Abstracts For Oral Presentations

Individual dosing and controlled drug delivery with matrix-minitablets for paediatric use
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Objective
High dose mini-matrix tablets of drugs with different physicochemical properties were investigated as drug delivery technology offering flexible release patterns and an easy and reliable dosing to small infants.

Methods
Matrix-minitablets were prepared by either direct compression or wet granulation with an insoluble polymeric matrix former followed by compression of the granules. Disintegrating minitablets were formulated by adding a superdisintegrant into the granule-mixture prior to compression.

Results
Drug release from matrix-minitablets occurs as a function of their aqueous solubility. Formulation parameters such as matrix size (100 μm – 4mm) and drug loading (>70%) were varied in order to counter-act the drug solubility effect on release. An increasing matrix size decreased, and an increasing drug loading increased the release rate, which facilitated flexible release patterns for all drugs. The type of the release retarding polymer and the preparation method also affected the drug release by influencing mainly the porosity of the final matrices. Drug/Kollidon SR blends showed a superior compressibility, which was a limiting factor for Carbamazepine, in case of direct compression. The best retardation, however, was obtained with tablets prepared by wet granulation using ethyl cellulose as polymer.

Conclusion
Employing the above mentioned parameters controlled drug delivery over 8 - 24 h is achievable for drugs with a solubility of ≤ 0.1 mg/ml – 100 mg/ml. An individually adjusted dose ranging from several up to 1000 mg can be administered without difficulties.

Bitterness comparison of original and generic products using ASTREE Electronic Tongue
Aranyos, Attila, Tokuyama Emi, Matsunaga Chiharu, Irie Tetsumi
Alpha MOS, Toulouse, France

Objective
The objective of this study was to investigate the optimal selection and concentration of excipients in order to achieve the best masking of an Active Principle (API).

Method
Various active formulations and their corresponding placebos (same formulations without the API) were analyzed using the ASTREE Electronic Tongue. E-tongue sensors are organic polymer coated semiconductors that respond to taste-baring ingredients in solutions.

Results
To evaluate the efficiency of the bitterness masking, the taste distance between each formulation and the corresponding placebo was calculated (Euclidian distance measured y E-Tongue). The shortest the distance, the better the masking. In the initial phase 6 sweeteners were screened to find the best candidates. ½ Factorial design was perfectly adopted to assess first and second order effects of the sweeteners. Two sweeteners, aspartame and glucose were having the best effect and the second order effect (combination) was also positive. Citrus and berry flavors were examined. With the help of an ANOVA test we could conclude that berry had a significantly better masking than citrus. In the final experimental phase the three lead ingredients concentrations were optimized simultaneously using a Full Central Composite Model (Alpha=1.63) with optimum reached with 0.08mg/ml aspartame, 20mg/ml glucose and 10mg/ml blueberry aroma.

Conclusion
An important number of candidate formulations were investigated using DOE and in-vitro taste measurements. The structured DOE approach allows to efficiently screen and optimize formulations while with the in-vitro assessment much of the complexities and time required for a human taste trial can be eliminated.
Pilot database addressing safety and toxicity aspects of excipients for paediatric medicines development
Salunke Smita, Dr. Catherine Tuleu
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Background: Commonly used excipients have been associated with elevated toxicological risks and safety issues in children. However, information is limited and it is often difficult to encompass available information in various published sources. In collaboration, the Eu and US Paediatric Formulation Initiatives are creating a searchable evidence-based database of pharmaceutical excipients addressing safety issues and toxicity aspects. The database will be publicly available online and ultimately will highlight gaps in excipient knowledge.

Aim of this present work was 1) To evaluate with various potential users and stakeholders the need for such database and 2) To design and demonstrate the feasibility of creating a pilot database.

Methods: To assess the need of the database, a survey was developed and administered widely. The overall database development entailed 1) identification and evaluation of the information sources, 2) methodological development and validation of search strategy/techniques for manual retrieval 3) Evaluation of relevance, validity, reliability of the data retrieved, 4) Abstraction and population of the data in the pilot database.

Results: The survey mainly informed on what type of relevant information were required by potential users and most difficult to obtain/not available from existing sources. Then the prototype database with propylene glycol as a model excipient was developed based on the user’s need as per the survey.

Conclusion: Successful completion of the pilot has led to an ongoing project to develop and expand the system towards a comprehensive source of computerized information concerning the toxicity and safety of the excipients for paediatric medicine.

Assessment of quality and clinical performance of unlicensed liquid captopril formulations used in the treatment of children with heart failure
Mulla, Hussain et al.
University Hospitals of Leicester, United Kingdom

Objectives. To assess from a quality and clinical perspective, two commonly used unlicensed liquid captopril formulations.

Design & Method. An oral imported solution (Bristol Myers Squibb) and an oral special suspension (Nova Labs Ltd) were characterized and their physicochemical and microbial stability studied during simulated “in use” conditions (6 weeks) and under recommended storage conditions (6 months). An open label, single dose, six-treatment, three-period, crossover trial in healthy adults investigated the bioequivalence of the 2 unlicensed liquid formulations relative to a licensed reference tablet.

Results. Both liquid formulations differed in pH, colour, opacity, osmolarity, viscosity, taste and smell. However stability and dose uniformity were good. Both test formulations failed bioequivalence with respect to Cmax and AUC (CHMP guidelines) as shown in Table 1 and Figure 1.

<table>
<thead>
<tr>
<th>Formulation Comparison</th>
<th>Cmax</th>
<th>AUC0-t</th>
<th>AUC0-∞</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution vs Tablet</td>
<td>0.73 (0.46 - 1.17)</td>
<td>0.79 (0.53 - 1.17)</td>
<td>0.82 (0.55 - 1.22)</td>
</tr>
<tr>
<td>Suspension vs Tablet</td>
<td>0.80 (0.50 - 1.29)</td>
<td>0.87 (0.58 - 1.31)</td>
<td>0.94 (0.63 - 1.42)</td>
</tr>
<tr>
<td>Solution vs Suspension</td>
<td>0.91 (0.56 - 1.46)</td>
<td>0.90 (0.60 - 1.35)</td>
<td>0.87 (0.58 - 1.30)</td>
</tr>
</tbody>
</table>

Figure 1: Mean Plasma Captopril Concentration Time Profiles for Test and Reference Formulations

Conclusions: The in vitro investigations revealed that the unlicensed liquid formulations were pharmaceutically acceptable, however they were not equivalent in vivo. Thus, healthcare professionals should not assume that unlicensed formulations designed for use in children are bioequivalent to a licensed formulation or to each other.
Paediatric doses from effervescent formulation delivered by the solid dosage pen
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Heinrich-Heine-University, Düsseldorf, Germany

Objectives: The aim of this study was to develop a paediatric effervescent formulation which can be individually dosed by a recently developed device. Different doses should be achieved by cutting off slices with different heights from cylindrical rods, which can directly be dissolved in water.

Design and Methods: A powder mixture of sodium hydrogen carbonate (Empprove, Merck, Darmstadt), mannitol (Pearlitol 160C, Roquette, Lestrem), tartaric acid (Caelo, Hilden), and 20% metoprolol tartrate (Microsin, Bucharest) was wet-extruded by a co-rotating twin-screw extruder (Mikro 27GL-28D, Leistritz, Nuremberg) using ethanol (96%) as liquid binder. Extrudates were dried during 60°C for 30 minutes. Drug concentration was determined by a UV-spectrometer Lambda 25 (Perkin Elmer, Rodgau-Juedesheim).

Results: Straight extrudates (length 5 cm, diameter 3 mm) could be achieved. To prove applicability the extrudates were placed in the device and different doses were adjusted using a screw and feed rate mechanism. Slices of different diameters were cut off using the cutting module (fig 1.). The slices were dissolved in 100 ml water to simulate a realistic use. Uniformity of mass variation and content according to Ph.Eur. specific 2.9.40 could be shown with acceptance values of 6.9 to 10.8.

Conclusion: A novel paediatric effervescent dosage form could be extruded which could be accurately dosed by using the Solid Dosage Pen. Thus, the new system offers the opportunity of individually dosed, quickly prepared solutions.

Fig. 1: Device

Paediatric formulations- Information needs of developing countries
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Pharminfotech Consultancy, Dunedin, New Zealand

Objective
To identify the information needs of developing countries with respect to pediatric formulations and pediatric drug administration.

Method
A database of pediatric formulations was made available on CD in April 2000. In 2006 the database was made available free of charge on a web site www.pharminfotech.co.nz
A free advisory service was associated with the database and information requests were invited by fax and email. Data on the questions and responses were collected for the period April 2001 to November 2009. The requests were categorised according to the specific medicine, class of medicine, availability of a medicine, general formulation questions (e.g. use of bases and preservatives), medicine administration issues, therapeutic category and miscellaneous.

Results
A total of 475 information request were received.
- About 70% of requests were for information on formulating a specific drug, most of which are commercially available in other markets
- Antibiotics, anti-TB, cardiovascular and antiretrovirals were the most frequently requested drug classes
- Quinine, prednisone and rifampin were the most frequently requested specific drugs
- About 20% of requests were for fundamental issues such as choice of suspending base or preservative
- Many information requests indicated severe supply problems (e.g digoxin, furosemide NSAID preparations)
- A significant number of requests indicated knowledge gaps by practitioners. For example, there appeared to be poor knowledge about alternatives to extemporaneous preparation of oral liquids.

Conclusions
The pattern of requests from developing countries indicates the need for:
1. Wider availability of pediatric formulations that are already commercially available
2. Access to standardized formulas using simple ingredients for preparations that are not commercially available
3. Educational strategies to promote the use of rational and effective alternatives to extemporaneous formulations.

Rational development of a taste masked paediatric formulation guided by electronic tongues
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Heinrich-Heine-University, Duesseldorf, Germany

Objective
The aim was to evaluate the taste masking efficiency of different cyclodextrins for bitter tasting quinine hydrochloride. The best formulation should be chosen via
electronic tongue measurements and improved by adding secondary taste masking agents.

**Design & Methods**

For formulation development quinine hydrochloride [QH], fructose, sodium saccharin, sucrose (Caelo), α-cyclodextrin, γ-cyclodextrin (ISP), β-cyclodextrin, hydroxypropyl-β-cyclodextrin, maltodextrin, glucose, mannitol (Roquette), sulfobutylether-β-cyclodextrin (CyDex Pharmaceuticals Inc.), sucralose (Tate & Lyle Sucralose, Inc.), and acesulfame potassium (Nutrinova) were used. Complexes were characterized by the taste sensing system TS-5000Z (Insent, Japan) and the α-ASTREE2 etongue (AlphaMOS, France).

**Results**

Both taste sensing systems detected the sulfobutylether-β-cyclodextrin (Captisol®) to have the best masking capacity for QH. Principal component analysis (PCA) showed that all formulations except the Captisol® formulation are located close to bitter tasting QH on the right side, meaning that they did not have an influence on the taste properties of QH (Fig. 1). This complies with results of human taste tests from literature. Sweeteners alone had no effect on the bitterness of quinine, but the addition of saccharin and acesulfame to the Captisol® formulation led to further improvement.

**Conclusion**

A liquid quinine hydrochloride formulation with improved taste properties was developed by guidance of electronic tongues. The possibility to investigate multi-component mixtures and to reduce human taste tests makes those systems a promising tool for rational formulation development for the paediatric population.

**ODT-Formulations: Fast dissolution not always allows fast disintegration**

**Ohrem Leonhard, Moddelmog Günther, Ognibene Roberto**

**Merck KGaA, Darmstadt, Germany**

Oral dispersible tablets (ODT) are currently of high interest due to the well recognized advantages of this new kind of formulation. The inherent definition of an ODT formulation asks for fast disintegration. But does this also lead to fast dissolution of the active?

**Methods:**

Tablets(11 mm flat faceted) were produced by direct compression using 5 different ODT Excipient systems and ibuprofene as API using an instrumented single punch press to a hardness of 75 ± 12N. Disintegration and in vitro dissolution were evaluated using the related USP methods. API dissolution was monitored inline by UV absorbance. The ODT excipients were characterized by their morphology (SEM), specific surface area and pore volume (BET).

**Results**

The disintegration and dissolution vary significantly even at similar tablet strength. One excipient showed a disintegration time of 35 s, a dissolution of 2 min (90% API), having a surface area of 3.5 m²/g and a porosity of 0.024cm³/g. Another excipient showed a disintegration of 98 s and dissolution of >> 90 min. Its much smaller surface of 0.3 m²/g and porosity of 0.0008 cm²/g give hint to explain the extended dissolution behaviour of all compared excipients.

**Conclusion**

The release profile does not necessarily follow the fast disintegration requirement for ODT formulations. This was explained with different surface areas and porosities of the excipients. Also retarding effects of polymers or swelling components contribute. Hence, care shall be taken in selection of an ODT excipient system regarding tablet strength and dissolution profile in addition to disintegration time.

**An investigation of drug manipulation for dose accuracy in paediatric practice**

**Richey, Roberta**

**Alder Hey Children’s NHS Foundation Trust, Liverpool, United Kingdom**

**Objective:** The use of unlicensed and off-label drugs for administration to children and neonates is well established and this necessitates the manipulation of some drugs with...
the purpose of achieving dose accuracy. This study aims to establish the nature and frequency of current clinical practice with regard to the manipulation of drugs for dose accuracy at the point of administration.

**Design and methods:** Two main methodologies will be used. A systematic review will be undertaken using a broad mapping review approach to identify and assess all the available evidence. Identification of drug manipulations and direct observation of the clinical practices in secondary care will be completed in all inpatient clinical areas in a large regional paediatric hospital, a district general hospital and a large regional neonatal unit.

**Results:** The systematic review has identified that there is a paucity of evidence on drug manipulation for tablets and a lack of any evidence for other dosage forms, the development of the systematic review and results will be presented. Initial results from direct observation will also be presented, these have identified that there is a wide range of drugs and dosage forms being manipulated and that the methods of manipulation are not consistent across different wards or hospitals.

**Conclusions:** The manipulation of drugs for dose accuracy is widespread practice in paediatric secondary care. However there is neither good evidence nor clear guidance for practitioners to support this practice.

**Transdermal iontophoresis: An opportunity in paediatric drug delivery?**

*Djabri, Asma et al.*

*University of Bath, Bath, United Kingdom*

Iontophoretic transdermal drug delivery is non-invasive, avoids variability associated with first-pass effect and oral absorption and provides individualized drug input via manipulation of the electrical current applied. This project investigated iontophoresis as a delivery option for ranitidine, phenobarbital and midazolam in children.

The *in vitro* iontophoresis of ranitidine, phenobarbital and midazolam investigated the effects of the pH of the vehicle, intensity of current and drug concentration on the iontophoretic flux across intact pig skin. Another series of experiments used tape-stripped skin to model the less resistant skin of premature babies.

Iontophoretic delivery of all drugs was more efficient than passive diffusion and optimized by increasing current intensity and by maximising the mole fraction of the drug in the driving electrode formulation. Cathodal delivery of phenobarbital was superior compared to anodal transport. The passive fluxes of midazolam and phenobarbital increased significantly when the barrier was compromised. Iontophoresis controlled midazolam and phenobarbital transport across intact or partially compromised skin but was undermined by the very high passive contribution when delivery took place through the fully compromised barrier.

In conclusion, iontophoresis can deliver therapeutically meaningful fluxes of ranitidine, phenobarbital and midazolam with acceptable patch areas. Iontophoresis controlled phenobarbital and midazolam input through intact and partially compromised skin, but further refinements of the technique will be required to control delivery of these two drugs through highly compromised skin.

**The European Paediatric Regulation – Is It Making A Difference? Experience From The UK**

*Branch, Sarah*

*MHRA, London, UK*

The Paediatric Regulation came into force in January 2007 and the objective of this presentation is to assess its impact on the authorisation of medicines suitable for children in the UK.

This study analyses the evolution of paediatric investigation plans (PIPs) into marketing authorisations for products intended for children. It also assesses the impact of the European initiative for the assessment of paediatric studies not submitted previously.

Up to July 2010, nearly 700 applications for PIPs had been submitted in Europe: 72% of applications have been for new medicines, an increasing proportion, 25% for existing products and only 3% for off-patent drugs intended for a new paediatric use. The Paediatric Committee has delivered 20 opinions on compliance with an agreed PIP – a reflection of the progress companies have made with completion of studies. So far in the UK this has resulted in six licence applications with associated PIPs leading to new information on paediatric use or new formulations suitable for children.

Considering the outcome of published assessments for older studies up to July 2010 (26 procedures): two have led to new paediatric populations for existing indications; one to a new indication; two products have had safety data added while seven have had other new information or clarifications included. Paediatric study data has been added to five products while there were no changes recommended for the remainder.

In conclusion, although initial progress may appear slow, tracking the movement of products through the regulatory process from PIP submission to granting of an
authorisation shows that we can expect an increasing number of products in the future specifically designed for the treatment of children.

**Paediatric oral solid dosage form preferences: A quantitative analysis among children and their parents**

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McNeil Consumer Healthcare, Ft. Washington, PA, USA

Historically, the majority of oral pediatric dosage forms have been hard, chewable tablets that leave residual particles in the mouth and teeth, features that children find unpleasant. Personal interviews with over 100 children suggest that softer chewy textures are preferred to harder, crunchier OTC medicine forms. The purpose of this study was to identify some soft textured oral dosage forms that are most aesthetically pleasing to children, while simultaneously, being perceived acceptable by parents. Thirty-one children (ages 6-11) and 30 parents were asked to evaluate 7 soft and chewy prototypes for a child's form of a chewable pain medication. Parents were shown drawings of the concept and asked to evaluate them in terms of appropriateness for their children. The children also evaluated the same drawings, and were provided placebo prototype to taste along with the drawings. Results indicated that a) soft and chewy dosage forms generate high appeal by both parents and children, b) children and parents may differ in what they perceive as appropriate and acceptable, with forms appearing too “candy-like” being rated lowest by parents and highest by children. These results suggest that softer textured medications are an improvement in pediatric medications, possibly improving compliance. However, manufacturers must insure that any new form addresses the safety concerns of parents. This can be accomplished through child-resistant packaging and reducing the “candy-like” appearance of the form.
A systematic review of the available scientific literature was performed to evaluate the use and safety of benzoic acid and sodium benzoate as antimicrobial preservative in oral pediatric formulations which are commercially available in the US, UK and Germany.

Information of more than 142 oral formulations for neonates and infants indicates that benzoic acid and sodium benzoate are the most frequently used antimicrobial preservatives in pediatric formulations. Besides their use as antimicrobial preservative in pharmaceutical products, benzoic acid and sodium benzoate are also employed as food additive, and for the treatment of patients with hyperammonaemia. Clinical data indicate that at high doses gasping syndrome can be observed in premature neonates but that low doses up to 5 mg/kg/day benzoic acid and 5.9 mg/kg/day sodium benzoate are safe for daily use in oral pediatric formulations.

The concentration of benzoic acid and sodium benzoate which is appropriate for a specific oral pediatric formulation is defined by the minimal concentration needed to comply with the requirements of the antimicrobial efficacy test defined in the European and US pharmacopoeia. Further they should not exceed the acceptable daily intake of 5 mg/kg/day benzoic acid and 5.9 mg/kg/day sodium benzoate, respectively.

**Ludiflash® as Excipient for Pediatric Use**

P. Hebestreit, F. Osswald, R. Widmaier, M.G. Herting

**BASF SE**

Ludiflash® is a formulation for fast-disintegrating solid oral dosage forms. The formulation of co-processed ingredients consists of three compendial excipients: Dmannitol, crospovidone (Kollidon® CL SF) and polymer dispersion based on polyvinyl acetate (Kollidac® SR 30D). It is designed to disintegrate on the tongue within a few seconds, giving a pleasant mouthfeel. Ludiflash® is suitable for direct compression manufacturing by simply blending the excipient with the active ingredient and a lubricant; it is thus a very cost-efficient production method.

Many drugs are currently not available in formulations suitable for administration to pediatric patients. However, Ludiflash®, formulated as orally disintegrating mini-tablets (ODMT), is especially suitable for pediatric use and may be considered an innovative technology platform for pediatric formulations. With Ludiflash, such ODMT can be obtained in sizes as low as 1 mm diameter. Disintegration of such small ODMT can be complete within a second or less than 10 seconds, depending on size and formulation. Considering the recent development and current regulations on pediatrics, BASF decided to support its customers by creating a special safety report for Ludiflash® which is available on the company’s URL: [http://www.pharma-ingredients.basf.com/ludiflash/default.aspx](http://www.pharma-ingredients.basf.com/ludiflash/default.aspx) In summary, the safety report reveals that there are no hindrances stemming from toxicological studies or clinical experiences with Ludiflash® to revent use of the excipient in pediatric patients.

**Comparison of Different Polymers for Fast Dissolving Oral Films**

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**Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf**

**Objectives:**
Paediatric patients have difficulties in swallowing or chewing solid dosage forms. Fast dissolving oral films are intended to disintegrate or dissolve within seconds. They offer advantages such as administration without water, ease of swallowing, rapid onset of action and convenience of dosing. For fast dissolving active pharmaceutical ingredients absorption through the oral mucosa is possible and may improve bioavailability. Cellulose derivatives like hydroxypropyl methylcellulose (HPMC) are commonly used as film formers for fast dissolving oral films. Kollicoat® IR, a polyvinyl alcoholpolyethylene glycol graft copolymer, was mentioned as film former as well. Kollicoat® protect (both: BASF SE, Ludwigshafen, Germany) is a new coating system based on Kollicoat® IR and polyvinyl alcohol. Aim of this study was to investigate the suitability of the three polymers for fast dissolving oral films and to compare the received films.

**Design and Methods:**
Drug-free films were manufactured via solvent casting method. The obtained films were analysed regarding their morphological properties, thickness, tensile strength and disintegration time.
Results:
Casting of all polymer solutions was possible. The received films obtained a thickness between 50 and 100 μm and were free from air bubbles. Especially the Kollicoat® protect films were easy to manufacture and had an appealing appearance. None of the films was bridie or sticky. All films disintegrated within 1 min and were of adequate taste.

Conclusion:
All film formers are suitable for fast dissolving films. Especially the new Kollicoat® protect may be a good alternative to the commonly used HPMC.

ODMT- A new concept for paediatric dosage forms
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Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf

Objectives: The aim of this study was to prove the suitability of ready-to-use excipients for preparation of child-appropriate orally disintegrating mini-tablets (ODMTs), a new opportunity in paediatrics (fig.1).

Design and Methods: Ludiflash® (BASF, D-Ludwigshafen), Parteck® ODT (Merck, DDarmstadt), Pearlitol® Flash (Roquette, F-Lestrem), Pharmaburst® 500 (SPI Pharma, USA-New Castle, DE), Prosolv® ODT and sodium stearyl fumarate (Pruv®, JRS Pharma, D-Rosenberg). Hydrochlorothiazide (Unichem, IND-Mumbai) served as model drug. 2-mm mini-tablets were direct pressed on the rotary tablet press Pressima (IMA Kilian, DKöln) by using one 19-tip mini-tableting tool (Ritter, D-Stapelfeld). Compression forces between 3 kN and 10 kN were used. Flow properties of the excipients and crushing strength of the ODMTs, as well as the simulated wetting test (SWT)- time, were investigated.

Results: The excipients showed a Carr’s Index between 17.0 and 25.3, which means a reasonable flowability. The crushing strength of the ODMTs ranged between 1.17 N and 17.6 N, depending on the compactability of the excipient. Furthermore, the ODMTs showed SWT- times between only 1.93 s up to 25.17 s. With several excipients, ODMTs with an excellent SWT- time of less than 5 s and a sufficient crushing strength above 10 N could be achieved.

Conclusion: Orally disintegrating mini-tablets are supposed to be very useful formulations for the treatment of young children and may be considered as a new technology platform for paediatrics.

Figure 1: ODMTs

TOPIC: Taste Masking and Taste testing
Optimization of Active Principle Bitterness Masking Using an Experimental Plan and an Electronic Tongue
Aranyos Attila, Buthmann Arne
α-Alpha MOS, Toulouse, France
β-Valeon

Objective
The objective of this study was to investigate the optimal selection and concentration of excipients in order to achieve the best masking of an Active Principle (API).

Method
Various active formulations and their corresponding placebos (same formulations without the API) were analyzed using the ASTREE Electronic Tongue. E-tongue sensors are organic polymer coated semiconductors that respond to taste-baring ingredients in solutions.

Results
To evaluate the efficiency of the bitterness masking, the taste distance between each formulation and the corresponding placebo was calculated (Euclidian distance measured y E-Tongue). The shortest the distance, the better the masking. In the initial phase 6 sweeteners were screened to find the best candidates. ½ Factorial design was perfectly adopted to assess first and second order effects of the sweeteners. Two sweeteners, aspartame and glucose were having the best effect and the second order effect (combination) was also positive. Citrus and berry flavors were examined. With the help of an ANOVA test we could conclude that berry had a significantly better masking than citrus. In the final experimental phase the three lead ingredients concentrations were optimized simultaneously using a Full Central Composite Model (Alpha=1.63) with optimum reached with 0.08mg/ml aspartame, 20mg/ml glucose and 10mg/ml blueberry aroma.

Conclusion
An important number of candidate formulations were investigated using DOE and in-vitro taste measurements. The structured DOE approach allows to efficiently screen and optimize formulations while with the in-vitro assessment much of the complexities and time required for a human taste trial can be eliminated.

Use of in vitro taste assessment to select the best-tasting food matrix for pediatric drug administration in clinical trials
Aranyos Attila, Ayouni Fatma
Alpha MOS, Toulouse, France

Objective
The objective of this study was to investigate various food vehicles that would be suitable for masking the bad taste of a pediatric drug, and to select the product that achieve the best masking for clinical trials.

Formulating Better Medicines for Children
Assessment of the use of FLAVORx® flavoring in select liquid antibiotics dispensed in the United States

Lavallee, Danielle
FLAVORx INC

Objective: The palatability of liquid formulations is often cited as a barrier to adherence in pediatric medicine. The objective of this study was to determine the extent to which enhancing palatability by adding FLAVORx® flavors to liquid medicine varies among commercially available antibiotics.

Design & Methods: This retrospective database review determined the ratio of specific liquid antibiotic formulations that had FLAVORx® flavoring added by outpatient retail pharmacies in the United States. Dispensing data from January 1, 2010 through April 30, 2010 for amoxicillin, amoxicillin/clavulanate potassium, azithromycin, cefuroxime, cefdinir, cephalexin, clindamycin, clarithromycin, and sulfamethoxazole-trimethoprim was obtained from a national pharmacy chain and matched to data from the FLAVORx® online database utilized by pharmacists when flavoring liquid medicine. The ratio of medications with flavored added was determined by dividing the total quantity of the medication dispensed by the frequency of the medicine-specific flavoring in the database. Flavors frequently utilized are also reported.

Results: FLAVORx® flavorings are added to some medications more frequently than others. Clindamycin, cefdinir, and cefuroxime were flavored most frequently (ratio = 0.05, 0.029, 0.021 respectively). In contrast, sulfamethoxazole-trimethoprim, amoxicillin and azithromycin were flavored most infrequently (ratio = 0.002, 0.001, 0.001 respectively). Bubblegum, grape and watermelon were the most common flavors utilized.

Conclusion: This study is the first to present data quantifying the extent to which flavors are utilized to improve taste. Certain medications appear to generate a demand for altering the taste. Further research is needed to determine the extent to which altering taste impacts medication adherence.

The ability of an electronic tongue to detect pediatric drugs mixed with coating

Polymers
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Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University, Düsseldorf

Objectives
To investigate the ability of an electronic tongue to detect quinine-HCl or ibuprofen in binary mixtures with various coating polymers.

Design & Methods
Taste properties of different coating polymers and coating mixtures (Kollicoat Protect, Lycoat 720, Pharmacoat 606, Eudragit EPO, Opadry tm, Lustre Clear 103) solved in phosphate buffer were analyzed using an electronic tongue (Insert TS5000Z). Furthermore, solution samples of binary mixtures of quinine-HCl or ibuprofen with the tested polymers were measured.

Results
Based on the taste properties obtained by the electronic tongue, most samples with coating polymers did not differ from the pure buffer solution. Merely Eudragit EPO influenced the taste properties (Fig.1).
Irrespective of most present coating polymers, quinine-HCl and ibuprofen can still be successfully detected by the taste sensing system. However, mixtures of Eudragit EPO and ibuprofen exhibited different taste properties which depended on the drug / polymer ratio. This effect might be caused by an interaction between the amino groups of Eudragit EPO and the carboxylic group of ibuprofen.

Fig.1: PCA map of coating polymers in buffer and binary mixtures with ibuprofen

Conclusions
The electronic tongue is able to quantify quinine-HCl and ibuprofen successfully in mixtures with various coating polymers. Only binary mixtures containing ibuprofen and Eudragit EPO exhibited different taste properties, which depended on the analyzed drug / polymer ratio.

This project (no. 15980) is financially supported by AiF which is gratefully acknowledged.
extemporaneous compounding especially with divided powders. Besides divided powders, we use also solutions, drops, enema and suppository for management of children.

**Design and methods:** Data on the past 3 years’ made-up divided powders as well as the top 10 ingredients were collected. Our practice to serve our clinics with paediatric formulations is shown.

**Results:** We prepare medicines for the Department of Paediatrics and Neonatology Ward. They have altogether 150 beds. Last year we compounded more than 100 000 (in 2007: 72 000, in 2008: 92 000) doses of divided powders treating children, neonates and prematures. The top 10 active ingredients are: furosemide, hydrochlorothiazide, aminophylline, captopril, potassium chloride, folic acid, lamotrigine, sodium chloride, caffeine, ursodeoxycholic acid.

**Conclusions:** Increasing numbers of required divided powders suggest that they feel it necessary to make up paediatric doses as far as possible. Divided powders are one of the possibilities to treat children with a safe and accurate dose of drugs. Pharmacist’s education is very important and if necessary, towards compounding pharmacy.

**Stability of oral suspensions with propranolol or theophylline compounded from tablets**

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**Objectives:** In Polish pharmacies capsules with powders prepared from tablets present the only approach practiced when oral paediatric formulations are unavailable. Since compounded oral suspensions are practically unknown, the aim of this study was to evaluate stability of oral suspensions with theophylline (T) and propranolol (P) compounded from tablets available on Polish market. The effect of different suspending media was investigated.

**Design and methods:** Suspensions with P (2 and 5 mg/ml) were prepared using Propranolol WZF 40 mg tablets (Polfa Warszawa) and Theovent 100 mg tablets (GliaxoSmithKline Pharmaceuticals) were used for suspensions with T (2-50 mg/ml). The following suspending media were studied: M1 - ORA-Sweet® (Paddock Laboratories), M2 – modified medium M2, M3 – simple syrup with glycerol and sorbitol, M4 – 2% methylcellulose solution. The suspensions were stored at 25°C and 4°C up to 35 days and visual and microscopic observations, pH and viscosity measurements as well as analysis of active substance content (HPLC or UV spectrophotometry) were performed.

**Results:** Fast crystallization of T in all media was observed when concentration of the drug was higher than 2 mg/ml. Neither pH change nor employing drug substance per se allowed for dissolving T at higher concentrations. The process of crystallization was inhibited but not eliminated in M4. Stability of P in all media was satisfying, however increase in viscosity of suspensions upon storage was observed.

**Conclusions:** Tablets with P did not present problems when used for compounded oral suspensions and recommended by USP 14 days stability can be easily achieved, since increase in viscosity does not present an application problem. The problem of fast crystallization of T remained unsolved and suspensions with an appropriate concentration of T were not prepared.

**Unlicensed drug use on german paediatric wards – identifying the present needs for Age appropriate formulations**

Hermes, Martin Barnscheid, Lutz Garsuch, Verena Schoetttler, Petra Dominguez Finke, Jessica, Breitkreutz Jörg

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**Objective**

The aim of our study was to determine the extent of unlicensed drug use on paediatric wards in Germany and to identify first progress three years after the EU-regulation 1901/2006 came into effect in January 2007.

**Design & Methods**

In 40 German hospital pharmacies all prescriptions of compounded drugs for paediatric patients were collected in 2006 and evaluated over a period of six months shortly before the enforcement of the EU-regulation. We checked the results against the “Priority-list” and the lists of “Paediatric needs” published by the EMA. For frequently prescribed active substances, we determined actual license status and analysed future trends using the EMA decisions on paediatric investigation plans published to date.

**Results**

More than 4,800 prescriptions were analysed. We found a huge demand for age appropriate formulations of common, off-patent drug substances. Referred to the most frequently prescribed cardiovascular drugs, this applies to 80 %. On 8 % (26) of the 317 active substances listed by the EMA, decisions on submitted PIPs are published. Off-patent medicines present only 3 % of all PIP applications. Compounds ranked at high positions have not been addressed by recent PIP-decisions.
Conclusions
Three years after the EU-regulation has come into force, only few applications for off-patent substances are under way to a license referred to all paediatric subsets. The development of new, age appropriate off-patent drugs still needs more incentives to bridge the today’s gap of paediatric medicines.

Extemporaneous Preparation of Paediatric Medicines: The Opinions of School Children
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Objectives: Children are increasingly acknowledged to have rights in the determination of the decisions that affect them [1]. There is a lack of information relating to children’s views about medicines [2]. Adults make the assumption that they can ‘guess’ the views of children because they were once children themselves [3]. The objective is to determine the views of children on the role of the Pharmacist extemporaneously preparing paediatric medicines.

Design and Methods: Children aged 8-14years (n=103) participated in fourteen focus groups within schools in Northern Ireland. A detailed guide was used to ensure that all focus groups are undertaken in a uniform manner. Discussions were audio-recorded and transcribed, prior to content analysis.

Results: Children as young as eight years were aware of the importance of the role of Pharmacists carrying out extemporaneous dispensing in order to make medicines available to sick children. The majority of children agreed that liquid formulations were most suitable for paediatric populations and believed Pharmacists had an important role in ‘making’ a medicine that the child would take. They agreed that taste, texture and appearance of medicines were important factors influencing whether or not a child would take a medicine. They recognised the Pharmacist as being an ‘expert’ in medicine and have the expertise to make such formulations.

Conclusions: This research is providing evidence that children years old are able to understand the role of the Pharmacist in preparing medicines extemporaneously for sick children and issues which surround this. This study provides a benchmark for further exploratory research in this area.

References:

Stability of Captopril And Propranolol Hydrochloride
Extemporaneous Paediatric Formulations
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*Department of Pharmacy Pharmaceutical Technology, Faculty of Pharmacy. University of Seville, ** Barcelona, *** Granada (Spain)

Introduction: Harmonization is needed in extemporaneous paediatric formulations from both Community and Hospital Pharmacies, even between various Health Center including small hospitals to improve standardization and quality of these unlicensed medicines.

Aim: To determine the stability of two unified extemporaneous paediatric formulations: captopril solution and propranolol hydrochloride syrup.

Methods: The physical and chemical stability of both drugs was determined in glass amber containers, at three different temperatures (4, 22 and 50°C) and for up to 90 days.

Captopril was dissolved in purified water at a concentration of 1 mg/ml with disodium edetate 0.1% w/v. Propranolol hydrochloride syrup included 1 mg/ml solution of citric acid, 20% w/v conservans water (sodium methyl p-hydroxybenzoate 0.05% and sodium propyl p-hydroxybenzoate 0.025%) and the drug at a concentration of 1 mg/ml in simple syrup.

Quantification of both drugs was carried out by stability indicating UV-Vis spectrophotometry methods, directly for captopril and after a colored reaction for propranolol hydrochloride.

Results: Measured pH of both formulations (2.6 and 4.1 respectively) remained the same for 90 days without any significant variation for any temperatures.

The results indicated that captopril content decreased by 5% after 20 days at 22 and 50°C, while only after 40 days at 4°C. Furthermore, content of propranolol hydrochloride formulations kept at 50°C lost 5% w/v within 15 days and within 30 days at 22°C, while 100% content was maintained during 90 days at 4°C storage.

Conclusions: This Captopril extemporaneous solution can be used up to 40 days if stored at 4°C whereas propranolol hydrochloride syrup can be kept up to 90 days at 4°C. In Spain it is common to keep liquid medicines in the refrigerator because it is a very hot country with some cities reaching 40°C.
Compounding For Pediatric Patients
Paula Tavares
LEF, Instituto de Formação e Inovação em Saúde

Objective(s)
Knowledge of the paediatric compounded preparations (PCP), in Portugal. Development and validation of oral pharmaceutical forms, establishing the galenic formula, the preparation procedure and the term of use supported with stability studies.

Availability of the pharmacotherapeutic information for informed hand over and suitable use of the PCP (package information leaflet). Design & Methods
Inquiry targeted to Community and Hospital pharmacies, asking about the active substance, dosage, dosage form, excipients, indications for use and posology. Analysis of the requests made to the Pharmaceutical compounding Information Center (CIMPI) from LEF. PCP selection for laboratory study, following the criteria: a) higher frequence of use; b) therapeutic need; c) trouble in the formulation or stability of the compound. Physic-chemical and microbiological stability study for 2 months. Edition of the Portuguese Galenic Formulary (PGF)

Results and Conclusions
30% of compounded preparations are paediatrics. 15% of the PCP are dermatological, 18% are for cardiovascular diseases and 15% are antiinflammatories. Powder packets represent 10%, capsules 5%, oral liquids 61%, topical liquids 10% and semisolids 14%. The PGF includes 184 paediatric compounded preparations corresponding to 92 active substances. The cardiovascular PCP represents 20%, dermatological 20% anti-inflammatories 16% and gastrointestinal 16%. PCP addressed to the NSC, Endocrine and metabolism and nutrition disorders represent 8% each. 66% of the PPC are oral liquids. Preparations contain suitable excipients for paediatric use and enable a simple preparation in the pharmacy. Package information leaflet is clear and simply organized. Recommendations on the dosage, posology and indication for therapeutic use are given for all PCP.

Ranitidine, Spironolactone and Furosemide Paediatric Extemporaneous Formulations: Preparation and Stability Study from Spanish Unified Perspective
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Introduction: Differences in physiology during the childhood development mean that the pharmacokinetic and pharmacodynamic data of children cannot be predicted from adult data.

Therefore, to guarantee a better administration, dosage and therapeutic adherence, choosing an adequate pharmaceutical form, is very important. The absence of paediatric presentation leads to Pharmaceutical Compounding (mainly solutions or suspensions in Spain) with a high variability on the design and the stability which may lead to dosing errors.

Aim: Development and stability study of paediatric formulations most demanded in Spanish hospital or community pharmacies, such as ranitidine, spironolactone, and furosemide to establish a single formulation criterion.

Methods: The compositions (Table 1) of the three formulations are unified.

<table>
<thead>
<tr>
<th>Active substance (mg/ml)</th>
<th>Excipients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine 15</td>
<td>Simple Syrup 50 ml; Purified Water q.s. 100 ml</td>
</tr>
<tr>
<td>Spironolactone 5</td>
<td>Simple Syrup q.s. 100ml</td>
</tr>
<tr>
<td>Furosemide 2</td>
<td>Sodium methyl p-hydroxibenzoate 0.68 mg, Sodium propyl p-hydroxibenzoate 0.34 mg, Sodium Phosphate 12 H2O-68.4 mg, Citric acid 1 H2O 0.58 mg, Simple syrup 0.4 ml, purified water 0.56 ml</td>
</tr>
</tbody>
</table>

Table 1. Composition of ranitidine, spironolactone, and furosemide extemporaneous paediatric liquids

The spectrophotometric analytical method was validated. The stability studied encompassed: Multiple Light Scattering (MLS), pH, rheology and concentration at three different temperatures (4, 25, 40°C) during 60 days. The results were statistically analyzed by Anova (p<0.05).

Results: Backscattering and Transmission spectra showed homogeneity for ranitidine and furosemide formulations. Sedimentation and flotation were observed for spironolactone syrup. The pH values, rheological behavior (pseudoplastic-non tixotropic) and concentration of ranitidine and furosemide showed no statistically significant differences at different time points regardless of the temperatures. However, concentration of spironolactone increased from the day 7, probably due to degradation metabolites produced at pH>5.
**TOPIC: Administration devices**

**Accuracy of a Generic Dosage Device For Administering A Pediatric Oral Suspension Formulation**  
McNally Gerry  
McNeil Consumer Healthcare

**Objective:**
Determine the impact of using a generic dosing device for the administration of an oral liquid pediatric formulation.

**Design and Methods:**
A common generic dosage delivery device (graduated spoon) was tested with an oral liquid suspension formulation. The 5mL and 10mL graduation lines were tested. Formulation was dispensed at a 45° angle for 2 seconds. All measurements were determined by weight in a control laboratory setting. The product formulation had a viscosity range of 2300 to 3500 cP. The 5mL and 10mL graduation lines were verified by weight using water prior to conducting the experiment.

**Results:**
The experiment assumed that a caregiver was able to accurately fill the dosing device to the desired graduation line prior to dispensing. When inverted for 2 seconds at 45° the dosing device delivered on average approximately 41% and 42% of the product for the 5mL and 10mL graduation lines respectively. Another experiment was conducted at a higher dispensing angle to determine the time required to deliver approx. 90% of a 10mL dose.

<table>
<thead>
<tr>
<th>Dosage Cup Verification</th>
<th>5 mL</th>
<th>10 mL</th>
<th>Average Density of Water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fill Weight (g)</td>
<td>4.996</td>
<td>10.040</td>
<td>0.9979 g/cm³ @ 21.2°C</td>
</tr>
<tr>
<td>Fill Volume (mL)</td>
<td>5.01</td>
<td>10.06</td>
<td>Average Density of Product</td>
</tr>
<tr>
<td>Percentage of target dose</td>
<td>100.13%</td>
<td>100.63%</td>
<td>1.2199 g/cm³ @ 21.2°C</td>
</tr>
</tbody>
</table>

The results of the experiment are summarized in the table above.

**Conclusion:**
The experiment demonstrates that generic dosing devices may not be appropriate for all product formulations. Calibrated dosing devices need to take into account product attributes such as viscosity and surface tension. Only devices provided with the product that have taken the product’s attributes into consideration should be used.

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**TOPIC: Age appropriateness of Formulations**

**Development and Analysis of Medicated Soft Chew Dosage Form Suitable For Paediatric Use**  
Michael Mok, Dr. Tuleu Catherine  
University of London School of Pharmacy

**Objective(s):**
Soft chewable dosage forms similar to gelatine gummy candies might be easier, more appealing and natural to chew for children, than a chewable tablet. The aim of this work was to assess the feasibility of formulating a sugar free, gelatine free medicated soft chew with a semi-solid elastic texture.

**Design & Methods:**
Hydrocolloids (low methoxy pectin, acacia gum, carrageenan, high acyl gellan gum) were formulated with various amounts of polyols (maltitol, erythritol, xylitol, and mixtures) to form soft chew cylinders (2x2.5cm), using an evaporation method. Quinine hydrochloride was used as a bitter model drug. The work was divided into three phases: 1) visual and tactile screening of soft chews, 2) further analysis of selected formulations with and without drug by Texture Profile Analysis (Instron 5567, 100N load cell) to quantify adhesiveness, cohesiveness, hardness, gumminess and springiness of the soft chews, 3) a dissolution test (apparatus 1 Caleva 8ST, 100rpm, 900 mL water 37°C) with the best formulations.

**Results:**
Carrageenan was found to be a suitable substitute for gelatine, and maltitol or a mixture of maltitol/xylitol (which avoided crystallisation) for sugar. However, addition of quinine significantly changed the texture of the soft chew which may affect palatability. The soft chew had an extended release dissolution profile which is unlikely to occur in vivo since the dosage form would be chewed and not swallowed whole.

**Conclusions:**
This preliminary work showed that medicated soft chew dosage forms are a technically challenging but feasible option.

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**Development of Hydrocortisone Mini-Tablets for Improved Paediatric Dosing**  
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School of Pharmacy & Biomolecular Sciences, Liverpool John Moores University, UK  
Medicines for Children Local Research Network, Alder Hey Children’s NHS Foundation Trust, UK

**Objectives:**
Hydrocortisone 10 mg tablets are routinely quartered to obtain the required dose for paediatric patients.
The aim was to investigate the feasibility of developing hydrocortisone mini-tablets for accurate paediatric dosing.

**Methods**

Hydrocortisone 10 mg tablets (Auden Mckenzie Ltd, UK) were quartered using a standard tablet cutter. A model hydrocortisone formulation for mini-tablet production was developed and 3 mm mini-tablets were manufactured using a Stylcam® 100R rotary press simulator. The weight uniformity of tablet quarters and mini-tablets was calculated and the strength of the mini-tablets determined. Drug release from quartered tablets and mini-tablets was evaluated and data were analysed for statistical significance (P < 0.05) using the MinitabTM software package.

**Results**

Robust mini-tablets (mean strength 1.73 ± 0.54 MPa) were successfully manufactured under simulated rotary press production conditions using a model hydrocortisone formulation. Mini-tablets displayed significantly better weight uniformity (mean = 16.1 mg, CV = 4.29%) when compared to quartered tablets (mean = 58.9 mg, CV = 13.6%). Although rapid and complete dissolution was achieved from both mini-tablets and quartered tablets, a high variation in the intended dose of 2.5 mg (83.5 – 115.5%) was observed with quartered tablets, whilst a significantly lower dose variation was achieved with mini-tablets (95.1 – 105.7%).

**Conclusion**

This research has illustrated the improved weight and dose uniformity achievable with hydrocortisone mini-tablets, which could improve accuracy of paediatric dosing over the current practice of manipulating ‘adult’ dosage forms by quartering tablets. The feasibility of industrial scale production of hydrocortisone mini-tablets has been demonstrated.

**Dosage forms attributes of oral Prescription Only Medicines licensed for children in 2008 in the UK**

Orlu Gul, Mine Rousseau Rene, Mok Micheal, Thiollier Thibaud, Tuleu Catherine

*University of London School of Pharmacy*

**Objective**

The EMEA reflection paper on paediatric formulation (2005) reflects on some general aspects of acceptability/preference of various dosage forms for different age group. Presently we wanted to assess which ones were available to be legally prescribed to children in UK prior full enforcement and expected outcomes of the EU paediatric regulation.

**Design and methods**

An excel database containing formulation attributes of oral POM with a paediatric license available in the UK as of 2008 was populated and exploited. Sources: British National formulary for Children (2008) and the electronic Medicines Compendium (http://emc.medicines.org.uk) which contains the summary of Product Characteristics and Patient Information Leaflet of around 3000 medicines.

**Results**

Ready-to-use liquids were not the majority (20%) of all the oral dosage forms licensed for children (n=491). Most of the products even licensed from birth were monolithic medicines such as tablets (of which 1/3 was scored) and capsules (of which 1/5 could be sprinkled) which is not acceptable for dose adaptation. 9% were multiparticulates (powders, granules) of which 2/3 were for reconstitution and 40% monodose. Only 7% of all formulations were modified release. Sugar-free formulations were the majority in almost every pharmaceutical form (solid, liquids). The flavours used were very eclectic. Potentially toxic excipients were found in liquids such as ethanol, propylene glycol, sulphites.

**Conclusions**

Age appropriate formulation is important for optimised therapy in children. We found some discrepancies in the type of dosage forms licensed for children and their age and ability. Further evidence-based research in suitability of paediatric dosage forms is required.

**Formulating cysteamine polymeric systems for the treatment of corneal crystals in cystinosis**

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2. Great Ormond Street Hospital Trust for Children, London WC1N 3JH, UK

**Objectives:**

In cystinotic patients, cystine crystal density can be reduced by the topical cysteamine 0.5% eye drop that is currently available in the UK. However, compliance is extremely poor due to the hourly recommended frequency of administration during the initial treatment phase followed by 4-6 times a day. The aim of the present work is to formulate a slow release cysteamine ophthalmic preparation to reduce this frequency, improve bioavailability/efficacy and greatly enhance the quality of life of cystinotic children.

**Design and Methods:**

After extensive screening, two polymers; sodium carboxymethyl cellulose (Na CMC) and Poloxamer 407 (in combination or not), were further investigated based on their compatibility with cysteamine, rheological behavior, osmolarity, drop size, surface tension, pH and in vitro cysteamine release characteristics. An iodimetric titration assay method was validated. Commercial ophthalmic preparations were also assessed for bench marking.

**Results:**

The best formulation containing 5% of Na CMC (pH 7.4) exhibited a viscosity of 96.2±1.5 mPa.s (20rpm, room temperature); a drop size of 46.7±0.9μL while the osmolarity
The surface tension was 77.2 \pm 1.3 mN/m. These results were in line with the commercial gels or in situ gelling systems tested. Moreover, Na CMC is a mucoadhesive polymer. In vitro release with Franz diffusion cell exhibited slower release (T50\% = 2h) compared to other formulations.

**Conclusion:**
It is expected that this formulation will reduce lachrymal drainage, increase drug ocular contact time and that it will demonstrate good tolerability. Future in vivo studies include corneal PK studies in New Zealand rabbits.

**Minitablets, how science and innovation drive children centric development**

Desset-Brethes Sabine
Novartis Pharma AG

**Objectives**
For oral pediatric dosing, solid multiparticulates like minitablets were recently favoured over liquids in the WHO report of the Informal Expert Meeting on Dosage Forms of Medicines for Children (2008). The present work demonstrates the potential of minitablets regarding their use in children, enabling dose accuracy, dose flexibility and blinding of clinical study.

**Design & Methods**
11 batches of minitablets (2mm, 7mg, 50\% drug load, 10kg batch size) were compressed. A representative sample of 30 minitablets per batch was evaluated for individual assay. The probability to meet CU requirements was assessed using Monte Carlo simulation.

**Results**
Mean assay values spanned from 97.8 to 101.9\% and standard deviation from 4.1 to 7.6. Assuming a “worst case” assay distribution, it was found that a unit dose of 1 minitablet has a 30\% probability to pass CU testing while a unit dose of 2 minitablets has a 97\% probability to pass CU testing. The minitablets were further encapsulated using unit doses of 2, 12, 24 and 48 active minitablets. The binding between the doses was achieved by mixing placebo to active minitablets up to a total number of 48, thereby avoiding the use of dummy in clinics.

**Conclusions**
Minitablets were demonstrated to provide accurate dosing down to 2 minitablets, to enable flexible dosing with pre-dispersed capsules containing 2, 12, 24 and 48 minitablets and to ensure best adherence, blinding between doses being achieved without the use of dummy.

**Rapidly dispersing tablets for administration to paediatric patients: a convenient and practical approach**

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**Introduction:** Compound V is a highly water soluble drug substance, which is presented as immediate release tablets for use in adults. The mode of action of this compound is conducive to evaluating its activity in areas of unmet clinical need in paediatric patients (1-18 years of age). Tablets of compound V are relatively small (6, 7 or 8 mm is diameter) and are therefore deemed suitable for children aged 6 years and over, and acceptable, though not necessarily preferable, for children aged 2 to 5 years [1]. An oral liquid preparation is ideal for administration to younger patients (< 2 years of ages) and to those who are unable to swallow intact tablets. However, the poor aqueous stability of compound V complicates the development of a liquid formulation with sufficient shelf-life. As an alternative to a liquid formulation and since compound V tablets are rapidly dispersing and dissolving, their dispersion in water was evaluated as a potential alternative to a liquid formulation for daily dosing of compound V. The work presented here was undertaken to support the use of dispersed compound V tablets as a convenient and practical approach for dosing paediatric patients.

**Methodology:** The acceptability of the excipients currently used in compound V tablets for paediatric use was evaluated by checking against the available literature (e.g. regulatory databases). Subsequently, the dispersion of compound V tablets was investigated in small volumes of water (up to 30 mL), which are convenient for patient dosing. As part of this investigation, the recovery of compound V from the dispersion (i.e. percentage that will be dosed) as well as its stability in the dispersion were evaluated. Administration using syringes and various types of giving sets (e.g. nasogastric tubing) was also evaluated to support dosing to critically-ill patients and those who are unable to swallow including neonates. Finally, the basic taste sensation of the compound was measured using the electronic tongue (e-tongue), in order to evaluate the need for a taste masking strategy if improvement in palatability was deemed necessary.
Results and Discussion: Excipient databases demonstrated that all excipients and their levels were suitable for use in paediatric patients. Dispersion in small volumes of water was rapid and complete within 5 minutes with mild swirling, and resulted in excellent recovery (> 95%). In addition, compound V was stable in the dispersion for at least 6 hours at room temperature, which provides sufficient time for administration. The dispersion was compatible with commercially available oral syringes and tube types, which allows significant flexibility for administration. Compound V was bitter when its basic taste sensation was measured using the e-tongue device.

Conclusion: The dispersion of compound V tablets provided a convenient and practical approach for presenting the drug to very young patients and those who are unable to swallow. The simplicity of administration allows it to be performed daily by a parent (at home) or a healthcare professional (at hospital). This approach is comparable to the use of single-dose unit sachets. This daily preparation approach using water would mitigate both the chemical stability issue and the need for dispersing agents which may contain preservatives. Furthermore, a number of dosage strengths will be available to ensure that a dispersion of a whole tablet would provide the required dose and circumvent the need for aliquoting a proportion of a dispersion of larger dosage units. The bitterness of compound V highlighted the potential requirement for taste masking and the development of a practical taste masking strategy is ongoing. Taste masking may either be done by dispersing compound V tablets in a commercially available vehicle (e.g. a fruit juice) or co-administering the dispersion in water with a fruit juice. Where required, compatibility studies with the dispersing vehicle will also be undertaken.

The availability and age-appropriateness of paediatric medicines
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2 Utrecht University, Faculty of Science, Utrecht Institute for Pharmaceutical Sciences (UIPS), Department of Pharmacoepidemiology and Pharmacotherapy
3 University Medical Centre Utrecht, Department of Clinical Pharmacy

Background
Optimal paediatric pharmacotherapy requires licensed, commercially available and age-appropriate medicines. In lack of these, health care professionals need to resort to extemporaneous preparations or off-label prescriptions. The EU Paediatric Regulation aims to improve this situation by incentives to increase the number of medicines approved for children. The aim of this study was to provide baseline information to evaluate the effect of the Paediatric Regulation by reviewing the availability and age-appropriateness of licensed, paediatric medicines in the Netherlands.

Methods
The availability of licensed, paediatric medicines was studied with help of the Z-index, the Informatorium Medicamentorum and the Summary of Product Characteristics. The nature of the medicines and the data for adults was studied as well. The age-appropriateness for children was evaluated concerning age, the ability to follow the authorised dosing recommendation, the suitability of the dosage form and the inclusion of potentially harmful excipients.

Results
3542 licensed, paediatric medicines were identified containing 703 active chemical entities. The proportion of paediatric versus all human medicines increased with age from 37-96%. The proportion varied for the administration route from 22% (dermal) to 81% (inhalation products) and for the therapeutic category from 11% (genito-urinary medicines) to 89% (antiparasites). When considering the real age-appropriateness of licenced medicines the available formulations were acceptable for 27-88%, depending on age.

Conclusion
The current baseline information confirms a limited availability of paediatric medicines, especially for younger children. Health care professionals should realize that licensed, paediatric medicines may not be age-appropriate.
Invasive fungal infections are the major reason of morbidity and mortality in severely immunocompromised children with cancer or following allogeneic blood stem cell transplantation. Only a few antifungal compounds are approved for paediatric patients. In fact, there is very limited data on their safety and therapeutic outcomes concerning this distinct patient population. Amphotericin B (AmB) deoxycholate, Fungizon®, is a broad spectrum antifungal agent mainly used to treat invasive fungal infections. However, this formulation presents a high nephrotoxicity that limits its clinical use. Microemulsion (ME) is a system that contains water and oil coexisting in thermodynamic equilibrium due to the presence of a surfactant/co-surfactant film at the oil-water interface. Several works showed that the efficacy and toxicity of AmB were, respectively, maintained and decreased when MEs were used as carrier for this drug. The aim of this study was to characterize a biocompatible ME, developed from a pseudo-ternary phase diagram procedure, containing AmB and evaluate this system as a new delivery system for paediatric applications. The physico-chemical parameters evaluated were: macroscopic appearance, pH, refractive index, conductivity, rheology, viscosity, droplet size and the AmB aggregation state on the system. The results reveal the favorable characteristics and huge potential of the ME system to decrease the toxicity caused by Fungizon®. Moreover, it was demonstrated that a lipid carrier can change the AmB overall activity and toxicity, suggesting, therefore, its therapeutic application. Additionally, the results about the AmB aggregation state to the carrier show that the AmB is strongly binding to the ME droplets and maintain its physicochemical and biological properties after incorporation. Therefore, the ME system was able to carry the AmB and the results showed that it can be used as one promising system to be applied at children by both intraocular or intravenous route.

Sesame oil emulsion systems: a valuable product for the treatment of diaper dermatitis

Secondarily infected dermatitis requires a different therapeutic approach. Candida albicans frequently contaminates diaper dermatitis and should be considered present at any diaper dermatitis that persisted for longer than 3 days. Treatment includes application of a topical antifungal cream. Depending on the composition, the mixture of surfactant, oil and water, may form supra-molecular aggregates with different structures which can significantly influence the drug release. The aim of this work was to develop several emulsion (EM) systems containing Tween® 20 and Span® 80 as surfactant, sesame oil (SO) as oil phase, and distilled water as an aqueous phase, and evaluate their in vitro antifungal activity. EMs with and without the zinc oxide (ZnO) were prepared. The structures of the systems were characterized by rheological behavior, particle size analysis, stability under storage, stability under centrifugation, pH evaluation and conductivity measurements. After the physicochemical characterization, the ZnO was incorporated in the systems. The rheological behavior reveals that depending on the composition the EM system could exhibit a tixotropic behavior. Stability studies showed that the inclusion of ZnO improves the stability of the EMs. Finally, the results of in vitro antifungal activity revealed that the ZnO enhanced the activity of SO inducing a synergic effect. Thus, the association of ZnO to sesame oil containing EMs may be an alternative in the therapy of diaper dermatitis when secondarily affected by candidiasis.