the nifedipine suspensions changed when they were exposed to artificial daylight for 7 days.

Sedimentation volumes of the unmixed nifedipine multi-dose suspensions during one month are illustrated in Figure 10 (V). No visible changes were observed in the suspensions made with Suspension Diluent A® and SyrSpend SF® Cherry vehicles. In all other suspensions, the presence of slight sediment was noticed. Suspensions compounded with Ora-Plus®/Ora-Sweet® and Hypromellose 1% had three distinct phases: a yellow solid powder sediment at the bottom of the flask, a yellow suspension phase in the middle of the suspension and a clear supernatant phase at the top (12 ml and 5 ml, respectively).

Multidose suspensions behaved differently during resuspension after storage for 4 weeks at room temperature (V). Suspension Diluent A®, Ora-Plus®/Ora-Sweet® and Ora-Plus®/Ora-Sweet SF® could be readily dispersed into a uniform mixture. However, the SyrSpend SF® Cherry suspension could not be mixed properly as it remained stuck to the walls of the cylindrical graduated flask. The Methylcellulose 1%/Syrup NF and Hypromellose 1% suspension required 20–25 and 5–19 s of mixing, respectively, before they formed a uniform mixture.

Table 16. Physical stability of drug-free hypromellose 1.0% solution during 12 months at room temperature (II).

		Viscosity (mPa.s)				
Storage time	**pH**	**A[a]**	**B[b]**	**Density (g/ml)**	**Osmolality[b] (mOsm/kg)**	**Surface tension[b] (mN/m)**
Before autoclaving	6.81	7.1	8.8	1.0004	8	49
After autoclaving	6.80	6.9	8.4	1.0006	8	48
3 months	6.77	7.4	8.6	0.9998	8	46
6 months	6.79	6.9	8.0	1.0000	8	44
12 months	6.94	7.6	7.5	1.0015	8	47

A Haake Falling Sphere Viscosimeter
B Haake Rotovisco RV2
[a]Reported as mean of five determinations
[b]Reported as mean of duplicate determinations

Table 17. Physical stability of nifedipine 1 mg/ml unit-dose suspension compounded with crushed tablets* (III).

		Viscosity (mPa.s)				
Storage time (days) and temperature	**pH**	**A[a]**	**B[b]**	**Density (g/ml)**	**Osmolality[b] (mOsm/kg)**	**Surface tension[b] (mN/m)**
Initial sample	7.00	16.0	10.6	1.0025	11	46
14 (22°C)	7.00	13.0	not detected	1.0042	12	46
14 (6°C)	7.02	13.0	not detected	1.0040	12	45
28 (22°C)	6.95	10.8	8.2	1.0003	11	44
28 (6°C)	6.94	12.0	8.2	1.0010	11	45

*Crushed tablet is Adalat® 10 mg retard (Bayer AG)
A Haake Falling Sphere Viscosimeter
B Haake Rotovisco RV2
[a]Reported as mean of five determinations
[b]Reported as mean of duplicate determinations

Table 18. Physical stability of nifedipine 1 mg/ml unit-dose suspension compounded with drug powder (III).

		Viscosity (mPa.s)				
Storage time (days) and temperature	**pH**	**A[a]**	**B[b]**	**Density (g/ml)**	**Osmolality[b] (mOsm/kg)**	**Surface tension[b] (mN/m)**
Initial sample	7.00	8.2	8.8	0.9987	10	49
14 (22°C)	6.91	8.3	not detected	1.0016	9	47
14 (6°C)	6.96	6.6	not detected	1.0011	8	47
28 (22°C)	7.13	10.3	11.3	1.0015	9	43
28 (6°C)	7.00	6.7	8.9	1.0002	8	46

A Haake Falling Sphere Viscosimeter
B Haake Rotovisco RV2
[a]Reported as mean of five determinations
[b]Reported as mean of two determinations

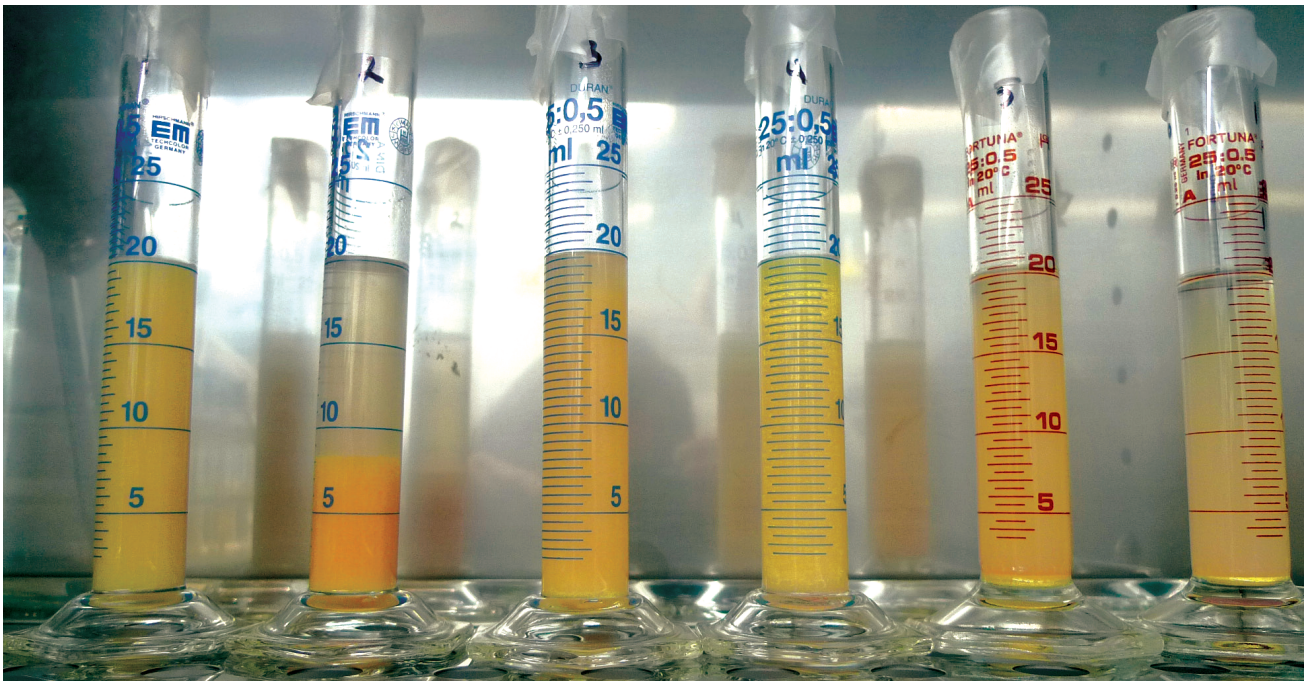

Figure 10. Sedimentation of the unmixed nifedipine 1 mg/ml multidose suspensions (20 ml) compounded with Suspension Diluent A® (left), Ora-Plus®/Ora-Sweet®, Ora-Plus®/Ora-Sweet SF®, SyrSpend SF® Cherry, Methylcellulose 1%/Syrup NF and Hypromellose 1% after one month storage at room temperature (unpublished data).

5.6 MICROBIOLOGICAL STABILITY OF FORMULATIONS (II, III, V)

No microbiological contamination was observed in any samples of drug-free hypromellose 1% during a period of 6 months at room temperature (II). Because of probable laboratory contamination, *Propionebacterium* was found in one of the samples at 12 months, but the duplicate test was negative (sterile).

The antimicrobial properties of nifedipine 1 mg/ml unit-dose suspension compounded with hypromellose 1% were examined (III). Freshly prepared 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 at room temperature or in a refrigerator (III).

The microbiological quality of non-sterile nifedipine multidose suspensions was studied after four weeks of storage at room temperature (unpublished data) (V). Nifedipine suspensions compounded with Ora-Plus®/Ora-Sweet®, Ora-Plus®/Ora-Sweet SF®, Methylcellulose 1%/Syrup NF and Hypromellose 1% contained some microbial contamination (2–6 CFU/ml) but suspensions compounded with Suspension Diluent A® and SyrSpend SF® Cherry were free of microbes.

6 Discussion

Although the tradition of compounding "lege artis" or "secundum artem" can be traced over a period of hundreds of years as a part of the professional skill of the pharmacist, the quality of the products being compounded has been inadequately studied. Many of the medicines used for neonates and children have not yet been licensed for this purpose and their use is considered off-label or unlicensed. This leads to a situation where attempts are made to modify an existing "adult" dosage form or an active ingredient and excipients are converted to an age-appropriate paediatric formulation. The dose required for a child may be delivered in a portion of a tablet designed for adult. However; the range of doses and dosage forms is so variable that preparation for stock is not possible and extemporaneous preparation is essential. Thus, the background to this research project was to combine these two uncertainties and to choose and examine suitable oral dosage forms for paediatric formulations, which could be used in different ages of children and be modified for different situations likely to be encountered in the hospital setting.

6.1 DOSAGE FORMS FOR PAEDIATRIC USE

In many situations, oral liquids are the most suitable dosage forms for infants. However, in one pilot study it was noted that uncoated mini-tablets (2 mm in diameter) seemed to be a very promising alternative to liquid formulation even for infants aged 6-12 months (Spomer *et al*., 2012). In the developing world, flexible solid dosage forms might be preferrable as the standard paediatric formulation to overcome the problems of cold storage, bulk trasportation and the availability of clean water to dissolve the formulations (Hoppu, Ranganathan and Dodoo, 2012). Thus, solid dosage forms such as oral powders, fast dissolving granules (sprinkles), granules, mini-tablets, orally disintegrating mini-tablets or dispersible dosage forms may be considered as alternatives to oral liquids (Salunke *et al*., 2011; Stoltenberg and Breitkreutz, 2011; Sam *et al*., 2012).

6.1.1 Capsules and oral powders

Children still have medication needs that are not met by the commercially manufactured products. The present results demonstrate that compounded nifedipine capsules, which are emptied before use could safely replace oral powders in paediatric medication (IV). Capsules are faster to compound than powders due to the possibility for serial production by manually operated capsule filling devices instead of individual weighing. Both dosage forms are widely used in European hospitals (Brion, Nunn and Rietord, 2003). In addition, many children, even those aged 3 to 5 years, can comfortably swallow small sized capsules.

Compounding of small capsules, such as size numbers 3 (0.30 ml) or 4 (0.21 ml), is acceptable when considering the recovered drug content, although the total weight of the oral powder should be 300 mg or more if one wishes to achieve the target content (IV, Figures 4–5). The loss of nifedipine during oral powder preparation and administration may be considerable, especially with powders, which have a relatively small mass, 100 mg or 50 mg. The surface area of capsule shell is smaller than the surface area of the powder paper, and this clearly reduces the loss of active ingredient.

Capsules to be emptied and powders are suitable formulations for infants, since they can be easily added to milk, other liquid or to some pleasant-tasting semi-solid food to prevent aspiration of a powder and to mask the taste. Oral solids are simple to use at home, and the

stability of the drug is usually good. However, administration through a nasogastric tube requires a liquid form of drug.

6.1.2 Unit-dose and multidose suspensions

Special caution is needed in dispensing extemporaneously prepared oral suspensions in multidose containers since the variation between doses may be considerable (V). Incorrect dosages may be dispensed from poorly mixed suspension bottles. However, the quality of many commercial vehicles seems to be good when compared to compounded vehicles (V). The nifedipine doses in commercial vehicles were repeatable and accurate although the bottles were inverted only three times, which may be the situation in every day life.

Sometimes there are recommendations issued to use extemporaneously prepared traditional Methylcellulose 1% suspension with Syrup NF in place of commercial Ora-Plus®/Ora-Sweet®. It was observed that the redispersion properties of Methylcellulose 1%/Syrup NF were significantly worse than those of Ora-Plus®/Ora-Sweet® (V, Tables 8 and 9). One explanation might be that the zeta potential of Methylcellulose 1%/Syrup NF was not optimized with excipients, such as electrolytes (Table 5). Here Methylcellulose 1% and Syrup NF were combined in the ratio 7:3 according to a traditional formula (Rappaport, 1983). According to USP, 1% to 2% methylcellulose dispersion can be mixed 1:1 with flavoured syrup to obtain a good suspension vehicle (The United States Pharmacopeial Convention, 2008). The quality of different ratios should be studied further. In addition, although compounded liquid formulations might be similar in terms of physicochemical properties, they might not be equivalent in vivo and thus not interchangeable (Salunke et al., 2011). Thus there is an evident need for standardised formulations and a universal suspending base.

With pharmacy-prepared Hypromellose 1% as the suspension vehicle, it was not possible to formulate an ideal nifedipine multidose suspension but it was possible to produce a unit-dose suspension that met the requirements of dose accuracy, stability, microbiological quality and safety (II, III, V). In order to increase the physical stability of a multidose suspension, product development in the future should include the optimization of zeta potential using the required excipients (Table 5). In the Kuopio University Hospital, these kinds of preservative-free unit-dose suspensions have been used successfully for many years and with many different medications. They have also been reported to be suitable for administering nimodipine 60 mg in unit-dose oral syringes for adult patients with acute subarachnoid haemorrhage (Soppi *et al*., 2007). As long as aseptic preparation methods were employed, microbial contamination would seem to be only of minor concern. Before administration, only a small amount of air needs to be drawn into the syringe to readily resuspend any settled particles. The suspensions that were compounded in this study flowed easily through the small-bore nasogastric feeding tube, and no tube occlusions occurred.

6.2 ORAL PAEDIATRIC NIFEDIPINE FORMULATIONS

6.2.1 Nifedipine

Licensed nifedipine products allow adults to benefit from once daily dosing, decreased risk of ADRs and formalised post-marketing surveillance (Standing and Tuleu, 2005). 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 ADRs because no sustained release formulation is available. For medicines that may need to be used more than twice daily, there is a recommendation that the suitability of administration for children in the outpatient setting should be evaluated (*European Medicines Agency EMA/CHMP/QWP/805880/2012 Rev. 2, 2013*). Extended release nifedipine is administered for children initially 0.25–0.5 mg/kg/d with the dose divided 1–2 times/d, and then titrated to the desired effect (max 3 mg/kg/d up to 120 mg/d) (Meyers and Siu, 2011). The usual

recommendation in hypertension is to administer a modified release preparation to avoid large fluctuations in blood pressure (Standing and Tuleu, 2005). There are much more data supporting the use of the immediate-release formulation of nifedipine in acute hypertension (Meyers and Siu, 2011).

In general, if one wishes to administer nifedipine orally to infants, one of the following methods has to be selected: 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 with special permission, or 4) preparation of extemporaneous suspensions, powders or capsules from crushed retard tablets or drug powder (Tuleu, Grange and Seurin, 2005; McCluskey and Brunn, 2011).

Unfortunately, different brands of nifedipine soft capsules contain different amounts of liquid and the volume of the content would need to be determined in order to make an accurate measurement (Rosen and Johnson, 1989; Tuleu, Grange and Seurin, 2005; McCluskey and Brunn, 2011). They contain polyethylene glycols as diluents and this might be harmful to infants. The required dose can be obtained for the use in infants by drawing the oily fluid from a 10 mg gelatin capsule into a syringe and administering the appropriate dose (Sahney, 2006; Seikaly, 2007). It is claimed that although short-acting nifedipine is a valuable drug for management of true hypertensive emergencies in children, it should be avoided in neonates because of the difficulty in accurately measuring the dose (Sahney, 2006).

It is known that splitting of tablets leads to significant fluctuations in the administered nifedipine dose (Tuleu, Grange and Seurin, 2005). Nearly all the individual masses of segmented Adalat® retard 10 mg tablets deviated by more than 10% from the average weight. The time for 50% of the nifedipine to be released from crushed tablets of Adalat® retard was 10 min, while for tablet halves it was 20 min and for whole tablets even longer, 25 min. The actual rate of dissolution in Adalat® retard tablets is controlled by the surface area of nifedipine crystals, but *in vitro* results have indicated that the tablets have only slightly extended release. Thus they may require three times daily dosing (BMJ Group, 2012). Real extended-release nifedipine tablets (such as Adalat® Oros 20 mg, Bayer on the market of Finland and Procardia© 30, 60 and 90 mg, Pfizer on USA) cannot be broken up as this would distrupt the drug delivery system (Sahney, 2006; Seikaly, 2007; Meyers and Siu, 2011; Finnish Medicines Agency, 2013).

In one published study, extemporaneous nifedipine 1 mg/ml suspension of a crushed Adalat® 10 mg retard –tablet and water produced doses ranging from 0.6 to 1 mg in the 1-ml syringes (Tuleu, Grange and Seurin, 2005). In unlicensed drops (Nifedipin-ratiopharm® Tropfen 20 mg/ml, Ratiopharm) nifedipine is dissolved in macrogol 200, which may have potential toxicity issues in children. In such a concentrated liquid, a small variation in volume can produce a large error in the delivered dose: five drops contained from 5.7 to 5.9 mg nifedipine instead of 5 mg.

Thus, extemporaneous suspensions, powders or capsules are the best option to produce nifedipine drug products for infants in hospitals. Although there has been progress in the treatment of paediatric hypertension, additional research is needed into the safety and efficacy of extemporaneous dosage formulations.

6.2.2 Excipients

The selection of the appropriate excipients for extemporaneous preparation is the responsibility of the pharmacist. It is clear the only essentials should be used in formulations intended for neonates. Solid drug formulations can mostly be composed using non-toxic excipients whereas toxicological risks are usually associated with excipients used in liquid formulations (Krause and Breitkreutz, 2008).

The amount of preservatives should be kept at minimum and hypertonic solutions should not be used. Adverse toxic effects have been reported in paediatric patients due to the use of inappropriate excipients both in extemporaneous and commercial products. The properties of

the excipients may have also an influence on the uniformity of content and on loss of drug substance during its dispensing. The amounts of all excipients in manufactured medicines should also be listed on the label so that practitioners can consider their potential safety e.g. for children (Nahata, 2009). The amount of polysorbate in Adalat® 10 mg retard is only 1 mg, and it is thus below the WHO acceptable daily intake (25 mg/kg) also in a portion of a tablet (Napi, 2013).

The ingredients in the present nifedipine oral powder and capsule studies were selected because of their flow properties and particle size distribution (I, IV). Both lactose and microcrystalline cellulose are widely used and safe excipients in solid oral pharmaceutical formulations. Due to intestinal immaturity, preterm infants have diminished levels of the lactase enzyme, which hydrolyses lactose, but it has been reported that expression of this enzyme can be induced by lactose ingestion (Guandalini *et al*., 2012). Symptoms of lactose intolerance rarely develop in children younger than 6 years. Lactose is also contraindicated in infants with galactosemia, a rare congenital disorder (Pawar and Kumar, 2002). There was some discussion in the 1970's about the persorption of microcrystalline cellulose after its per oral administration (Pahlke and Friedrich, 1974 and 1975; Seidemann, 1976).

The excipients to be used in the suspension formulation for neonates and infants have to be selected carefully (II, III, V). There are some recommendations and limits for use, and the dose-response relationship has to be considered. Commercial vehicles may contain excipients, which may cause concern. In the UK, the Food Advisory Committee has recommended that carrageenan should not be used as suspending agent in infant formulas (Rowe, et al., 2012). WHO has set an estimated total acceptable daily intake of 10 mg/kg for parabens and 2.5 mg/kg for saccharin sodium (Pawar and Kumar, 2002). Saccharin is approved for children over three years old (Pawar and Kumar, 2002; Costello, 2007; Rowe *et al*., 2012). Sodium benzoate can produce nonimmunological contact urticaria and non-immunological immediate contact reactions (Rowe *et al*., 2012). If one reviews these vehicles, then parabens is present in Suspension Diluent A®, Ora-Sweet®, Ora-Plus® and Ora Sweet SF®, and in addition, Ora-Sweet SF® contains saccharin and Ora-Plus® contains carrageenan (V). Sodium benzoate is used in SyrSpend SF® Cherry and in Methylcellulose 1%.

In addition, high osmolality vehicles are inadvisable for neonates and infants. Hypertonic solutions, over 400 mOsm/kg, may cause injury to the GI tract of neonates (Polo *et al*., 2007, de Villiers, 2009b). Ora-Sweet®, Ora-Sweet SF® and Methylcellulose 1%/Syrup NF are hyperosmolar vehicles: 3240 mOsm/kg, 2150 mOsm/kg and 1125 mOsm/kg, respectively (V). Instead, the osmolalities of Suspension Diluent A®, Ora-Plus®, SyrSpend SF® Cherry and Hypromellose 1% are low: 17 mOsm/kg, 230 mOsm/kg, <50 mOsm/kg and 8 mOsm/kg, respectively.

Preservative-free cellulose gels like hypromellose are believed to be safe and suitable for neonatal use and easy to administer through a nasogastric tube (III). Hypromellose E50 has also been used as a vehicle for hydrochlorothiazide 2 mg/ml suspensions at a concentration of 1.5% (Tötterman *et al*., 1994). Unfortunately customized amounts of hypromellose 50 mPa.s cannot be purchased nowadays and this will restrict its use in the future.

The pharmacist must consider the system's capability to resist microbial growth. It has been reported that Methylcellulose 1%/Syrup NF dilutions in ratios greater than 1:1 have failed the European Pharmacopoeia quality assurance criteria for efficacy of antimicrobial preservation (Ghulam *et al*., 2007). Sodium benzoate, which was used as preservative in this formulation, is effective only at pH 5.0 or lower, while the pH of the vehicle was 6.6 (de Villiers, 2009a).

6.3 UNIFORMITY OF DOSAGE UNITS

The uniformity of dosage units is a major factor if one wishes to assure the repeatability of dosages and thus, the dispensing of a safe and effective medication. Although uniformity testing is a requirement of European Pharmacopoeia and USP Pharmacists' Pharmacopeia, actual results can seldom be found in peer-reviewed journals. In addition, the test is not a pharmacopoeial requirement for multidose suspensions (European Directorate for the Quality of Medicines & Health Care, 2013).

6.3.1 Critical steps in compounding process

Hand crafted procedures are widely used in hospital and community pharmacies. Crushing of tablets is the critical point in the powder mass preparation. The importance of the crushing technique becomes emphasized in small size oral powders, where more variation in content can be observed. Manual tablet crushers are mostly used, and in fact, here electrical crushers were not found to be very practical. Commercial tablets have a specific content uniformity variation of their own, which may lead to some variation in the modified dosage forms.

The grinding time and technique can influence the resulting homogeneity of the powder mixture by affecting the electrostatic properties of the powder. Mixing the powder mass with a mortar and pestle may introduce a variable in the procedure. It also has to be noted that particles may become segregated if they need to be stored before dispensing. The particle size of the crushed nifedipine tablet, which was less than 100 μm, was about the same size as the excipients and in this way it was possible to prevent stratification between large and small particles (II).

6.3.2 Redispersion of suspension

A suspension should dispense drug particles uniformly after brief shaking of the bottle, so that the desired dose can be measured accurately (Nahata, 1999d). In practise, the compounding pharmacist does not have the possibilities of the industrial formulator to control flocculation with electrolytes, polymers and surfactants. Thus the best choice is to use polymers or protective colloids to increase the viscosity and to provide a mechanical barrier by coating the individual particles.

The significance of the zeta potential on the physical stability of a suspension is well-known (Sinko and Singh, 2011). It is apparent that crushing of tablets may produce charged particles. The desired zeta potential may be acvieved by the addition of excipients, such as electrolytes and/or buffering agents including sodium phosphate and sodium citrate as in Ora-Sweet®, Ora-Sweet SF®, Ora-Plus® or SyrSpend SF® Cherry (Table 5). Xanthan gum included in Suspension Diluent A®, as itself, is an anionic material (Rowe *et al.,* 2012). Wetting properties may be improved by surfactants such as those present in Ora-Plus® and SyrSpend SF® Cherry. Viscosity increasing agents were used in all of the suspension vehicles in the present study to retard the settling of dispersed particles.

After 1 week of storage at room temperature, the nifedipine multi-dose suspension prepared with Methylcellulose 1%/Syrup NF failed to provide more than 70% of its intended dose if it was shaken only three times (V, Table 9). Since the doses drawn from the bottle were similar and the standard deviation was small, the most likely explanation is that there had been cake formation in the suspension. The nifedipine-Hypromellose 1% suspension lost less than 30% of the dose in one-week storage and the doses were variable but this might be a consequence of the inadequate mixing (V, Table 10). The compact sediment at the bottom of the multi-dose container in nifedipine suspensions compounded with Methylcellulose 1%/Syrup NF or Hypromellose 1% required prolonged shaking before it could be reconstituted into a uniform suspension.

Suspensions should always be shaken well before use to ensure uniform distribution of the solid in the vehicle (The United States Pharmacopeial Convention, 2008). However the

command “Shake well before using“ may be understood in different ways in the pharmacy, on the ward and particularly at home. Many dosing errors may occur because patients do not observe handling intructions (Deicke and Süverkrüp, 2000). Pharmacopoeias require that suspensions should be redispersible but none of them provides specifications about how this can be verified experimentally. Thus, pharmacopoeial monographs on oral liquids should include a standardized procedure for testing the redispersibility of suspensions.

Mixing techniques of suspensions are important if one wishes to obtain the required amount of liquid. In published stability studies, suspensions are usually mixed very well and properly to achieve a good sample: for example shaken for about ten to 30 seconds or vortexed for 60 seconds or shaken on a wrist-action shaker for 10 minutes, then allowed to stand for 2 minutes and gently inverted three times (Nahata and Morosco, 2003a, 2003b and 2004; Nahata, Morosco and Brady, 2006; Trissel, Zhang and Koontz, 2006; Winiarski *et al*., 2007; Aliabadi *et al*., 2011). Proper mixing is important for homogenous samples but these tests do not reveal the possible mixing problems in daily life. Thus the results of these studies may not reflect the actual use of the suspension.

6.4 CHEMICAL STABILITY OF NIFEDIPINE

Compounded nifedipine powders, capsules and suspensions provided adequately stability for storage and use in hospitalised patients (I, III–V). Since the preparations were stable in the secondary package but unstable if not properly stored, it was necessary to label products clearly to prevent storage without secondary package. 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 (III). The analytical results of powder papers, capsules and unit-dose syringes tend to display greater variations because these are distinct dosage units rather than aliquots of drugs in solution (I–IV).

Nifedipine crystals are more stable than nifedipine solutions because the effect of light is a surface phenomenon (Thoma and Klimek, 1985b). Nifedipine solution in methanol underwent more than 10% photodegradation in approximately 5–10 minutes (Grundy, Kherani and Foster, 1994). On exposure to daylight in winter, 10% of nifedipine in solution was degraded in about 7 minutes and in summer 10% degradation only required about 1 minute (Thoma and Klimek, 1985a). The degradation of nifedipine in solutions occurs three-fold faster in normal daylight than under exposure to a 40 W light bulb (Thoma and Klimek, 1991a).

Tuleu, Grange and Seurin (2005) found that crushed nifedipine tablet in an extemporaneous water suspension (1 mg/ml) started to degrade after 15 min of exposure to light, and 7% had degraded in 30 min and 11% had disappeared within 60 min when stored on the bench not protected from light. Nahata, Morosco and Willhite (2002) investigated the stability of nifedipine in two oral suspensions and found them to be stable for up to three months in refrigerator and at room temperature if they were stored in amber plastic bottles. Nifedipine was taken from punctured liquid-filled capsule and vehicles were Methylcellulose 1%/Syrup NF (1:13) and Ora-Plus®/Ora-Sweet® (1:1). Both suspensions were shaken for 10 minutes before sampling.

Dentinger, Swenson and Anaizi (2003) found that extemporaneously prepared nifedipine 10 mg/ml oral solution packaged in amber glass bottles or amber oral syringes wrapped in aluminium foil retained more than 90% of the initial concentration for 35 and 14 days, respectively, at 22–25°C when exposed to fluorescent light. Instead, samples stored in amber syringes but not wrapped in foil had lost over 20% of the initial nifedipine concentration within 7 days. The nifedipine solution in that study was prepared from nifedipine powder with polyethylene glycol 400, glycerol, and peppermint oil. In a stability study of a nifedipine cardioplegic solution, it was noted that even when protected from light with a brown plastic

wrapper and refrigerated, nifedipine concentrations decreased to less than 90% of original potency within approximately six hours (Bottorff *et al*., 1984).

A decrease of 20% in nifedipine content has been observed to occur after 18 hours when a pulverized tablet in a sealed paper was stored under normal laboratory light, i.e. a mixture of daylight and fluorescent light (700 lux) (Ohkubo, Noroi and Sugawara, 1992). In another study there was more than 10% photodegradation of nifedipine in powder within 24 hours of artificial sunlight exposure (Grundy, Kherani and Foster, 1994). Solid nifedipine showed complete 100% photodecomposition within 6 hours when exposed to sunlight (Sadana and Ghogare, 1991). Gold-shaded fluorescent lighting (over 525 nm) appeared to prevent nifedipine degradation during compounding (McCluskey and Brunn, 2011). Thus, nifedipine must be protected from light very carefully during compounding and storage (Thoma and Klimek, 1991b).

7 Conclusions

According to these studies, the following conclusions can be drawn:

The individual needs of each child can be satisfied with age-appropriate nifedipine oral dosage forms. In these studies, nifedipine 1 mg/dose was compounded into capsules, powders or single-dose and multidose suspensions.

1. Capsules, whose contents are emptied prior to use, provide an alternative to oral powders for preparing paediatric oral solid medications. The content uniformities capsules and oral powders met the established requirements. However, the nifedipine amount was less than 80% of the theoretical value in oral powders of total weights either 100 mg or 50 mg.
2. Nifedipine oral powders were chemically stable for up to one year when stored at room temperature or in refrigerator as long as they were protected from light.
3. A 1.0% hypromellose solution displayed the best properties as a suspending agent for unit-dose suspensions. Steam sterilized preservative-free hypromellose 1.0% solutions were microbiologically satisfactory and could be kept at room temperature for at least 6 months.
4. Nifedipine unit-dose suspensions were chemically, physically and microbiologically stable throughout the 4-week study period when stored at room temperature or in a refrigerator protected from light. The content uniformity of the unit-dose suspensions met the established requirements.
5. When exposed to artificial daylight, nifedipine in either powder or suspension degraded rapidly at room temperature. Overall, 20–30% photodegradation of the nifedipine occurred within three hours.
6. Multi-dose suspensions compounded with Methylcellulose 1%/Syrup NF or Hypromellose 1% require mixing by inverting the bottle 10–15 times to comply with the content uniformity test. In contrast, the commercial suspension vehicles passed the test if the bottle was inverted only three times.

The art of compounding has a long tradition; however, there have been few scientific investigations into this area. These results offer practical tools for the assessment and resolving the daily challenges encountered in compounding of paediatric oral formulations in pharmacies.

In further studies it would be worthwhile to determine whether nifedipine doses under 1 mg fulfil the requirements of content uniformity. In addition, extemporaneous suspension vehicles should be further examined.

8 References

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Compounding of Paediatric Oral Formulations

Extemporaneous Nifedipine Capsules, Powders and Suspensions in the Hospital Pharmacy

Compounding has remained an integral part of hospital pharmacy practice since the lack of appropriate manufactured paediatric formulations is a worldwide problem. This study investigated the pharmaceutical quality of different extemporaneous oral formulations for paediatric use from preterm newborns to children. The question to be answered is whether nifedipine preparations dispensed as hard gelatin capsules, oral powders or as unit-dose or multi-dose suspensions are sufficiently uniform and stable?

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