Abstract ID: 2

Net Promoter Score Model for Evaluating Paediatric Medicine Acceptability: Validation and Feasibility Study

Okhee Yoo[1,2]; Britta S von Ungern-Sternberg[2,3]; Lee Yong Lim[1,2]

[1] Pharmacy, School of Allied Health, The University of Western Australia (UWA), Perth, Australia 6009, Okhee.yoo@uwa.edu.au

[2] Institute for Paediatric Perioperative Excellence, UWA, Perth, Australia 6009

[3] Emergency Medicine, Anaesthesia and Pain Medicine, Medical School, UWA, Perth, Australia 6009

Introduction

There is an increasing amount of information available regarding children's preferences for medicinal formulations, including their preferred dosage forms. However, the final medicinal formulation is typically evaluated based on taste scores, a method borrowed from the food industry. Efforts have been made to unify taste evaluation methods, but it remains unclear whether these taste scores effectively reflect acceptability. The current evaluation system lacks a definitive cutoff taste score to determine if a medicine is acceptable. A novel approach proposed by our laboratory involves applying the Net Promoter Score (NPS) model, originally developed for business to assess customer satisfaction, to the evaluation of medicinal taste. Although other areas of the health system are beginning to incorporate NPS for patients' satisfaction surveys, its application in this context remains unexplored. Our aim is to establish a validation methodology to assess the feasibility and clarity of applying NPS to Medicine Acceptability Score (MAS) using existing data.

Method

We utilized previously published data on taste scores for six formulations. The questions were structured into two formats: one assessing the taste score using a 5-point hedonic scale and the other gauging willingness to take the medicine if sick (WTA) on a yes or no scale. The MAS is calculated by excluding passive scores and determining the difference between the percentage of promoters and detractors (Figure 1). For the WTA question, the deviation from 50% was recorded as either positive or negative. The passive range was identified based on the correlation between WTA and the MAS.

Results

When the WTA is negative, the MAS is negative across all tested passive scores, categorizing such formulations as unacceptable (Table 1). To achieve a concurrent MAS from the lowest to highest WTA scores, only the 2-4 passive category matched this order, making it the most appropriate passive category for the 5-point hedonic scale.

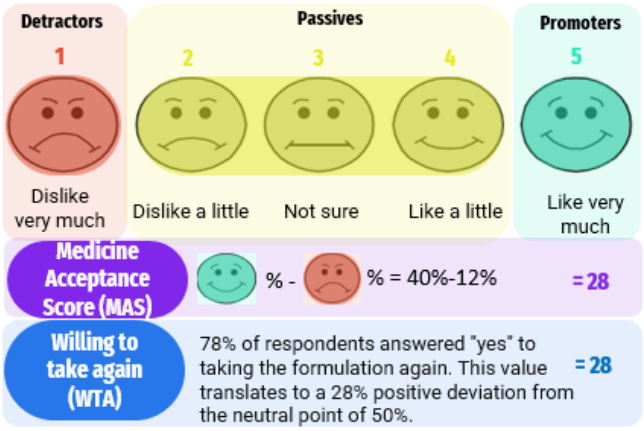

Figure 1. Example of MAS Calculation from a 5-Point Hedonic Taste Score with Passive Scores of 2-4 and Willingness to Take Tramadol Taste-Masked Chewable Tablet (n=68)

Table 1. Medicine Acceptability Scores (MAS) and Willingness to Take Again (WTA) Based on Different Formulations and Passive Taste Scores. Midazolam=MDZ; Flucloxacillin=FLX; Tramadol=TRM; TMT = Taste-Masked Chewable Tablet; LQD = Oral Liquid Formulation

Pass-ives	MDZ TMT	FLX TMT	TRM TMT	MDZ LQD	FLX LQD	TRM LQD
2-3	29	19	50	-51	-7	-34
2-4	**0**	**4**	**28**	**-56**	**-10**	**-41**
3	21	12	41	-76	-18	-59
3-4	-9	-3	19	-81	-21	-66
WTA	**11**	**17**	**28**	**-13**	**-28**	**-16**

CONCLUSION

This study has demonstrated that a MAS can be used to determine whether a medicinal formulation is acceptable using a single score. Further validation is required for positive controls of chronic medications and acute medications, as these formulations may have different threshold acceptability levels for medicinal formulations.

Abstract ID: 3

Title: Odour acceptability of oral flucloxacillin formulations: A sensory study.

Ayat Elgammal[1,2]; Liz Sheehan[3]; Margaret Shine[3], Reda Mohamed[4], Margaret Bermingham[2], Abina Crean [1]
[1] SSPC, the SFI Pharmaceutical Research Centre, School of Pharmacy, University College Cork, Ireland
[2] Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Ireland
[3] SRL Pharma, T12 XF62, Cork, Ireland
[4] Rotunda Hospital, Dublin, Ireland

Introduction

Palatability 'the overall appreciation of a medicinal product in relation to its smell, taste, aftertaste and texture', as highlighted by the *EMA Guideline on the Development of Age-appropriate Formulations* [1] is one of the key elements of paediatric medicine acceptability. While the relationship between medicine taste and acceptability has received much attention, the role that the odour of medicine plays in patient acceptability has been somewhat neglected to date. Smell not only influences a patient's perception of a medicine's acceptability prior to ingestion, it is also the main contributing sense to the determination of a substance's flavour [2] . Oral antibiotic acceptability is a key consideration to ensure adherence and effective treatment. Flucloxacillin, a widely prescribed oral antibiotic, is reported as an unpalatable antibiotic for paediatric patients, with its malodour a contributing factor [3]. The aim of this study was to evaluate the odour acceptability of oral flucloxacillin formulations through a sensory study.

Methods

The odour acceptability of four flucloxacillin formulations containing 250 mg of flucloxacillin sodium and a control aqueous solution were assessed. Formulations assessed were (i) 5 ml of a commercial solution, (ii) one commercial gelatin capsule, (iii) the dose in thirteen 4 mm minitablets, and (iv) the dose in thirteen 4 mm minitablets formulated to reduce smell. The order of sample presentation to volunteers was randomized. Prior to assessing flucloxacillin formulations, the smell acuity of volunteers was assessed using validated commercially available 8-item Sensonics™ smell test kits. Each study participant received each sample, smelled it and completed a smell questionnaire individually and privately thereafter. The formulation smell assessment questionnaire comprised of two questions. The first question was to rate the smell acceptability of each sample by using visual analogue scales (VAS) of 10 cm length ranging from 0 ("extremely un-acceptable") to 10 ("extremely acceptable"). Any score above 5 was rated as 'acceptable'. The second question was to describe the smell of the product by selecting descriptors from a list of possible descriptors with definition (aromatic, pungent, plastic, musty, rotten, fruity, with the option for the volunteer to select 'other' and describe). Ethical approval was granted by the Clinical Research Ethics Committee of the Cork Teaching Hospitals (CREC), reference number ECM 4 (n) 06/02/2024 & ECM 3 (p) 05/03/2024

Results:
Forty human panelists conducted the study. The smell acuity assessment determined that 21 participants (52%) had normal ability to smell (normosmia), 18 participants (45%) had a reduced ability to smell (microsmia) and 1 participant (3%) had full loss of smell (anosmia). The aqueous solution control and minitablets were rated to have the least unacceptable odour with a mean score of 2.8 and 2.9 respectively. The commercial solution, commercial capsule, and minitablets formulated to reduce smell were ranked a more acceptable formulations with a mean score of 8, 7, and 7.9 respectively. The smell of the flucloxacillin aqueous control solution and minitablets were described as pungent, musty, plastic, and rotten, 91% of selected descriptions, with remaining 'other'. The smell of commercial liquid formulation was described as mainly fruity (63%), aromatic (32%), with 5% of descriptions noting pungent (5%). The commercial capsule was described as mainly odourless (65%) along with musty (13%), plastic (7%) with other (15%). The minitablets formulated to reduce smell were described as odourless (77%), pleasant (15%) and musty (3%).

Conclusion:
The majority of the participants rated the odour of the flucloxacillin capsule formulation and minitablets formulated to reduce smell as acceptable and odourless. Next steps are to further investigate flucloxacillin minitablets and capsule formulations for paediatric patients, by evaluating and optimising their overall palatability and swallowability.

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Abstract ID: 4

Development of child-appropriate extended-release tablets based on lipid matrix systems

Stefanie Broocks; **Melanie Gebhardt; Sandra Klein**

University of Greifswald, Department of Pharmacy, Felix-Hausdorff-Straße 3, C_DAT, 17489 Greifswald, Germany
stefanie.broocks@uni-greifswald.de

Introduction

Solid oral dosage forms, such as tablets, are the most commonly administered dosage forms in the drug therapy of adults. However, the typical size of a tablet is usually too large to be administered to children. Young children in particular find it difficult or impossible to swallow tablets designed for adults. There is therefore a need for smaller tablets to ensure safe and more effective treatment and adherence. Frequency of administration is also a key factor in adherence, with repeated administration of medication throughout the day placing a heavy burden on children and their caregivers. Accordingly, there is a clear need for extended-release (ER) oral dosage forms for paediatric use. However, there are currently very few such dosage forms on the market. One possibility for the development of ER formulations would be the use of matrix systems. In addition to the typical swelling and erodible hydrophilic systems, non-swelling and non-erodible lipid matrix systems represent an interesting alternative for the development of matrix-based paediatric formulations. The aim of the present work was therefore to develop a paediatric size ER tablet formulation based on a lipid matrix system, paying particular attention to the safety of the excipients used in relation to the target patient group.

Methods

Table 1. Composition of the tablets [%, w/w], Compritol® = glycerol dibehenate, HPMC = hydroxypropylmethylcellulose, EC = ethylcellulose.

	C1	HPMC1	EC1	C2	C1EC	C3EC
Propranolol HCl	39,6	39,6	39,6	19,8	39,6	19,8
Compritol® 888 ATO	44,5	-	-	64,3	44,5	44,5
HPMC K100M	-	44,5	-	-	-	-
EC 10 cP	-	-	44,5	-	13,4	33,2
$CaHPO_4$ *2 H_2O	13,4	13,4	13,4	13,4	-	-
Magnesium stearate	1,5	1,5	1,5	1,5	1,5	1,5
Silicon dioxide	1,0	1,0	1,0	1,0	1,0	1,0

Propranolol HCl ER tablets of different matrix formers and their combinations (Table 1) were produced using a EK0 (Korsch, Germany) tablet press equipped with a 5 mm round, biconcave single-tip punch. The highest possible compaction force was selected. All tablets were analysed for weight and tensile strength. In addition, all tablets were tested for drug release in the first hour to check for dose-dumping. For this purpose, a single tablet was incubated in quintuplicate (n=5) in 10 mL phosphate buffer pH 6.8 at a temperature of 37 ± 0.5 °C with continuous shaking at 180 rpm. Samples were analysed using a spectrophotometer (U-2900, Hitachi, Germany) at a wavelength of 289 nm. Dissolution studies of selected formulations were performed in triplicate (n=3) using the Mini-Paddle apparatus (USP2, DT 720, Erweka, Germany) in 250 mL (for 19,8% propranolol HCl) or 400 mL (for 39,6% propranolol HCl) phosphate buffer pH 6.8 at a temperature of 37 ± 0.5 °C and an agitation speed of 75 rpm for 18 hours. Drug release was quantified online at a wavelength of 289 nm using a Cary 8454 UV-spectrophotometer (Agilent, USA).

Results

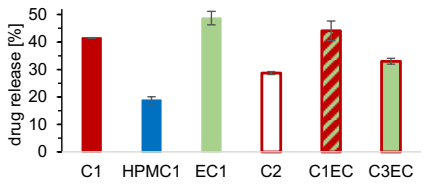

Figure 1. Drug release within the first hour, n=5 ± S.D..

During the one-hour incubation, it quickly became clear which formulations would lead to the most promising release results. As expected, tablets with lower drug load and higher matrix content performed best. Formulation C3EC was selected as the most promising lipid-based formulation because, in addition to a low release of the highly soluble propranolol HCl within the first hour, it was easy to process and there were no problems with tableting. When the release behaviour of this formulation was examined over a period of 18 hours, no clear differences were found compared to the hydrophilic HPMC1 formulation. As expected, the Compritol® formulation showed no visible erosion over the test period.

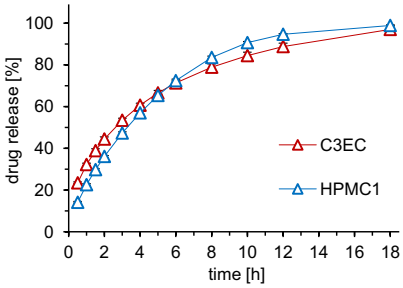

Figure 2. Propranolol HCl release from a Compritol®- (C3EC) and a HPMC-formulation (HPMC1) in the Mini-Paddle apparatus (250 or 400 mL phosphate buffer pH 6.8, 37 ± 0.5 °C, 75 rpm); n=3 ± S.D..

Conclusion

In the present study, a lipid-based formulation with good production properties and a release behaviour similar to a swelling hydrophilic matrix was developed. Although it prolongs the release of the highly soluble propranolol HCl only to a limited extent when used as the sole excipient in a formulation, the results of the present study indicate that Compritol®, in combination with other matrix formers considered safe for paediatric use, is a promising excipient for the manufacture of paediatric ER tablets and thus represents an interesting alternative to hydrophilic matrix formers.

Abstract ID: 5

Assessment of choking hazard of an age-appropriate patient-centric novel dosage form designed to minimize choking hazards in special patient populations

Srinivasan Shanmugam
Adare Pharma Solutions, 845 Center Dr, Vandalia, Ohio, 45377, USA, +1-551-263-6246

INTRODUCTION

The provision of age-appropriate dosage forms for the pediatrics receives much attention recently, with both the FDA and the EMA requiring companies to develop paediatric dosing solutions. Scientists from industries, academia, and focus groups such as EuPFI, continue to address various issues including novel formulation strategies, with appropriate emphasis on palatability and acceptance. Parvulet® represents an innovative approach to solving the problem of acceptability, particularly to children and the old who may have difficulty in swallowing. On wetting, Parvulet® forms a soft easy-to-swallow mass that is well suited to the delivery of a wide range of drugs regularly dosed to children. Choking hazards present significant risks, particularly for pediatric and geriatric patients who often face difficulties swallowing conventional dosage forms. The development of age-appropriate, patient-centric dosage forms, such as Parvulet®, aims to mitigate these risks. This study assesses the choking hazard associated with Parvulet®, a novel formulation designed to form a soft, easy-to-swallow mass upon hydration.

METHODS

The assessment involved both clinical evaluations and laboratory tests. Clinical evaluations included electromyography (EMG) to measure swallowing muscle activity, video fluoroscopy to visualize the swallowing process, and patient questionnaires to gather subjective feedback on the ease of swallowing and any discomfort experienced. Laboratory tests measured the rheological properties of the hydrated Parvulet® formulation, comparing it to various food textures defined by the International Dysphagia Diet Standardization Initiative (IDDSI) guidelines [1, 2]. Spreadability tests, vane tests, and dip-and-retract cone methodology were used to evaluate the consistency, viscosity, and ease of swallowing the formulation [3, 4]. The spreadability test measured the force required to spread the hydrated mass, while the vane test assessed the internal resistance of the mass to shear. The dip-and-retract cone methodology evaluated the adhesion properties, ensuring the formulation did not stick excessively to the mouth or throat [5].

RESULTS

The Parvulet® formulation demonstrated favorable results in both clinical and laboratory settings. EMG and video fluoroscopy showed that the formulation significantly reduced the effort required to swallow compared to conventional solid dosage forms. Patients reported a higher ease of swallowing and less discomfort with the Parvulet® formulation [1, 2]. Upon hydration, Parvulet® formed a soft mass with a consistency similar to IDDSI Level 4 (pureed) foods, minimizing the risk of choking [3]. The spreadability test indicated that the hydrated mass had low adhesion and was easily manageable by both pediatric and geriatric patients. Vane tests confirmed the appropriate consistency for safe swallowing, with the formulation exhibiting low internal resistance, making it easier to swallow even for patients with dysphagia [4]. The dip-and-retract cone methodology showed minimal detachment forces, indicating low choking risk, and confirming that the formulation did not stick to the mouth or throat excessively [5].

CONCLUSION

The Parvulet® dosage form significantly minimizes choking risks in special patient populations, offering a safer alternative to conventional solid oral dosage forms. The detailed clinical and laboratory assessments confirm that Parvulet®'s rheological properties align well with those required for safe swallowing, particularly in dysphagic patients. These findings support the broader application of Parvulet® in clinical settings, enhancing patient safety and medication adherence for both pediatric and geriatric populations.

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Abstract ID: 6

Safety and acceptability of placebo pellets co-administered with a swallowing gel in healthy volunteers

G. Craye[1], A. Debunne[1], S. De Buyser[2], M. Baudelet[3], M. Petrovic[4], C. Vervaet[1], P. Tomassen[5], V. Vanhoorne[1]

[1] **Ghent University,** Laboratory of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Ghent, Belgium

[2] **Ghent University**, Biostatistics Unit, Faculty of Medicine and Health Sciences, Ghent, Belgium

[3] **Ghent University,** Department of Otorhinolaryngology, Ghent University Hospital, Ghent, Belgium

[4] **Ghent University**, Department Internal Medicine and Paediatrics, Faculty of Medicine and Health Sciences, Ghent, Belgium

[5] **Ghent University**, Department of Head and Skin, Faculty of Medicine and Health Sciences, Ghent, Belgium

INTRODUCTION

Pellets, small spherical particles (0.5-2 mm), offer therapeutic benefits , including dosing flexibility, uniform gastrointestinal dispersion and controlled release [1]. Individuals with dysphagia struggle with swallowing, resulting in reduced therapy adherence and increased aspiration pneumonia risk. Conventional oral solid dosage forms such as tablets and capsules pose challenges for this population, and there is a limited availability of alternative oral dosage forms [2]. Aim of the current study was to investigate the safety and acceptability of oral administration of placebo pellets combined with CE-marked swallowing gels in healthy volunteers. Eight different formulations, varying in pellet size, mass and type of swallowing gel were evaluated.

METHODS

A 2x2x2 factorial randomized balanced incomplete block design evaluated the safety and acceptability of 8 unique formulations, varying by pellet sizes (500µm versus 1000 µm), pellet masses (250mg versus 750mg) and swallowing gels (Gloup Zero (GZ) versus Gloup Forte (GF)). The primary objective was to evaluate the investigator-reported swallowing safety of 8 unique formulations via the Penetration Aspiration Scale (PAS) during a Fiberoptic Endoscopic Evaluation of Swallowing (FEES). PAS scores of 1 and 2 were considered safe, scores ≥ 3 indicated potential risk for dysphagia patients. The secondary objective was to evaluate investigator- and participant-reported swallowing acceptability of 8 unique formulations. Investigator-reported acceptability was evaluated using a modified Yale Pharyngeal Residue Severity Rating Scale (YPRSRS) for residual pellets at the vallecula and the sinus piriformis, post rinsing. YPRSRS scores of 1 and 2 were considered acceptable, scores ≥ 3 were considered unacceptable. Participant-reported acceptability was evaluated using an eight-item Visual Analogue Scale (VAS) summary score (0-80), with higher scores indicating greater acceptability. The individual VAS scales evaluate taste, pellet perception in the mouth and pharynx, residual pellet perception in the mouth and pharynx, swallowability, stickiness, and visual aspect. A mean difference of four was considered the smallest clinically relevant difference.

RESULTS AND DISCUSSION

In total, 204 formulations were administered to 34 healthy volunteers. All formulations were considered safe (PAS ≤ 2) for administration to dysphagia patients (RF 99.51%, 203/204) except for the 'GF 750mg 1000µm' formulation (RF 96,15%, 1 out of 26 administrations of 'GF 750mg 1000µm'). From the investigator's point of view, all formulations were considered acceptable (YPRSR score ≤ 2) (RF 100%).The eight-item summary VAS score, to assess the participant-reported acceptability, ranges from 53.7 points (/80) (GF 750mg 1000µm) to 65.7 points (/80) (GF 250mg 500µm).The mean difference between pellet mass conditions 250mg and 750mg was estimated at 8.59 points (95% CI: 6.63 – 10.54), in favour of 250mg (after averaging for swallowing gel and pellet size).. The estimated mean difference between pellet mass 250mg and 750mg (in favour of 250mg and after averaging for pellet size) was larger for GF (estimated at 11.33 points) compared to GZ (estimated at 5.84 points). We could not find a significant mean difference between swallowing gel conditions and pellet size conditions.

CONCLUSION AND FUTURE PERSPECTIVES

All formulations are generally safe for administration in healthy participants, except for the 'GF 750mg 1000µm' formulation (1 unsafe swallowing event out of 26). Based on clinical considerations, it might be less advisable to administer a formulation with at least one unsafe swallowing event to dysphagia patients. Notably, all formulations are considered acceptable by both investigator and participants. The effect of a smaller pellet mass on the higher mean participant-reported acceptability, was statistically as well as clinically relevant.The results of this study in healthy volunteers will serve as the basis for a subsequent study that will investigate the safety and acceptability of the administration of placebo pellets in combination with a swallowing gel in dysphagia patients.

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Abstract ID: 8

Printed drug-loaded temporary tattoos – A novel, highly acceptable pre-treatment option for pain-free vaccinations for children

Manuel Zettl[1]; Matthias Wolfgang[1]; Laura Wiltschko[2,3], Reingard Raml[2], Eva Roblegg[1,3], Simone Eder[1], Martin Spoerk[1,4]

[1]Research Center Pharmaceutical Engineering GmbH, Inffeldgasse 13, 8010 Graz, Austria

[2]HEALTH – Institute for Biomedical Research and Technologies, Joanneum Research mbH, Neue Stiftingtalstrasse 2, 8010 Graz, Austria

[3]Institute of Pharmaceutical Sciences, Pharmaceutical Technology and Biopharmacy, University of Graz, Universitaetsplatz 1, 8010, Graz, Austria

[4]Institute for Process and Particle Engineering, Graz University of Technology, Inffeldgasse 13, 8010 Graz, Austria

INTRODUCTION

Up to now, vaccinations cause unnecessary pain, anger and tears for children and frustration for their parents from their early life on. Applying local anaesthetics prior to the vaccination can prevent the majority of these hurdles. The current application methods, namely via creams, ointments, gels or sprays, can easily be washed or rubbed away, negatively affecting drug absorption through the skin. Additionally, neither of these options is child-friendly nor has high acceptance rates among children. To this end, we developed a novel, pain-free and non-invasive drug administration concept on temporary tattoos, on which the drug is inkjet-printed onto the tattoo motive in a personalised way (pharmaceutically by adjusting the drug loading and active area, and aesthetically by using superheroes, unicorns, or simply anything appealing and fancy enough to be put on the skin in a fitting size), acting similarly to dermal patches.

METHODS

For the preparation of the drug-loaded ink, a 1:1 weight-based mixture of pre-heated prilocaine and lidocaine (Sigma-Aldrich Handels GmbH, Vienna, Austria) was mixed with absolute ethanol (Carl Roth GmbH & CoKG, Karlsruhe, Germany) in a 1:9 ratio to achieve a eutectic mixture. The ink was deposited onto tattoo paper (Skullpaper, Cottbus, Germany) decorated with a motive of choice using the piezoelectric drop-on-demand inkjet-printer PiXDRO LP50 (SUSS MicroTec, Eindhoven, The Netherlands) equipped with the DMC-11610 printhead (Fujifilm Dimatrix Inc., Santa Clara, USA). To circumvent any printer inconsistencies, the drug content was monitored inline using the non-destructive near infrared hyperspectral imaging (NIR-HIS) sensor Helios NIR EC32 (EVK DI Kerschhaggl GmbH, Raaba, Austria). After applying tattoos of specific drug loading, which was varied systematically based on the number of deposited layers, onto human abdominal skin explants from plastic surgery, the ex-vivo skin permeation was tested by sampling biopsies and analysing them via HPLC-MS.

RESULTS

Temporary tattoos of different lidocaine/prilocaine loadings were accurately inkjet-printed via adjustment of the number of layers. The lidocaine/prilocaine content was monitored and verified via the quantitative near infrared model and the presence of lidocaine/prilocaine amorphous eutectic was proven via differential scanning calorimetry. Both the drug layer and the decorative image were accurately transferred onto artificial skin, building the basis for a correct medical treatment and high acceptance by paediatric patients, respectively. In the ex-vivo permeation studies, lidocaine and prilocaine were found in the upper dermis only after 30 min with their concentrations increasing with increasing time and reaching their maximum after 4 hours.

CONCLUSION

In summary, we showed that drug-loaded temporary tattoos provide a convenient and child-friendly alternative to tablets or syrups, with consistent printability, outstanding aesthetics, facile application to skin, an easy dose adaptations and drug permeability through human skin into both the upper and lower dermis. The NIR-HIS approach guaranteed the correct drug concentration and distribution and, thus, delivers high quality dosage forms for every single print. In addition to the anaesthetic showcase, this novel dosage form can be a powerful tool to treat allergic reactions, mosquito itches, neurodermatitis, psoriasis and many other dermal diseases.

Abstract ID: 9

Personalized Medication using 3D Printing: Case studies in a University Hospital

Presenting Authors: Elisabeth J Ruijgrok [1]; Jayeeta Sengupta [2];
Authors involved in the study: Elizabeth J Ruijgrok[1], Sejad Ayyoubi [1]; Javier E Maduro [1]; Eveline van Kampen [1]; Renz van Ee [2]; Marc Hoppenbrouwers [2]; Anton Aulbers [2] Jayeeta Sengupta [2]

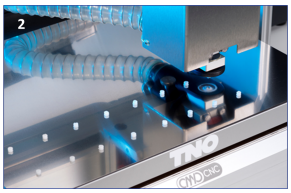
[1] Erasmus MC, University Medical Center, Department of Hospital Pharmacy; Rotterdam, the Netherlands, e.j.ruijgrok@erasmusmc.nl
[2] Netherlands Organization for Applied Scientific Research (TNO), 3D Food & Pharma Printing Department, Eindhoven, the Netherlands, jayeeta.sengupta@tno.nl

The current medical treatment paradigm of "one size fits all," where patients receive the same drugs at the same doses and frequencies, is inadequate for all treatments and needs to be tailored according to patient needs. Two recent studies in an university hospital in the Netherlands, focused on pediatric medication, demonstrate how 3D printing technology can offer personalized medication solutions to address these limitations.

The first study addresses challenges in pediatric medication, particularly with flecainide, a drug for abnormal heart rhythms in children. Standard 50 mg tablets are unsuitable for pediatric use, requiring manual manipulation for oral administration, thereby increasing medication error risks. Researchers utilized the semi-solid extrusion (SSE) 3D printing technique to create personalized flecainide tablets. A pharmaceutical formulation comprising flecainide, poloxamer, and lactose was developed to make a printable paste. The 3D printed tablets, designed using CAD and tested against European Pharmacopoeia (EP) criteria, met all EP standards, including tests for uniformity of dosage units, uniformity of content, uniformity of mass, dissolution, and disintegration. This research marks a significant step toward the clinical use of 3D printed flecainide tablets, enhancing dosage accuracy and safety in pediatric care.

The second study focuses on adrenal insufficiency (AI), where the current standard of care (SOC) results in fluctuating cortisol levels, leading to adverse health outcomes and reduced quality of life. The study aimed to develop a 3D printed, personalized, sustained-release (SR) hydrocortisone tablet for consistent cortisol delivery. Using 3D printing techniques, 10 mg hydrocortisone tablets were created and compared with commercially available slow-release tablets and manually filled capsules. The 3D printed tablets exhibited stable release profiles similar to commercial tablets, with drug content closer to the intended 10 mg dose. Additionally, the manufacturing costs of 3D printed tablets were significantly lower than those of commercial tablets. This study suggests shifting from manually filled capsules to 3D printed formulations, reducing pill burden and allowing for customizable dosing.

These studies demonstrate practical, scalable solutions for creating personalized pediatric medications using 3D printing technology, emphasizing clinical application for precise and safe administration tailored to individual patients. Building on these studies, current research showcases 3D printing's practical application in hospital pharmacies. The next phase expands personalized medication to various conditions, exploring multi-material 3D printing and integrating it into healthcare systems, addressing technical and regulatory challenges, and transforming medication delivery, especially in pediatric settings. These efforts promise improved healthcare management and enhanced patient well-being and safety.
These studies show successful implementation of 3D printing for personalized pediatric medications, its advantages over traditional methods, and its potential for broader healthcare applications. This work benefits healthcare professionals, researchers, and policymakers aiming to enhance precision medicine and patient outcomes through innovative technology.



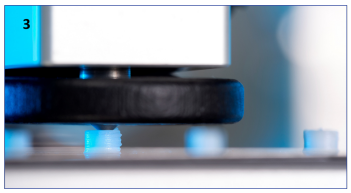


Fig. 1, 2, 3: 3D Printer set up for semi solid extrusion printing
Fig. 4: Printed tablets of different sizes and shapes

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Abstract ID: 11

Development and verification of standard vehicles for investigating the compatibility of oral paediatric drug products with fruit juices

Carolin Eckert[1], Cordula Stillhart[2], Leonie Wagner[2], Emmanuel Scheubel[2], Isabelle Prevot[2], Marc Lindenberg[2], Sandra Klein[1]

[1] Institute of Pharmacy, Felix-Haussdorf-Strasse 3, 17489 Greifswald, Germany
[2] F. Hoffmann-La Roche Ltd., Grenzacherstrasse 124, 4070 Basel, Switzerland
carolin.eckert@uni-greifswald.de

INTRODUCTION

To improve palatability and swallowability, it is common practice to administer oral medicines to children together with small amounts of dosing vehicles [1], which include various types of liquids and soft foods [2]. However, the commonly used vehicles vary both between product types and within vehicle types in terms of their nutritional composition and physicochemical properties. The aim of this work is to create a standard vehicle toolbox that can be used to simulate the variability in the composition and physicochemical properties of these vehicles. Standard vehicles that mimic the composition and physicochemical properties of fruit juices (simJuice) were chosen as a starting point.

MATERIALS AND METHODS

30 different fruit juices were characterised for their nutritional composition and physicochemical properties as described in [1]. All tests were performed in sextuplicate (n = 6) and with the exception of osmolality, the parameters were recorded at 25 °C. To avoid simulating each original vehicle of fruit juice, a Design of Experiments (DoE) approach was used, combining and varying the minima (MIN), maxima (MAX) and the centre point (CP) of the properties of the original vehicles, taking into account pH, buffer capacity, osmolality and surface tension (Table 1). Their physicochemical properties were determined using the same methods as for the original vehicles. For initial verification, *in vitro* dissolution experiments were performed with an original vehicle and a set of simJuice vehicles according to Freerks *et al.* [3].

Table 1. DoE for the development of the simJuice vehicles; Θ = centre point, - = minimum, + = maximum of target property.

Run	pH	Buffer capacity	Osmolality	Surface tension
1 ("CP")	Θ	Θ	Θ	Θ
2	+	-	-	+
3	-	-	+	+
4	-	+	+	-
5 ("MAX")	+	+	+	+
6	+	-	+	-
7	+	+	-	-
8 ("MIN")	-	-	-	-
9	-	+	-	+
10	Θ	Θ	Θ	Θ

RESULTS

Nine simJuice vehicles that represent selected combinations of MIN and MAX values of the target values, as well as a combination of their CP values were successfully developed. The liquid simJuice vehicles, for which all target values were either the MIN (simJuiceMIN), the CP (simJuiceCP) or the MAX (simJuiceMAX) values of the physicochemical properties were the three main simJuice vehicles. The respective target values for pH, buffer capacity, osmolality and surface tension were successfully met, exemplary shown for pH and osmolality in Figure 1. As can be seen from Figure 2, similar release profiles were obtained when simulating co-administration of furosemide mini-tablets with original and standard vehicles.

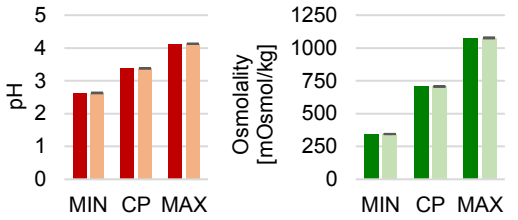

Figure 1. Target values (dark columns) and actual values (light columns, mean of n = 6(±S.D.)) for simJuiceMIN, simJuiceCP and simJuiceMAX.

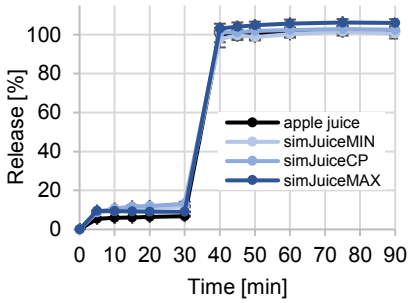

Figure 2. Furosemide release of the mini-tablets in simulated gastric (0-30 min) and small intestinal conditions (30-90 min) of infants when simulating tablet co-administration with original and standard vehicles for fruit juice; mean of n = 3(±S.D.).

CONCLUSION

With the overall goal of developing a global standard vehicle toolbox that can be used for *in vitro* studies to provide reliable information on drug-vehicle interactions, the present study successfully developed a set of standard vehicles that mimic the basic composition and various physicochemical properties of fruit juices.

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Abstract ID: 12

Individualised dosing using an innovative minitablet dosage manager

Jafar Shendi [1]
[1] OnDosis AB, GoCo House - Mölndal Sweden , j.shendi@ondosis.com, +46736827636

OBJECTIVE
Paediatric pharmacotherapy faces the challenges of formulation to address the willingness of the children to take their medication. Compared to regular-sized tablets and capsules, minitablet formulations do not only improve swallowability in children, but also enable more individualised dosing, which is desirable for a variety of therapies, e.g. from the aspect of safety, age-appropriateness, or weight-based dosing. The objective of this study was to evaluate the effectiveness of an innovative device technology to accurately dispense flexible doses of minitablet formulations with different physical characteristics. The investigational device is designed for commonly used minitablet formulations in the pharmaceutical industry, with tablet sizes ranging from approximately 2 to 3.5 mm. This presentation focuses on the initial proof of concept covering dispensing data from a subset of formulations as well as physical characterisation of the formulations in scope.

METHODS
The technology under evaluation is a handheld connected electromechanical device that is intended to dispense minitablets and consists of a control unit and a medicine-containing cartridge (currently under development by OnDosis AB, Sweden). Two coated mini-tablet formulations were included in the study. Physical characterisation of the formulations included: diameter-to-height (D/h) ratio measured in optic microscope, weight measurement using a digital scale, and hardness measured by dynamometer. For each dispensing test series, device cartridges were filled with approximately 1000 minitablets. In each test series, a minimum of 30 consecutive doses (ranging between 1 and 30 tablets per dose) were dispensed. A total of 855 doses and approximately 12060 minitablets were dispensed. Samples were inspected for damage before and after dispensing under optic microscope (x10 magnification).

RESULTS
Minitablet characteristics (formulation 1 and 2, average value): Diameter 2.1 and 2.1 mm, D/h ratio 0.9 and 1.0 , weight 8.8 and 7.4 mg, hardness 19.6 N and 21.2 N.

Dispensing accuracy: Formulation 1: 100% accuracy for dose sizes of 5 and 15 minitablets. For doses sizes 10, 20 and 30 minitablets, 10 doses out of 345 had a dispensing deviation of one minitablet, resulting in a total performance of 99.9% (as a function of total number of minitablets). Formulation 2: 100% dispensing accuracy for all tested dose sizes (1, 2, 3, 4, 6, 8, 12 and 24 minitablets/dose).

Visual inspection: No minitablets showed visible damage after dispensing.

CONCLUSION
The innovative dosage manager technology under evaluation has the potential to dispense reliably, accurately and without visible damage across the tested samples of formulations and enables a possibility for individual dosing therapies by delivering the specified dose for individuals. Further research with a wider range of minitablet characteristics and larger sample size is planned.

Abstract ID: 13

Investigating the influence of co-administered milk on the *in vitro* disintegration of mini-tablets with taste-masking coatings

Frank Karkossa; Esther-Sophie Poloni; Sandra Klein

University of Greifswald, Department of Pharmacy, Felix-Hausdorff-Straße 3, C_DAT, 17489 Greifswald, Germany
frank.karkossa@uni-greifswald.de

Introduction

Taste-masking is a common technique used to make medications with an unpleasant taste more palatable to patients. One approach to improve the taste of immediate release (IR) solid oral dosage forms is to use polymer coatings. After passing through the oral cavity, they should release the drug in the proximal gastrointestinal (GI) tract to ensure drug absorption. For poorly water-soluble compounds, drug dissolution in the GI tract is a critical process that might be improved by taking medication with a fatty meal or drink such as milk. However, concomitant intake of medications with different types of milk may also affect the dissolution of the coating polymer, preventing the drug from being released at the target site in the GI tract. The objective of this study was to examine the *in vitro* dissolution behavior of commonly utilized taste-masking coatings in response to milk types with different macronutrient profiles.

Methods

Five millimeter biconvex mini-tablets containing riboflavin as a model drug were produced using a rotary-type tablet press. Different polymer types were used as taste-masking coatings, which were processed by spraying coating liquids onto the mini-tablet cores applying three different target weight-gains using a drum coater. The drum-coating parameters were adjusted for each polymer. The disintegration of the coated mini-tablet formulations in different types of milk and milky drinks was evaluated using a novel disintegration setup based on a compendial reciprocating-cylinder apparatus. The onset of riboflavin release was an effective indicator of tablet disintegration. To determine the precise disintegration times, samples were collected from the disintegration medium and analyzed for the presence of riboflavin using a fluorimetry assay with excitation at 370 nm and emission at 530 nm.

Results

Results from the disintegration studies in various milk types showed that, as expected, both the coating type and level significantly influenced the disintegration time of the tested formulations. In terms of the macronutrient composition of the disintegration media, fat content was the most significant contributor to a delay in disintegration time. Disintegration tests in condensed milk, the medium with the highest fat content and 7.5% weight gain formulations, resulted in disintegration times that exceeded the total test duration of 15 min (Figure 1). Mini-tablets with HPMC/PEG or PVA/PEG coatings were the only formulations that ensured disintegration within 15 minutes. Interestingly, the dissolution of the PVA/PEG coatings was less sensitive to the media composition.

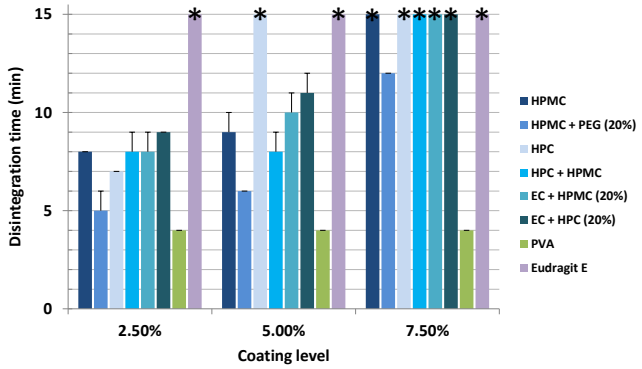

Figure 1: Disintegration times of mini-tablets with different taste-masking polymer coatings at different coating levels in condensed milk (10% fat), means of n=3 ± S.D., *indicates a disintegration time of > 15 min.

Conclusion

The results of this study indicate that the type of milk co-administered with medication can have a substantial impact on the dissolution of taste-masking coatings and the initiation of *in vivo* drug release. These findings highlight the importance of considering both drug properties and formulation characteristics when providing dosage recommendations. Additionally, the study results can be beneficial in choosing coating polymers that are less prone to variations in dosing conditions, making them more suitable for formulations of poorly water-soluble compounds that can benefit from co-administration with milk to improve bioavailability.

Abstract ID: 14

Multifunctional excipients for pediatric oral suspensions

Pawel Balcerzak; Liliana Miinea; Elena Draganoiu; Mariona Venceslao
Lubrizol Life Science, 9911 Brecksville Road, Cleveland, OH, USA pawel.balcerzak@lubrizol.com, liliana.miinea@lubrizol.com, elena.draganoiu@lubrizol.com, mariona.venceslao@lubrizol.com

Oral solid dosage forms remain the preferred method of drug administration, however, the pediatric population has poor compliance with tablets and capsules. Oral suspensions are a viable alternative dosage form with clear benefits in dosing flexibility and ease of swallowing. Formulating suspensions does not come without challenges, including particle growth, sedimentation, caking and adhesion of particles to the container, which affect dispersion uniformity, even upon vigorous shaking, potentially leading to dosing errors. To offset these challenges the selection of excipients, especially the suspending agent is critical. Carbopol® polymers are crosslinked polyacrylic acid polymers excipients that are efficient rheology modifiers at low inclusion levels and exhibit high yield value being effective suspending agents.[1] Carbopol polymers have mucoadhesive properties[2] which can bring additional benefits such as protective tissue coating and improve drug bioavailability. Our research was focused in using the multifunctionality of Carbopol® polymers to develop a sugar-free, *no-spill* "*permanent suspension*" (no need for shaking) formulation with improved sensorial properties.

Materials
Acetaminophen, Carbopol® 971P NF polymer; sorbitol 70%; sucralose; flavors; methyl paraben sodium; polysorbate 80; sodium hydroxide; sodium hydrogen phosphate. Two commercial suspensions were used as benchmarks.

Methods
Suspension preparation: Part A: acetaminophen, deionized water, polysorbate 80. Part B: sucralose, Carbopol® polymer, sodium hydrogen phosphate, sorbitol, paraben salts, sodium hydroxide (10% aq), deionized water. Part A was added to part B under mixing followed by flavor and color addition. The target dose strength was 250 mg acetaminophen/5 mL suspension. The inclusion level of Carbopol polymer (0.5% - 1%) and its degree of neutralization, as well as the concentration of electrolytes in the formulation (sodium hydrogen phosphate 0% -1%) were varied and their impact on the suspension properties evaluated. Viscosity of the suspensions was measured using Brookfield viscometer. *The no-spill* property was qualitatively estimated by placing the formulations in a spoon and shaking/rotating the spoon. The mucoadhesive properties of the suspensions were measured using Lubrizol internally developed method.[2]

Results
The acetaminophen suspension preparation was achieved using a cold process. Viscosity of the formulations was controlled by adjusting the level and degree of neutralization of Carbopol® polymer and the level of electrolytes in the formulation. The viscosity values ranged from 2000 cP to 13000 cP.
Formulations containing Carbopol® polymer exhibited higher retention (up to 30 minutes) on the mucoadhesive membrane (better mucoadhesion) than the benchmark formulations (less than 2 minutes retention). This property can be translated in increase sensorial benefits such as protective tissue coating (soothing effect). Carbopol® polymers imparted no-spill properties to oral suspension formulations when compared to benchmark formulations without Carbopol® polymers. The no-spill effect was more pronounced with higher inclusion level of Carbopol® polymer. The suspensions prepared with Carbopol® polymer showed no sedimentation for the duration of the study, with no need for shaking to resuspend the drug.

Conclusion
Carbopol® polymers enabled a sugar-free, *no-spill* "*permanent suspension*" (no need for shaking) formulation with mucoadhesive properties. The model drug used was acetaminophen, however the formulation is expected to be applicable to a broad range of drugs. The suspension preparation was achieved using a cold process, which allows for time and energy savings and ease of scalability and manufacturing.

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2. Lubrizol webpage Mucoadhesive-Polymers-in-Pharmaceutical-Formulations.pdf (lubrizol.com)

Abstract ID: 15

From Bench to Bedside: Solid-State Extrusion 3D Printing of Sulfamethoxazole & Trimethoprim for Clinical Translation

M. Stoops[1], M. Annereau[1], S Ramos[1], F.-X. Legrand[2], R. Mazet[3], A. Rieutord[1]

[1] Clinical Pharmacy Department, Gustave Roussy Cancer Campus, 94800 Villejuif, France
[2] Université Paris-Saclay, CNRS, Institut Galien Paris-Saclay, 91400, Orsay, France
[3] Grenoble Alpes University Hospital Center, 38700, La Tronche, France

Introduction:

Sulfamethoxazole/Trimethoprim association (SMX/TMP ; Bactrim®) is a cornerstone of pediatric infectious prophylaxis care, especially in oncology, providing essential treatment against infections[1–3]. However, the palatability of Bactrim's oral suspension poses significant challenges, often resulting in poor adherence among pediatric patients[4,5]. The unpleasant taste, documented in various studies, leads to suboptimal dosing, increased infection risk, delayed treatments, and potentially compromised survival outcomes[6,7]. Pediatric dosing ranges for Bactrim span from 400/80 mg/day to 800/160 mg 3 times/week, requiring a formulation that balances efficacy and palatability. To address these challenges, we explored the development of a 3D-printed sulfamethoxazole/trimethoprim formulation. Our goals were to provide a customizable pharmaceutical form with improved taste, microbiological security, chemical stability over time, and robust physical stability before and after printing, allowing for on-demand production.

Method:

Formulations were designed in accordance with preformulation work focused on the poor palatability/solubility of the active ingredients, then printed using a 3 dimensions printer (MEDIMAKER 2) with semi-solid extrusion technology. The chosen formulation underwent rigorous monitoring to ensure safety for use in children. A study of physical stability (mass, organoleptic and rheological characteristics, water loss) and chemical stability (content and appearance of degradation products) was conducted on the printing inks contained in syringes and on the printed gummies in accordance with ICH guidlines[8]. Characterization of inks and gummies through rheology, thermogravimetry, differential scanning calorimetry (hyperDSC), X-ray powder diffraction and Fourier-transform infrared microscopy, accompanied this formulation process. Finally, a palatability study involving 12 healthy adults was conducted to compare the developed formulation with the currently used oral suspension in children. Using a hedonic sensory approach, the texture, sweetness, and immediate/delayed bitterness were compared.

Results:

The formulation process focused on reducing prolonged bitterness using masking techniques, polymer dispersion and bilayer gummies, separating the two APIs. The gummies demonstrated the expected chemical and physical stability, with no degradation products appearing after two months, and optimized drying conditions allowing for packaging 24 hours after printing. Microbiological stability was confirmed by low water activity ($a_w < 0.5$). *In-vitro* dissolution indicated bioequivalence with commercial tablets, and the palatability study revealed a preference for the gummies over the traditional oral suspension, with a significant reduction in bitterness ($p < 0.01$). These results were supported by a characterization aimed at addressing the practical needs of the pharmacist, at the service of the patient. Surprisingly when gummies were formulated in two distinct layers of the active ingredients it resulted in significantly reduced bitterness, a key finding for improving patient adherence.

Conclusion:

A palatable and stable over 6 months gummies formulation, suitable for pediatric populations, was developed (soft, reduced bitterness, suitable sweetness). Considering the bitterness of TMP and its enhancement by colocalization with SMX within the solid dispersion, both single-layer and bilayer solutions were proposed. Following successful initial use in this population, a clinical study is currently being set up.

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Abstract ID: 16

Establishing a National Priority List of Pediatric Drugs in Canada – A Case for Close Collaboration with Regulators

Raphael Kraus[1], Charlotte Moore-Hepburn[2], Margaret Czesak[3], Alysha Croker[3], Myles Leach[3], Wardah Vacher[3], Denis Lebel[4], Hélène Roy[4], Sophie Bérubé[5], Catherine Litalien[1]

[1] Goodman Pediatric Formulations Centre (GPFC) and Department of Pediatrics, CHU Sainte-Justine, Montreal, Canada, raphael.kraus.med@ssss.gouv.qc.ca, catherine.litalien.med@ssss.gouv.qc.ca
[2] Child Health Policy Accelerator, Department of Paediatrics, Hospital for Sick Children and Canadian Pediatric Society, charlotte.moorehepburn@sickkids.ca
[3] Centre for Policy, Pediatrics and International Collaboration, Health Products and Food Branch, Health Canada, margaret.czesak@hc-sc.gc.ca, alysha.croker@hc-sc.gc.ca, myles.leach@hc-sc.gc.ca, wardah.vacher@hc-sc.gc.ca
[4]GPFC and Department of Pharmacy, CHU Sainte-Justine, Montreal, Canada, denis.lebel.hsj@ssss.gouv.qc.ca helene.roy.hsj@ssss.gouv.qc.ca
[5] GPFC of the CHU Sainte-Justine, sophie.berube.pharm.hsj@ssss.gouv.qc.ca

Introduction: In 2020, Health Canada (HC) developed the Pediatric Drug Action Plan (PDAP) to address the many challenges/barriers to accessing medicines for children, with the ultimate vision that children and youth in Canada be consistently treated with the medicines they need in age-appropriate formulations.
Methods: In 2022, a Pediatric External Reference Group (PERG; comprised of 10 pediatricians and pharmacists with representation across Canada as well as 2 observers from Health Technology Assessment (HTA) organizations) was established to provide expert guidance and formal recommendations to HC. The PERG fulfilled its mandate by consulting with the broad Canadian pediatric healthcare community to identify specific pediatric medicines needed to address areas of unmet need and engaging in a sequential process of nomination and prioritisation. A 60-day nomination period began in mid-March 2023. Drugs were nominated using a 5-question online form on an HC-hosted website. Specifically, the pediatric healthcare community was invited to nominate drugs that address diseases/disease areas with high unmet medical need(s) and/or drugs lacking commercially-prepared child-friendly formulations. Each nominated drug was considered eligible if 1) it was approved for use in children for the requested indication in another comparable foreign jurisdiction, 2) it was not already approved or under review by HC for the requested indication, 3) it had not previously been denied approval in Canada. Submissions lacking necessary requested information (i.e. concentration, strength and/or form) were excluded. Eligible drugs were categorised based on the status of the active substance (AS)/medicinal ingredient (MI) for the requested indication and/or formulation as follows[1]:

- New drug: AS/MI not authorised by HC as a prescription product (i.e. unavailable to both adults and children in Canada)
- New indication: AS/MI currently available in Canada, but lacking the requested indication in children
- New formulation only: AS/MI currently available with a pediatric indication in Canada but lacking a child-friendly formulation
- New indication and formulation: AS/MI currently available in Canada but lacking both the requested pediatric indication and a child-friendly formulation

Although all eligible nominated drugs were recognized as important, HC mandated that the PERG develop a rigorous and transparent method to identify 40 products of highest priority. We therefore consulted pharmacists and relevant pediatric subspecialist physician's groups to identify the top two priority drugs per therapeutic area (TA) to be included in the final list (x/40). In parallel we applied strict objective and subjective scoring criteria to calculate a total priority score for each nominated drug (higher scores representing greater urgency). Those drugs with the greatest total priority scores (y/40) were then included to complete a total of 40 drugs ($x + y = 40$). Data analysis was performed by HC with the assistance of the GPFC.
Results: There was a total of 905 nominations with 196 drugs nominated only once and 154 drugs submitted by multiple nominators (ranging from 2-18) for a total of 350 of which 118 met all eligibility criteria. Drugs selected as top priorities in each TA by subspecialists and pharmacists (n=32) were automatically included on the draft list of 40 drugs. The remaining 8/40 included drugs were selected based exclusively on total priority score irrespective of TA. The resulting draft list included 11 new drugs, 5 drugs requiring new indications, 10 drugs in need of new formulation only and 14 in need of a formulation and a new indication. The TAs of infectious disease (n=7), hematology/oncology (n=5), neurology (n=5), and psychiatry (n=5) together accounted for more than half of the 40 included drugs.
Conclusion: The NPLPD initiative—the first of its scale in Canada—represents the culmination of years of dedicated effort and direct collaboration between the government of Canada and the pediatric medical community, a truly exceptional partnership for a mid-sized pharmaceutical market such as Canada. Regarding next steps, HC will lead a public consultation as well as targeted consultation with industry, provincial and territorial governments, and HTA organizations over the summer/fall of 2024. Formal publication of the list is expected during winter 2024-2025. Regulatory or policy changes could be considered to realize meaningful change in access.

[1] Note: these classifications are unrelated to the submission or application types used by HC and are not based on the specific market authorization of any specific product. They are descriptive definitions meant for a broad audience.

Abstract ID: 17

Forging New Partnerships to Advance Pediatric Formulations: An Update on NIH Activities Supporting Product Development

Sheryl Zwerski[1]; James Cummins[2]

[1] Division of AIDS/National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health, 5601 Fishers Lane, Bethesda, MD 20892, zwerskis@niaid.nih.gov, +1 301-402-4032

[2] Division of AIDS/National Institute of Allergy and Infectious Diseases, U.S. National Institutes of Health, 5601 Fishers Lane, Bethesda, MD 20892, cumminsje@nih.gov, +1 240-292-4800

INTRODUCTION

The Division of AIDS (DAIDS), a division of the National Institute for Allergy and Infectious Diseases (NIAID) within the U.S. National Institutes of Health (NIH), has undertaken a comprehensive program to support and advance pediatric formulations through multiple funded activities expected to start in mid-2024. These activities are supported by a contract (Resources to Advance Pediatrics and HIV Prevention Sciences; RAPPS) with preclinical resources intended to fill gaps in early product development and advance products into clinical testing.

METHODS

A major RAPPS activity is the development of a pediatric oral film formulation for Rifapentine intended for a minimal age range of 0-2 years. The Target Product Profile (TPP) and an overall product development plan are currently being refined. Through a partnership with the IMPAACT clinical network that is funded by DAIDS, discussions are ongoing to determine the clinical testing program. IMPAACT has the global reach and the maternal and pediatric HIV and TB expertise needed to support these studies. Assuming successful film development and clinical testing, DAIDS will be identifying partners to take on large scale product manufacturing and implementation/roll-out of the final pediatric product.

Another RAPPS activity is a pilot project to determine if machine learning and artificial intelligence can be used to enhance the EuPFI STEP (Safety and Toxicity of Excipients for Pediatrics) database by expediting data entry and expanding the functionality of user queries. If successful, these tools could increase the number of available excipients and improve its overall usefulness to product developers.

RAPPS is also supporting two projects that could potentially enable development of a universal bitter blocker for pediatric formulations. This activity represents a high-level commitment made by DAIDS to improve child friendly formulations and is included in the Rome 6 Pediatric Action Plan on Child Health.

Finally, in coordination with WHO's Global Accelerator for Pediatric formulations (GAP-f), DAIDS has committed to using the RAPPS contract to co-create a pediatric technology innovation hub. The hosting functions of the hub will include horizon scanning of available technologies, a suitability and feasibility assessment, and technology matching to prioritized drugs. DAIDS is currently in discussions with WHO to define the basic structure and major workstreams of the technology hub, including potential collaborating partners.

CONCLUSIONS

As described above, NIAID has initiated several key projects designed to advance the field of pediatric formulations. These activities, through partnerships with organizations such as EuPFI and WHO, include development an oral film formulation, expansion of excipient safety information, advancement of bitter blocking technology, and matching innovative technologies to drugs prioritized for pediatrics.

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Abstract ID: 18

Development and evaluation of omeprazole and esomeprazole magnesium-based delayed-release tablet formulations for paediatric use

Stella Roumpou, Chrystalla Protopapa, Angeliki Siamidi, Marilena Vlachou
Division of Pharmaceutical Technology, Department of pharmacy, National and Kapodistrian University of Athens, Greece

INTRODUCTION

Esomeprazole is the S-isomer of Omeprazole, which is a racemate of the S- and R-enantiomer. Esomeprazole has been shown to inhibit acid secretion to a similar extent as Omeprazole, without any significant differences between the two compounds in vitro. They both exert their stomach acid-suppressing effects by preventing the final step in gastric acid production by covalently binding to sulfhydryl groups of cysteines found on the (H+, K+)-ATPase enzyme at the secretory surface of gastric parietal cells. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus (1). This action, makes the two compounds very potent candidates for pathological conditions, such as gastroesophageal reflux disease (GERD) and the treatment of acid-related diseases of children, which are common conditions seen in clinical practice (2). Moreover, these agents can produce faster and more complete symptomatic relief compared to other medicines (3). With respect to their dosage, adults are usually treated with 20 mg once a day before a meal, and may be taken for more than 8 weeks for certain conditions. The dose for children, 1 year of age and older, is based on body weight and must be determined by the paediatrician. In view of the fact that currently there are no any children tailored-made formulations, we report herein our preliminary studies on the preparation and in vitro release characteristics of paediatric oral tablets of Omeprazole and Esomeprazole, using a gastroresistant coating. Children differ from adults in many aspects including drug administration, toxicity, and taste preference. These particularities lead to the reduced production of paediatric medicines. Many formulations are not suitable for children, which leads to the unlicensed use of adult medicines (4).

MATERIALS

Omeprazole and Esomeprazole magnesium were purchased from Tokyo Chemical Industry Co., Ltd. Apart from the active ingredients, the tablets were comprised of sodium alginate (medium viscosity), lactose monohydrate, magnesium stearate and Eudragit L100-55.

METHODS

The Omeprazole and Esomeprazole magnesium matrix tablets were prepared by direct compression, using the above excipients. The samples were analyzed using a UV spectrophotometer at λmax 295 nm (pH 4.5) and λmax 301 nm (pH 6.8), in the case of Omeprazole, and for Esomeprazole magnesium, at λmax 293 nm for both, pH 4.5 and 6.8. The corresponding dissolution curves were prepared.

RESULTS AND DISCUSSION

The % release curve of Omeprazole and Esomeprazole magnesium versus time from F1 were constructed. In both cases, an almost 10% release was observed at pH 4.5, due to the inclusion of Eudragit L100-55 in the tablets' dry coating. The formulation containing Omeprazole, showed an almost quantitative release at t=105 min, whereas the formulation containing Esomeprazole magnesium, 88% release, at t=150 min. This delayed and lower release of Esomeprazole magnesium from various multiparticulate-based branded enteric-coated pellets or granules has been previously reported in the literature (5).

CONCLUSION

The developed 5 mg paediatric formulations of Omeprazole and Esomeprazole magnesium seem to satisfy the requisite for children use release profile of these compounds. Yet, more experiments need to be conducted to verify this hypothesis.

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Abstract ID: 19

Achieving individualised dosing with pellet formulations combined with an innovative device technology

Emelie Svensson[1]; Linus Engdahl[2]; Abraham Manuel James[3]
[1] OnDosis AB, Gemenskapens gata 9, 431 53 Mölndal, Sweden, e.svensson@ondosis.com
[2] OnDosis AB, Gemenskapens gata 9, 431 53 Mölndal, Sweden, l.engdahl@ondosis.com
[3] OnDosis AB, Gemenskapens gata 9, 431 53 Mölndal, Sweden, a.james@ondosis.com

INTRODUCTION
Today, solid oral medicines are often presented as relatively large tablets or capsules at one or a few dose strengths that do not offer the possibility for fine dose adjustments, which is often desirable in pharmacological treatment of children where treatment efficacy needs to be carefully balanced against side-effects. Alternative dosage forms such as small pellets have the potential to offer more flexibility in dosing, easier titration, and more precise doses in-between the doses offered in currently available solid formulations. The aim of the present study was to evaluate the dosing accuracy and precision of an innovative device technology that was designed to enable individualised and flexible dosing of medicines formulated as pellets.

METHODS
The technology under evaluation is a handheld electromechanical device intended to hold and dispense flexible doses of medicines formulated as pellets or granules (OnDosis Dosage Manager, currently under development by OnDosis AB, Mölndal, Sweden). The device consists of a reusable control unit with embedded software that controls a flexible dispensing mechanism, and a disposable medicine-containing multi-dose cartridge. Each cartridge consists of two chambers, from which one or two medicine formulations can be dispensed simultaneously with adjustable dose sizes at predetermined fine dose increments within safety limits determined for each specific medicine.

Forty-four (44) cartridges were filled with placebo pellet formulation produced by fluid bed coating technology (mean pellets size 654µm [D50], span value 0.154). Thirty doses were dispensed from each cartridge, representing either a 'high' (300 mg target delivered dose, TDD) or a 'low' (50 mg TDD) dose size (total mass). Each dispensed dose was weighed using a laboratory balance with 0.01 mg accuracy. For half of the samples, pellets dispensed from each chamber within a cartridge (corresponding to 50% of the total TDD, i.e. 150 mg and 25 mg, respectively) were weighed separately.

RESULTS
The dispensing performance for 'high' and 'low' doses was Mean 310.5 mg (SD 7.1 mg, n=324) and Mean 49.1 mg (SD 1.9 mg, n=329), respectively, which represents on average 103% and 98% of the TDD.

The dispensing performance per cartridge chamber was Mean 159.3 mg (SD 5.3 mg, n=330) and Mean 158.9 (SD 5.2 mg, n=322) for the 'high' dose, and Mean 24.8 mg (SD 1.6 mg, n=330) and Mean 25.0 (SD 2.1 mg, n=328) for the 'low' dose.

CONCLUSION
The results suggests that the technology under evaluation can dispense dose sizes between 50 and 300 mg total mass with high accuracy and precision both for medicines consisting of a single pellet formulation and for medicines where the medicine consists of two separate formulations at 50:50 ratio. Thus, it is believed that medicines consisting of one or two pellet formulations combined with device technology has the potential to introduce finer and more individualised dose adjustments compared to traditional tablets and capsules, where every dose strength requires its specific formulation.

Abstract ID: 20

Pan-India study on user perspectives of minitablets for paediatric treatments

Soniya Notani; Elisa Alessandrini; Smita Salunke

UCL School of Pharmacy, United Kingdom, soniya.notani.21@ucl.ac.uk ; elisa.alessandrini@ucl.ac.uk; s.salunke@ucl.ac.uk

Introduction: Minitablets have been identified as a promising dosage form for the paediatric population (1). However, there is limited evidence-based data available on acceptability of minitablets, particularly concerning the size and number of minitablets, ease of handling, ease of administration and choice of packaging. Additionally, there is insufficient information on whether there are differences in user opinions based on socio-economic status, health condition, or level of experience. Existing literature also identifies that healthcare workers and caregivers are often reluctant to adopt new dosage forms (2). The slow uptake of these new dosage forms by policy makers in low- and middle-income countries (LMICs) is one of the challenges in accessibility and distribution of new dosage forms. Hence, this project aims to investigate user perspectives from LMICs on using minitablets versus conventional tablets for paediatric treatments.

Methods: A descriptive cross-sectional pan-India study was conducted with parents of children aged between 0 to 12 years using a paper-based survey. Parents were recruited from two main settings: schools and hospitals. They were contacted via email/network and provided with information sheets. Ethical approvals were obtained from these institutions. A pilot questionnaire was developed to assess various user aspects such as socioeconomic status, health condition, perceived swallowability wr.t to number and size, types of minitablets (e.g.: oro-dispersible etc), administration methods, choice of packaging, ease/comfort of handling minitablets and willingness to use minitablets over conventional tablets. Responses from hospitals were recorded via one-to-one interview whereas workshops were conducted in schools. The recruited parents responded to the questionnaire on behalf of their children aged 0 to 12 years. Various sizes of minitablets and conventional tablets (1.5mm, 3mm, 4mm, 6mm, 8mm, 10mm and 12mm), quantities (5, 10, 20, 50, 100 and 200) of minitablets and different types of packaging (stick pack, sachets, capsules and unit dose dispenser) were shown to parents during the study. For this abstract the results are confined to parents only.

Findings: A total of 60 parents were recruited from schools and hospitals, comprising 45% first-time parents and 55% second-time parents. 52% of the parents were classified as middle or upper middle class, while 48% fell into the lower middle-class category. 45% parents reported their children to be either healthy or experienced acute illnesses, while 55% reported their children had chronic conditions or were recovering from surgery.

When asked for prior experience with medicines, 60% parents reported using liquids, primarily for 1-8 years old and 40% reported taking solid dosage forms such as tablets or capsules. The children taking solid forms were predominantly between 2-11 years. In terms of minitablets, 40% of parents reported that they or their children had previously seen or taken minitablets. Among all participants, 67% were willing to administer 1.5mm tablets, 26% were willing to administer 3mm tablets, and 7% were willing to administer 4mm tablets. Of the 67% who chose 1.5mm tablets, the majority of children were aged 2-8 years. For the 26% who chose 3mm tablets, most were from the 6-11 years age group, and for the 7% who chose 4mm tablets, the majority were aged 9-12 years. The parents reported the ability of taking minitablets if fewer than 10 tablets were administered at a time, especially for 1.5mm. The willingness to administer number of minitablets varied for as per socioeconomic status particularly for 1.5mm size tablet. 47% of lower middle-class parents were willing to administer a greater number of tablets (up to 50) as compared to upper middle-class parents who stated willingness for up to 10 tablets only. Additionally, the health condition of the children also seems to have an effect on selecting the size of the minitablet. Majority (59%) parents of chronically ill children selected 3mm and 4mm sized minitablets while the parents (74%) with healthy children chose 1.5mm.

With regards to ease of handling minitablets, 30% of parents reported difficulty with 1.5mm tablets; while all other sizes were described to be easy to handle. Socio-economic status influenced this perception, 70% of lower middle-class participants said they could easily handle 1.5mm minitablets once removed from the packaging, whereas only 40% of upper middle-class participants found them easy to handle. For the type of minitablet, overall, 55% of Participants said they preferred a minitablet that melts on the tongue and 45% would prefer a tablet that dissolves in water. Out of which, 57% of children recovering from chronic illnesses or surgery preferred minitablets that melt on the tongue, while 56% of healthy children favoured minitablets that dissolve in water. Depending on the socio-economic status, 64% of children from the lower middle-class category said they favour minitablets that melt on the tongue, whereas for children from the upper middle-class category 66% of the children preferred minitablets that dissolve in water. With regards to administration of minitablets with soft food the majority (46%) of parents with children aged 1-8 years used chocolate, ice cream, milk, and jelly, 33% preferred juice or water for age 12 months- 5 years, and 21% reported using dal (lentil soup) and rice for ages 5-12 years. More than 50% of parents from lower-income background employed manipulation strategies to encourage their children to take medicine, while more than 80% of parents from high income background said that their children eventually take tablets after some initial resistance. Regarding the packaging for minitablet 35% of parents selected a device dispensing one tablet at a time, while 65% choose a package containing multiple tablets they could count and administer. Among these, the majority (70%) selected stick packs followed by sachets (20%) and capsules (8%) as their preferred packaging for minitablets. With regards to administering one conventional tablet vs multiple minitablets at once, it was seen that majority of parents were willing to administer minitablets as opposed to one conventional tablet irrespective of size of the tablet (5mm – 12mm).

Conclusion: In conclusion, this study underscores that the acceptability of dosage forms is multifaceted, influenced by socio-economic status, parental education, affordability, prior experience, perceived benefits, ease of use, cultural relevance, and the availability of support and training. Factors such as tablet size, the number of minitablets to be administered at once, the child's health condition, packaging design, and ease of handling minitablets outside the package are pivotal in shaping preferences and practices. Socioeconomic status and parental education played a role in medication administration strategies. The pilot phase of this research identified significant gaps in survey methodology, particularly in effectively correlating tablet characteristics with tablet number and size, the use of food, association between all these parameters in relation with socioeconomic status as well as treatment experience. Moving forward, revisions to the questionnaire are essential to accurately capture these correlations. Future plans include expanding the study to encompass LMICs, conducting a comprehensive survey across India, other LMICs, and European nations. This expanded scope aims to compare responses from parents, caregivers, and children, thereby deepening our understanding of paediatric preferences and fostering advancements in minitablet administration and manufacturing practices.

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Abstract ID: 21

Parent acceptability of different forms of oral hydrocortisone

Dr Jennifer Duncan[1], Dr Louise Bracken[1], Gabrielle Seddon[1], Amy Hill[1], Dr Amy Nuttall[1], Ellie Clarke[1], Pauline Blundell[1], Sarah Madine[1], Andrea Gill[1]

[1] Alder Hey Children's NHS Foundation Trust (AHFT), Liverpool, UK. Contact Andrea.Gill@alderhey.nhs.uk

INTRODUCTION

Hydrocortisone is used as a long-term replacement therapy in Congenital Adrenal Hyperplasia (CAH). Accurate dosing, patient acceptability, and ease of administration of the available dosage forms are vital as treatment is life-long [1]. Prior to the introduction of a licensed granule formulation (Alkindi®) in April 2019, the use of unlicensed or off-label hydrocortisone in AHFT, was widespread. The aim of this audit was to assess the acceptability of different formulations of oral hydrocortisone to children and parents.

METHOD

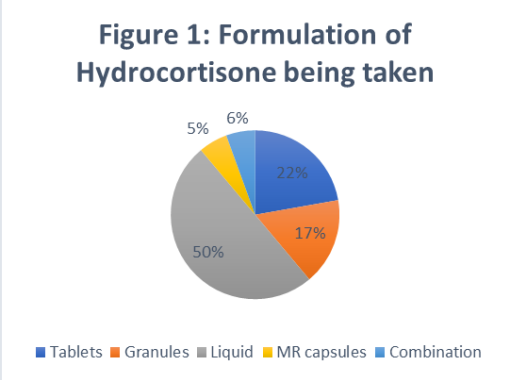
This clinical audit was registered with the Trust in April 2021 (No.6367). The questionnaire was developed using Microsoft Forms. With permission, it included the validated Pediatric Oral Medicines Acceptability Questionnaires (P-OMAQs) 7-day recall version for caregivers (P-OMAQ-C) [2]. Most questions utilised a Likert rating scale, with 5 being positive and 1 being negative. Formulations with a score of 3 or above were considered acceptable. Questionnaires were piloted with one family.

Patients under the care of AHFT with CAH, aged 6 months to 17 years and taking an oral form of hydrocortisone were included in the audit. Non-UK residents, non-English speaking and non-classical CAH patients were excluded.

KEY FINDINGS

Data collection took place between 1st February 2022 and 1st May 2023. Thirty-eight eligible patients were identified. Nine families were unable to be contacted and excluded. 18 of the 29 remaining families completed the questionnaires (response rate: 62%).

- Patients were aged 1 to 17 (mean 8.1, median 7, IQR 7) years; 13 were female (72%).
- Families obtained their supply of hydrocortisone from their GP (56%) or a combination of their GP and hospital (33%).
- Current hydrocortisone formulations are shown in Figure 1.
- Seven out of 18 (39%) families reported changing formulation(s). Reasons provided for changing to an alternative are shown in Table 1.
- Parents rated overall acceptability of their current formulation of hydrocortisone using the P-OMAQ-C standard questions. This included acceptability from the perspective of a parent (frequency of dosing, amount to give, smell) and their child's perspective (frequency of dosing, size of dose, smell, taste, mouth-feel and ease of swallowing). Mean acceptability scores reported are shown in Table 2.
- Acceptability scores from the perspective of the parent and acceptability for their child was the same for 9 patients (50%), differed by one point in 5 patients (28%) and by more than one point in 4 patients (22%).



Response	Number of responses (n=11)
Difficult to obtain prescription (3/11)	3
As advised by medical team (5/11)	5
Difficult to give the medication to my child (3/11).	3

Table 1: Responses to question: As a parent, what was your reason(s) for switching the type of hydrocortisone being taken? You can select more than one answer, if needed.

CONCLUSIONS

Assessment of acceptability of medicines for children in a real-world setting is possible. Parents described difficulties in obtaining, storing, and administering oral hydrocortisone, however, all rated their child's current hydrocortisone formulation as acceptable. Parent and child acceptability differed in 50% of cases.

Dosage Form Type	Mean acceptability score (n=18)				
	Liquid (n=9)	Tablet (n=4)	Granules (n=3)	Capsule (n=1)	Comb'n (n=1)
	Mean Score				
Acceptability from parent's perspective	4.4	4.5	4.7	5.0	3.0
Acceptability for their child	4.7	4.8	2.7	3.0	5.0

Table 2: Parent acceptability rating for different Hydrocortisone formulations

ACKNOWLEDGEMENTS

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Abstract ID: 22

Stability Study of Pediatric Oral Suspensions Indicated in the Treatment of Cardiovascular Disease

Courtaney Davis[1]; Kendice Ip[1]; Daniel Banov[1]; Maria Carvalho[1]; Fabiana Banov[1]; Oleksandr Zdoryk[2]

[1] Department of Research and Development, Professional Compounding Centers of America, Houston, Texas, United States

[2] Department of Pharmaceutical Technologies and Quality Assurance of Medicines, Institute for Advanced Training of Pharmacy Specialists, National University of Pharmacy, Kharkiv, Ukraine

Introduction

The purpose of this study was to investigate the physicochemical and microbiological stability of three compounded pediatric oral cardiovascular suspensions: captopril (1 mg/mL and 5 mg/mL), hydrochlorothiazide (5 mg/mL and 10 mg/mL), and metoprolol (1 mg/mL and 10 mg/mL) formulated with a commercial oral suspending vehicle (PCCA SuspendIt). These active ingredients belong to different pharmacological groups and are used to treat a variety of cardiovascular conditions. Commercial pharmaceutical forms of these drugs are not available for pediatric patients, leaving a gap in dosing options. Therefore, the primary means of serving this population is through extemporaneous compounding of oral suspensions.

Method:

Ultra-high-performance liquid chromatography (UHPLC) methods were developed and validated for the determination of the chemical stability of captopril, hydrochlorothiazide and metoprolol in the oral suspending vehicle. Various forced degradation conditions were employed, including acidic, basic, oxidative, and heat degradation. The results revealed that potential interfering degradants do not affect the analytical peaks of the drug substance, and the factors contributing to the significant degradation of the drug substance in the suspension were identified. Test suspensions were prepared for each active ingredient (two concentrations) and evenly distributed into 4 oz prescription oval amber plastic bottles. Hydrochlorothiazide and metoprolol test suspensions were stored in an environmentally controlled chamber at a relative humidity of 60±5 %, temperature of 25±2°C. Captopril test suspensions were stored in a laboratory refrigerator at a temperature of 5±3°C. For the stability study of the suspensions, one test bottle was taken from the place of storage at predetermined time points: 0, 7, 14, 30, 60, 90, and 180 days. Physical properties such as pH, color/appearance and odor were also observed. All measurements were performed in duplicate. The determinations obtained on day 0 were set as baseline for comparison purposes. Antimicrobial efficacy tests were performed to control microbial growth during storage. This test was conducted on 0, 90 and 180 days of storage, in accordance with the USP Chapter <51> Antimicrobial Effectiveness Test.

Results:

Captopril showed a degradation of 20.04% under the influence of heat, which indicates sensitivity to elevated temperatures and justifies the choice of refrigerator as storage condition. Captopril also showed susceptibility to oxidative conditions, which emphasizes the need to use a tightly sealed closure system. Hydrochlorothiazide showed a degradation of 20.31% under acidic conditions, which emphasizes the need to control the pH in the formulation during extemporaneous compounding. This study demonstrates the robust stability of the compounded pediatric oral cardiovascular suspensions formulated with the commercial oral suspending vehicle. The chemical stability of the captopril, hydrochlorothiazide, and metoprolol suspensions remained within the acceptable range of 90-110 %. All suspensions kept their organoleptic characteristics, namely color/appearance and odor. The pH measurements were all within the expectations, as follows: 3.07-3.28 for captopril; 3.14-3.46 for hydrochlorothiazide; and 3.81-4.09 for metoprolol. Antimicrobial susceptibility test results (Aspergillus brasiliensis, Candida albicans, Pseudomonas aeruginosa, Staphylococcus aureus, and Escherichia coli) were consistently approved (pass) for the three active ingredients. These results underscore the versatility of using a suspending vehicle in the formulation of pediatric oral cardiovascular suspensions, providing compounded alternatives for captopril, hydrochlorothiazide, metoprolol tartrate at various strengths with a beyond-use-date that meets desired stability criteria.

CONCLUSION

This study demonstrates that the compounded pediatric oral cardiovascular suspensions are physically, chemically and microbiologically stable for 180 days for captopril (refrigerator), and hydrochlorothiazide and metoprolol tartrate (room temperature). This study provides a viable compounded alternative for hydrochlorothiazide, metoprolol tartrate and captopril in a liquid dosage form with an adequate beyond-use-date date to meet patient needs. The study's documentation of stability over a bracketed concentration range for each formulation increases flexibility for compounding pharmacists in customizing pediatric cardiovascular suspensions. This flexibility ensures that healthcare providers can tailor formulations to meet specific patient needs while maintaining required stability and safety standards.

Abstract ID: 23

Predictive dissolution testing of a novel taste-masked multiparticulate dosage form of artesunate/amodiaquine for paediatric malaria therapy

Frank Karkossa[1]; Fang Liu[2], Sandra Klein[1]

[1] University of Greifswald, Department of Pharmacy, Felix-Hausdorff-Straße 3, C_DAT, 17489 Greifswald, Germany
[2] University of Hertfordshire, Department of Clinical, Pharmaceutical and Biological Sciences, College Lane, Hatfield AL10 9AB, UK

Introduction

Malaria is a global health burden with millions of infections. Currently, more than half a million deaths are reported each year. In more than 75% of cases these are children under the age of 5. Commonly used combination therapies for malaria treatment in Africa include artesunate (AS) and amodiaquine (AQ), available as ASAQ bilayer tablets for oral treatment. Due to the tablet size, this formulation can hardly be swallowed by young children, so a modification step (crushing and/or dispersion) is required prior to administration. However, as AQ has a poor taste, this modification step can significantly affect children's compliance. The aim of the MMASQ project was to develop a novel taste-masked multiparticulate ASAQ formulation to improve malaria treatment in young children. In the context of this project, the focus of the present study was to demonstrate the potential for similar *in vivo* drug release characteristics of the ASAQ bilayer tablet and the novel taste-masked multiparticulate formulation by predictive dissolution testing based on paediatric gastrointestinal (GI) physiology.

Methods

Drug release from the ASAQ pellet and tablet formulations was evaluated using the Kiddy-Size Dissolution System (KiDS), a novel dissolution device developed by Karkossa *et al.*, which allows for the simulation of GI-conditions of different paediatric age groups[1]. In this project, the gastrointestinal conditions of a one-year-old infant and a five-year-old preschool child were simulated following fasted administration of an age-appropriate ASAQ dose using a novel set of paediatric biorelevant media that allow for the simulation of gastric and small intestinal conditions in different age groups[2]. The simulated gastric residence time was 30 min. Thereafter, the media composition was switched from an acidic gastric environment to a bicarbonate-buffered small intestinal environment and the KiDS was connected to an automated pH controller. This setup allowed then for the simulation of the pH gradient that the ASAQ formulations would undergo while passing through the small intestine (pH 6.5 to pH 7.2). Samples were removed at predetermined time points, subjected to a specific sample preparation procedure and then analyzed using a validated HPLC method. All experiments were carried out in triplicate.

Results

Results of the *in vitro* dissolution study indicated that *in vivo* AS release from both formulations, i.e. the bilayer tablets and the novel pellet formulation will be complete in conditions of the stomach and upper small intestine, For AQ, an immediate and complete drug release under gastric conditions was observed for both formulations. However, precipitation was evident with similar precipitation rates after simulated entry in to the small intestine. This appears to be a result of the *in vitro test conditions*, which did not provide sink conditions. For the *in vivo* performance, this phenomenon will likely not be relevant, as the AQ dose dissolved in the stomach is not emptied into the small intestine as a bolus, where it is immediately absorbed, so that such high AQ concentrations will not occur. However, if such concentrations are still achieved , the *in vitro* data clearly indicate that the precipitation characteristics are independent of the dosage form, suggesting equal plasma levels.

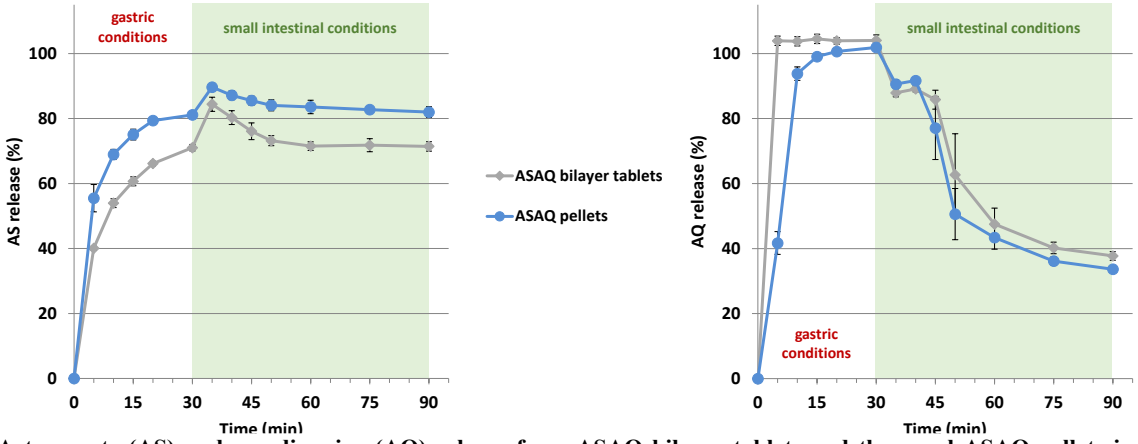

Figure 1: Artesunsate (AS) and amodiaquine (AQ) release from ASAQ bilayer tablets and the novel ASAQ pellets in the infant administration scenario, mean of n = 3 ± S.D..

Conclusion

The results of the *in vitro* study, which mimicked typical dosing conditions for children, indicate that the applied taste-masking approach does not affect the rapid release characteristics of the two antimalarial drugs. The successful combination of improved taste properties and the desired release characteristics has great potential to close an important gap in paediatric malaria therapy.

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Abstract ID: 24

Innovative Formulation Strategies for orodispersible Loratadine Dosage Forms

T. Kipping[1], J. Lu[2], B. Liang[2], A. von der Brelie[3]

[1] Merck Life Science KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany

[2] Merck M Lab™ Collaboration Center, 2F, Building A, No. 2727, Jinke Road, Zhangjiang Hi-Tech Park | Pudong Shanghai 201203, P.R. China

[3] Merck Life Science KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany;
e-mail: almut.vonderbrelie@merckgroup.com, phone: +49 151 1454 2848

INTRODUCTION

Loratadine, an antihistamine medication, is widely prescribed for the treatment of various allergic conditions in pediatric patients because of its efficacy in the treatment of allergic disorders. Considering the unique physiological and psychological needs of children, kids-friendly orodispersible mini-tablets and films were developed. The API Loratadine is classified as a class II drug based on the Biopharmaceutical Classification System due to its low water solubility [1]. To increase the low solubility, it was aimed to produce orodispersible films by hot melt extrusion - a solvent-free process which, through heating and mixing, disperses the API with a matrix polymer, helping to increase the dissolution rate and improving the solubility. Loratadin's high thermal stability makes it suitable for this technology. Due to its intensively bitter taste, the high-intensity sweetener neotame was added to the formulation for taste optimization and enhanced acceptability by the patients.

METHODS

Orodispersible mini-tablet (ODTM, 3 mm): produced by wet granulation with low shear mixer (Planetary mixer N50/ Hobart with peristaltic pump Pumpdrive 5201/ HeidolphTM;speed 136 rpm, flow rate 10 g/min; drying process in vacuum oven (Thermicon/Heraeus); vacuum: 200 mbar, temp.: 50°C, drying time: 20 h). A free-fall mixer is used for the tableting mixture (Turbula® T2A/Willy A. Bachofen AG; mixing time: 5 min, screw speed: 47 rpm). For tableting, a single punch press is used (STYL'One Evo/MEDELPHARM; pressure: 1.7 kN, speed: 10%). The tablets are characterized by diameters, tensile strength, tablet hardness (MultiCheck ERWEKA, n=20), disintegration time (DISI4 BIOMATION; n=6) and dissolution time of API in simulated gastric fluid, pH 1.2, n=6).

Formulation: Loradatine (50% w/w), mannitol-based ODT excipient system (46% w/w), magnesium stearate (1% w/w), polyvinyl alcohol (PVA) 4-88 (0.9% w/w), SiO2 (0.5% w/w) and neotame (0.06 % w/w).

Orodispersible film (ODF): produced by hot melt extrusion technology (twin-screw extruder connected with sheet take-off unit/Thermo Scientific is used, extruding temp.: 190 °C, screw speed: 500 rpm). The pre-mixed powder of Loratadine and particle-engineered PVA 4-88 is continuously fed into the Thermo Process HYG extruder feeder by using the twin-screw feeder, and triacetin is continuously fed into the extruder by peristaltic pump after the feeding port of powder feeding. Set up the feeding speed of solid material (mixture of PVA 4-88 and Loratadine) and liquid material (triacetin) at about 9:1. Tools are used to cut the cooled film into different shapes and sizes with to achieve the desired film weight. The films are characterized by diameters, weight, disintegration time in 900 ml water (n=3) and dissolution time in 500 ml simulated saliva (pH 6.7) with 0.6% polysorbate 80 (50 rpm, n=3) at 37°C (USP Type II).

Formulation: Loratadine (7.5% w/w), PVA 4-88 (82.47% w/w), triacetin (10% w/w), neotame (0.03% w/w)

RESULTS

Robust and hard ODMTs are obtained with an average disintegration time of 78 ± 7 s meeting the requirements of Ph Eur (< 180 s). A fast drug release is achieved in simulated gastric fluid. For the ODFs, a smooth processibility is recognized, and homogeneous and fast integrating films are obtained with a disintegration time of 35±2 s, 33±1 s and 45± 6 s. The ODFs show a fast drug release profile with enhanced solubility of the API Loratadine in simulated saliva (pH 6.7) - faster than pure API.

CONCLUSION

ODFs of the drug Loratadine may offer enhanced therapeutic benefits for children. Due to their potential for age-tailored API doses by varying thickness and shapes, they offer an interesting potential for personalized and age-appropriate dosages.

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Abstract ID: 25

An Investigation into the Feasibility of a Novel Genericised Paediatric Dispersible Platform

Karis M. Clifton[1]

[1] GSK, David Jack Centre for R&D, Harris's Lane, Ware, Hertfordshire, SG12 0GX, UK, karis.m.clifton@gsk.com,

INTRODUCTION

The development of paediatric formulations face barriers such as long development timelines, and acceptability concerns. A placebo dispersible tablet can be manufactured, and API added post-compression in a semi-solid lipid vehicle. Six lipids with varying hydrophilic-lipophilic balance (HLB) values were assessed as vehicles for API addition. Those with a higher HLB value should disintegrate quicker [1].

MATERIALS AND METHODS

A placebo formulation was compressed to 10mm round tablets using specialized tooling to create a design feature for lipid filling. Each of the 6 lipids were added to the tablet at 20 µL volume (Table 1). Disintegration testing was performed using water at 20ºC on the DisiTest 50 bathless apparatus. Disintegration testing was performed in 3 scenarios: 1. Placebo cores only, 2. Placebo cores with each semi-solid lipid. 3. Placebo cores with each semi-solid lipid combined with API.

Excipient	Description	HLB
Lipid A	Lauroyl polyoxyl-# glycerides	9
Lipid B	Lauroyl polyoxyl-# glygerides	14
Lipid C	Stearoyl polyoxyl-# glycerides	11
Lipid D	Mixture of lauroyl polyoxyl-# glycerides and PEG #	14
Lipid E	Polyoxyl # hydroxystearate	15
Lipid F	PEG-# Hydrogenated castor oil	13

Table 1. Semi-Solid Lipids used as API vehicle (# used as surrogate for a number to aid anonymization).

RESULTS AND DISCUSSION

Placebo cores disintegrated within 16 seconds. Scenario 2 resulted in the termination of lipids C and F from further testing due to these samples not disintegrating within 10 minutes. Lipids A, B, D and E were progressed to scenario 3. The data appears to show increased variability with an increase in DT time and hence was log transformed prior to analysis to stabilize the variance. The one-way ANOVA revealed the lipid group means were statistically significantly different from each other (0.0423) . The pairwise comparisons suggest that lipids B and E are significantly lower than lipid A, with a fold change of 0.3 and 0.5 respectively from A and hence showed the most promise in terms of low disintegration time (Table 2). Lipids B, D and E have HLB values of >14 and are to be progressed for further work. Lipids A, C and F are not recommended for this platform. Further research is required to reduce disintegration time to comply with Ph. Eur. 2.9.1.

Group1	Group2	Pr >|t|	Fold Change	Lower 95% Confidence Limit	Upper 95% Confidence Limit
Lipid E	Lipid B	0.1460	0.62930	0.30821	1.28487
Lipid E	Lipid D	0.0554	0.50245	0.24609	1.02587
Lipid E	Lipid A	0.0101	0.30672	0.15022	0.62625
Lipid B	Lipid D	0.4307	0.79843	0.39105	1.63019
Lipid B	Lipid A	0.0490	0.48740	0.23872	0.99516
Lipid D	Lipid A	0.1273	0.61045	0.29898	1.24640

Table 2. Pairwise Comparisons between lipid disintegration time, presented (due to the log transformation of the data) as fold changes of the form Group 1 / Group 2, with 95% confidence intervals around the fold changes.

CONCLUSIONS

The suitability of the combination of semi-solid lipids combined with a generic placebo dispersible tablet was assessed whilst noting improvement of the formulation is required to reduce disintegration time.

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Abstract ID: 26

ATAXIA TELANGIECTASIA: DRUG REPOSITIONING FOR PEDIATRIC TREATMENT OF A RARE GENETIC NEUROLOGICAL DISEASE

Cinzia Cimino[1,2]; Teresa Musumeci[1,2]; Claudia Carbone[1,2]; Angela Bonaccorso[1,2]; Agata G. Copani[1]; Rosario Pignatello[1,2]

[1] Department of Drug and Health Sciences, University of Catania, via S. Sofia 64, 95125 Catania, Italy; cinzia.cimino@unict.it

[2] NANOMED, Research Centre for Nanomedicine and Pharmaceutical Nanotechnology, University of Catania, Catania, Italy.

INTRODUCTION

Ataxia telangiectasia (A-T), also known as Louis-Bar syndrome, is a rare genetic condition which involves a mutation in the ATM (ataxia-telangiectasia mutated) gene, resulting in neurological disorders, telangiectasias and often tumor appearance[1]. Other complications are recurrent respiratory infections for immunological impairment, diabetes and radiosensitivity. The incidence is 1:40.000 to 1:300.000[1], with a median survival of 18-25 years. The mechanism of A-T occurrence is still unknown, and the currently employed therapeutic approach is mainly focused on the treatment of symptoms and the monitoring for the prevention of complications[2]. Based on these considerations, the aim of the Pharma-HUB project, financed by the Italian Minister for Health, is the development of a biomedical and pharmaceutical national Hub for pediatric repositioning of active drug compounds for the treatment of A-T disease, focusing mainly on the central nervous system (CNS).

METHODS

The project started with *in silico* drug repositioning studies, after the identification of the pharmacological targets and of the pathways involved. The molecules selected by *in silico* studies are being tested on 2D-3D *in vitro* biological models, to verify their neuroprotective activity, while technological platforms are being developed starting from dosages and the pharmaceutical forms currently available for adult use. Two experimental approaches are being pursued: a galenic approach, focused on the reformulation of commercially available drug products for the need of pediatric administration, and an innovative approach, to develop new drug delivery system platforms for nose-to-brain (N2B) administration, basing on European Pharmacopoeia and N2B requirements, respectively.

RESULTS

In silico studies allowed to select some molecules that could interact with the pharmacological target, and, among them, diosmin was chosen for its safety in adults[3], despite no toxicological data are available in children. AIFA approved medicines containing diosmin are mainly used for the treatment of venous insufficiency and capillary fragility and are generally formulated as tablets or cream; the galenic approach development is still ongoing. Basing on the physicochemical features, the innovative approach focused on the development of a nanostructured lipid carrier (NLC). The technological characterization demonstrated the suitability of the platform for the intended targeted drug delivery to the CNS via N2B, since this route was selected for the possibility to bypass the blood brain barrier (BBB) through the trigeminal or olfactory nerves pathways[4].

CONCLUSION

The future studies will deal with further characterization steps and development of the galenical products. Moreover, *in vivo* validations in mouse A-T models will be performed, and finally a set of clinical trials, in comparison with the current available (but not specific) therapy, will be carried out.

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Abstract ID: 27

Easy Scale-up of Wurster Processes for Pellet Drug Layering and Taste Masking

Annette Grave[1]; Adèle Rakotonirina[1]
[1] Glatt Pharmaceutical Services GmbH & Co. KG; Werner-Glatt-Str. 1, 79589 Binzen, Germany

INTRODUCTION

The administration of bitter tasting active pharmaceutical ingredients (API) to children requires effective taste masking optimisation. Pellets are ideal dosage forms: a pre-defined dose of API can be applied by layering. These small particles have a round shape, uniform and smooth surface, narrow particle size distribution and can be further coated with functional excipients [1] to achieve e. g. a taste masking, enteric protection or the controlled release of the API in defined parts of the gastro-intestinal (GI) tract. It is possible to produce different dosages appropriate for children by the adaption of the amount of pellets to be filled into capsules or sachets. Having the suitability of paediatric consumers in mind, formulations of small-sized pellets offer a valuable base for increased compliance and improved age-appropriate dosage forms.

Manufacturing processes for pellet layering and coating are often considered as challenging, especially the scale-up from development scale to pilot and production scale [2, 3]. In this work a proven and established scale-up concept for pellet layering and coating applying the Wurster technology will be presented.

MATERIALS AND METHODS

The hardly soluble API was layered on CELLETS® 350, followed by a seal coat (HPMC) and a taste masking coat (EC / HPMC), using Glatt´s Wurster technology. The process was developed at the 0.5 – 1 kg scale (GPCG 1 / 2 / 3, 6" or 7" Wurster), scaled-up to the 40 kg pilot scale in two trials (GPCG 60, 18" Wurster) and then to the final production scale of 190 kg (GPCG 60, 32" Wurster, two trials). Important scale-up parameters are batch size (BS), inlet air volume (IAV), spray rate (SR), temperatures (inlet air (IAT), product (PT), outlet air (OAT)), and atomisation air pressure (AAP) [Figure 1]. Process parameters for the next process step were determined with a scale-up model equation, maintaining the inlet air velocity and evaporation capacity (product humidity) in the process [Figure 2]. The final pellets were characterised for particle size, bulk density, residual moisture, assay and dissolution [Figure 3].

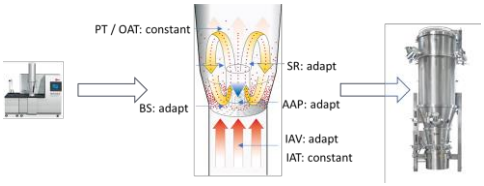

Figure 1. Schematic overview of process parameters for scale-up

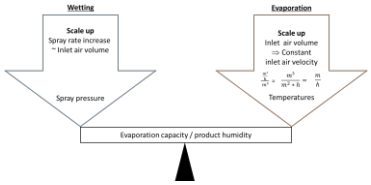

Figure 2. Balance of factors influencing wetting and evaporation for constant product humidity

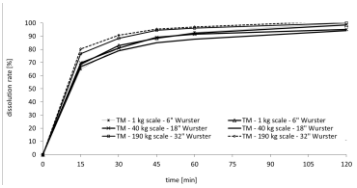

Figure 3. Dissolution profiles of development scale, pilot scale and production scale batches

RESULTS

Two scale-up trials were performed in the 40 kg-pilot scale with yields of 98 – 99 %, assay values of 99 – 100 % and dissolution profiles within the specification. The scale-up to the production batch size of 190 kg was performed in two trials with comparable results.

CONCLUSION

Taste masking of pellets by Wurster technology was successfully scaled-up to the production scale of 190 kg maintaining good yields, assay values and the intended dissolution profile. Scale-up parameters for fluid bed processes can easily be pre-calculated. The basis for scale-up and reliable processes in the production scale is a founded process development and optimisation in the development scale (e. g. 1 – 4 kg).

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Abstract ID: 28

Title: The human descriptive sensory panel - a tool for understanding how bitter taste is impacted during formulation

Liz Sheehan[1], Margaret Shine[1], Sandra Lenihan[2], Hans-Christian Meyer[3], Abina Crean[4]

[1] SRL Pharma, T12 XF62, Cork, Ireland

[2] Department of Process, Energy & Transport Engineering. Munster Technological University, Cork, Ireland

[3] Fresenius Kabi Deutschland GmbH, Bad Homburg, Hesse, Germany

[4] SSPC, the SFI Pharmaceutical Research Centre, School of Pharmacy, University College Cork, Ireland

Introduction

It is well established that the 'bitter' taste of medicines is a major contributary factor to medicine palatability leading to reduced patient acceptability, adherence, and effective treatment. During the development of medicines designed for oral administration, all aspects of the formulation that impact a medicine's acceptability must be considered.

Understanding how each component of the formulation impacts the sensory profile, particularly the bitter taste of a formulation is key to optimising the sensory characteristics of the medicine and increasing the likelihood of patient adherence.

Method

During this study, we present a stepwise research program showing how a human descriptive sensory panel was established and used to provide objective data during the investigation of various formulation approaches to reducing the bitter taste of model bitter compounds.

Spray dried solid dispersions and microemulsion formulation approaches were explored for their potential as taste masking platform technologies. Following the recruitment, training and validation of the panel to measure bitterness and key sensory attributes, bitterness threshold concentrations for the model compounds, caffeine, quinine HCl, quinine base and sucrose octaacetate (SOA) were determined.

Results:

The spray dried solid dispersions developed consisted of microparticles of the bitter compound molecules dispersed in a matrix of a pH responsive polymer, Eudragit E PO™. The descriptive sensory panel were effective in proving that the solid dispersion systems developed reduced the perceived bitter taste of both the water-soluble and poorly water-soluble model compounds investigated.

Conclusion:

Descriptive sensory profiling of a range of microemulsions prepared showed differences in the sensory characteristics 'overall', 'oily' and 'bitter' taste between the formulations. The ability of microemulsion prepared from SMEDDS system #2 was further investigated to determine its taste masking ability and was found not to be suitable as an oral liquid dosage form to mask the bitter taste of poorly water-soluble drugs.

Abstract ID: 30

Development of loratadine minitablets using 3D printing technology

Nevena Branković[1]; Dejana Cupeljić[1]; Aneta Stojmenovski[2]; Marko Glišić[3], Darija Knežević Ratković[1]; Biljana Gatarić[1]; Nataša Bubić Pajić[1]; Anđelka Račić[1]

[1]Pharmacy Department, Faculty of Medicine, University of Banja Luka, Bosnia and Herzegovina, andjelka.racic@med.unibl.org

[2] Centre for Biomedical Research, Faculty of Medicine, University of Banja Luka, Bosnia and Herzegovina

[3] Department of Mechatronics, Faculty of Mechanical Engineering, University of Banja Luka, Bosnia and Herzegovina

INTRODUCTION

In children's age, liquid dosage forms are the most popular because the risk of suffocation is avoided and the probability of taking the full dose increases. However, it is safe to use solid dosage forms in children over 6 years of age, but individual swallowing abilities should be taken into account (1). The focus of 3D printing technology is on the personalization of treatment because the dosage form of the drug could be made according to the individual needs of patients (2). The main goal of this study was to develop loratadine 3D printed minitablets using the soaking technique.

MATERIALS AND METHODS

Minitablets design having predefined dimensions of 6 mm (diameter) × 3 mm (height) were built in SolidWorks software. These templates were printed in Ultimaker S3, 3D printer (UltiMaker, Holland) using PVA filaments. 3D printed minitablets (~0.5 g) were immersed in the saturated loratadine solution with and without sodium lauryl sulfate (SLS) as described in Table 1. The drug content was determined by HPLC method. The release of loratadine from the 3D printed minitablets and referent product was determined using USP dissolution apparatus II (Erweka DT720, Germany).

RESULTS

The drug content was 5.1 ± 0.04 mg. In both tested formulations, the minitablets achieved more than 85% drug release in 60 minutes (Figure 1). The amount of the drug dissolved at the end of the experiment was similar compared to the commercial tablets (87.99%) and was 94.97% (T), 88.69% (TS), respectively.

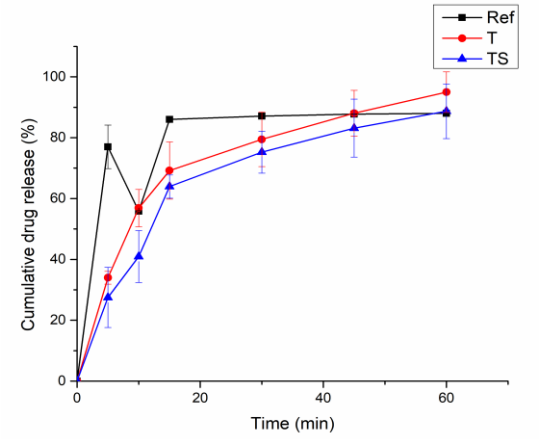

Figure 1. *In vitro* release of loratadine from 3D minitablets and referent product

Composition (%, w/w)	T	TS
Loratadine	5	5
SLS	-	1
Ethanol	q.s. ad 100	q.s. ad 100

Table 1.Composition of drug solution for the loading of loratadine in 3D printed minitablets

CONCLUSION

3D printed loratadine minitablets were successfully prepared by a simple soaking technique. This approach could be considered a useful strategy for personalized therapy. SLS as a solubilizer has not significantly modified the drug loading efficiency.

ACKNOWLEDGEMENTS

The authors would like to thank WMTA Banja Luka for the assistance in printing 3D minitablets**.**

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Abstract ID: 33

Gel Forming Tablets: Formulations with different gel former combinations and their characterization

Peter Kuehl[1]; Leonie Wagner[2]; Tatiana Ribeiro[3] ; Si Ying Lai[4]

[1] F. Hoffmann-La Roche AG, Basel, Switzerland, peter.kuehl@roche.com, +41 61 687 7455

[2] F. Hoffmann-La Roche AG, Basel, Switzerland, leonie.wagner@roche.com

[3] F. Hoffmann-La Roche AG, Basel, Switzerland, tatiana.ribeiro@roche.com

[4] F. Hoffmann-La Roche AG, Basel, Switzerland, si_ying.lai@roche.com

INTRODUCTION

Gel forming tablets have been identified as attractive, alternative dosage form for children that have difficulties in swallowing monolithic solid dosage forms [1]. The advantages of tablets, such as long term stability and utilization widely available conventional manufacturing technologies are combined with easy administration of a swallowable, semi solid form on a spoon. The use of gel formers is well known from matrix tablets with slow water ingress designed for sustained release [2]. However, the possibility to create formulation systems that are rapidly gelling has not been explored more broadly beside the available gel forming system Parvulet™ containing gel former gellan gum [3]. The intrinsic property of hydrogel formers to build a strong solid gel barrier that prevent from further ingress of water into the tablet need to be overcome with the selection of suitable gel formers and a tailor made formulation compositions including a wicking agent. A variety of gel formers with different characteristics is desired to adapt the formulation to the properties of the incorporated drug. A combination of two gel formers provides an opportunity to optimize the formulations of gel forming tablets.

METHODS

Round, flat faced tablets containing two different gel formers, diluents, a wicking agent, a lubricant and optionally a drug were manufactured at small scale applying conventional manufacturing processes of blending, roller compaction and tablet compression. Formulations containing different combinations of gel formers were screened, subsequently adapted in the quantitative levels, and finally selected optimized compositions manufactured at increased scale with model drugs and as placebo tablets. The properties of the formulation variant were characterized with respect to water uptake. A method to record the mass increase over time due to water uptake using a tensiometer was applied and optimized. Images of tablets taken from top view by digital camera equipped to a microscope were recorded during gelling and processed by image analysis. Gel forming tablets containing model drug acetaminophen or ibuprofen were subjected after gelling exemplarily to dissolution testing in phosphate buffer 6.8.

RESULTS

Early screening studies could identify formulation systems that were rapidly gelling completely within less than 180 seconds. The uptake of a limited amount of 2-3 mL water available on a spoon resulted in suitable gel properties with respect to swallowability and avoidance of potential spillage from the spoon. Manufacturability of tablets with sufficient mechanical strength has been proven with optimized formulations. The inclusion of a drug and the tablet dimensions have a crucial impact on the progression of the water ingress and hence the formation of the gelled bolus.

CONCLUSIONS

The results of the conducted formulation characterization studies showed that the development and manufacturing of gel forming tablets using suitable gel formers other than gellan gum and using wicking agents is a viable option to provide pediatric medication to younger children not able to swallow solid tablets. Applied characterization methods were able to guide the development towards optimized properties and performance of the tablets. Drug properties and dose will drive the selection of the best gel former combination among the variety of assessed combinations and will determine the optimal tablet dimensions. Tailor-made optimized formulations depending on the drug are necessary. Placebo tablets may be developed as gel forming carrier system for sprinkle of granules and capsule content.

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Abstract ID: 34

Solubility measurement of BCS class II drugs in fasted state paediatric and adult simulated intestinal fluid

Zoe McKinnon[1]; Abdullah Saggah[1]; Hannah Batchelor[1]; Ibrahim Khadra[1]; Gavin Halbert[1]

[1] Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 161 Cathedral Street, Glasgow, G4 0RE, United Kingdom, zoe.mckinnon@strath.ac.uk

INTRODUCTION

Many factors control the bioavailability including the solubility and dissolution of a drug in the gastrointestinal (GI) environment. The lack of data on the GI physiology of paediatric patients results in the use of adult models for predicting oral absorption (Batchelor et al., 2014). Based on a clinical study that characterised fasted human adult intestinal fluid aspirates, five simulated intestinal fluid (SIF) recipes were designed which encompassed the full range of samples in this study. Additional paediatric simulated media were also prepared based on data from a paediatric population (Pawar et al., 2021). The equilibrium solubility of two poorly soluble drugs (griseofulvin and fenofibrate) was determined in each of the simulated intestinal media to better understand the potential variability in GI solubility. The aim of this work is to provide experimental data to study the differences in solubility of poorly soluble drugs in paediatric SIF (pSIF) compared to that of a suite of adult media (Riethorst et al., 2016).

METHOD

Solubility studies were performed in triplicate. The composition of each media point studied can be found in Table 1. An excess of drug was added to each media and pH was adjusted to target using KOH or HCl. The tubes were mixed for 1 hour after which the pH was measured and adjusted accordingly if required. Tubes were mixed at 37 °C for 24 hours. Post-incubation, 1 mL from each tube was centrifuged for 15 minutes then the supernatant was analysed by HPLC.

Table 1: Composition of media used (mM), limited to colloidal materials and solubility of drugs reported

Media Point									
Paediatric (pSIF)				Adult (SIF)					
Component	Min	Median	Max	Component	Min	Q1	Median	Q3	Max
Na taurocholate (mM)	0.1	0.18	0.6		1.60	2.34	3.10	5.43	36.18
Lecithin (mM)	0.2	0.2	0.2		0.17	0.16	0.39	0.57	5.78
Na glycocholate (mM)	-	-	0.42	Na oleate (mM)	0.07	1.18	1.69	2.59	15.03
				Cholesterol (mM)	0.04	0.06	0.08	0.12	0.20
pH	6.5	6.5	6.5	pH	2.41	7.23	7.92	7.75	8.01
Results									
Griseofulvin (μM)	28 ± 1	33 ± 1	33 ± 1		107 ± 2	165 ± 5	164 ± 2	187 ± 12	307 ± 7
Fenofibrate (μM)	1.9 ± 1	2.1 ± 1	1.3 ± 1		22 ± 1	28 ± 1	39 ± 1	41 ± 1	171 ± 1

CONCLUSION

This study shows that poorly soluble drugs are sensitive to changes in the composition of SIF. As expected, the solubility of the drugs is much lower in pSIF than measured in the series of adult media therefore the bioavailability of the drugs in paediatric patients may be lower and dose adjustment could be required. There is a greater need for more accurate pSIF that better represents the relevant conditions in the paediatric GI tract which in turn can aid in the development of biorelevant solubility tests assisting in the development of paediatric oral medications.

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Abstract ID: 35

Calcium phosphate microcapsules for paediatric drug delivery

Jonas Kost[1]; Jörg Huwyler[2]; Maxim Puchkov[2]
[1] Galvita AG, Mattenstrasse 22, jonas.kost@galvita.com
[2] University of Basel, Klingelbergstrasse 50, joerg.huywler@unibas.ch

INTRODUCTION

Requirements for paediatric drug products foster the introduction of novel patient-friendly drug delivery strategies based on smart materials with combined actions and multiple functionalities.[1] Galvita has developed an inorganic calcium phosphate microparticle with a hollow internal structure, introduced as a biocompatible and multifunctional microcapsule: the Template Inverted Particle (TIP). These microcapsules are composed of pure tricalcium phosphate and have excellent compactability. The unique particle geometry is maintained during compaction thanks to its exceptional structural integrity. The hollow structure of TIP offers exceptional drug-loading capacities of up to 45% (v/v). Benefiting from the material's high wettability and water uptake rates, TIP tablets immediately disintegrate in the oral cavity into primary particles, regardless of the loaded drug's properties.[2] The TIP technology is clinically tested in healthy volunteers and demonstrates how these multifunctional microcapsules can be applied as a pharmaceutical excipient for oral drug delivery.[3] The TIP technology, being a versatile and cost-effective platform, has the potential to facilitate the formulation development process of patient-friendly medicines and is particularly well suited to paediatric formulations.

RESULTS

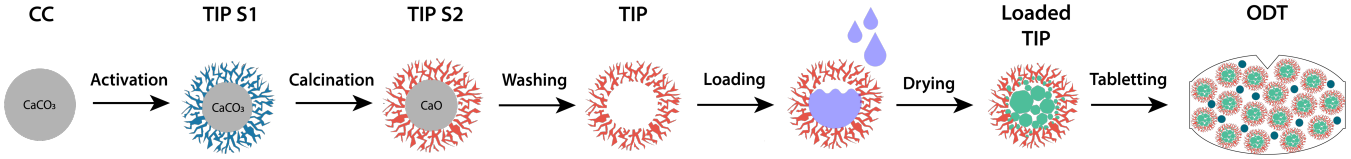

Figure 1.: Schematic illustration of formulation development with TIP. Calcium carbonate (CC) is activated to TIP Stage 1, where a calcium phosphate shell surrounds a carbonate core. Upon heating above 700°C, the calcium carbonate core degrades to CaO (TIP Stage 2). The CaO core is washed out, creating a large hollow cavity within the TIP microcapsules. Subsequently, the TIP microcapsules are drug-loaded using a solvent evaporation method. In the final formulation step, drug-loaded TIP particles are blended with a disintegrant and compacted into hard, rapidly disintegrating tablets.

CONCLUSION

The good compaction behavior of TIP, combined with its large encapsulation capacity, makes TIP an excellent multifunctional excipient for oral drug delivery. Its high porosity and water up-take rate result in rapid tablet disintegration. Therefore, TIP is a platform solution for designing ODTs and age-appropriate drug delivery strategies. The preservation of defined particle geometry, a key feature of TIP, supports its use as a fully functional self-loading microcapsule for oral drug delivery. TIP is made of non-toxic, biodegradable material and is widely accepted as a food additive. Ongoing studies focus on further clinical evaluation of drug-loaded TIP-ODTs.

Keywords: Excipient, microcapsules, tricalcium phosphate, patient-friendly, paediatric, drug delivery

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Abstract ID: 36

Exploring the Implications of Poor Patient Acceptability on Adherence and Clinical Outcomes: A Pharmacometrics case Study with Deferasirox

Elisa Alessandrini[1,2*], Anisa Khan[2], Alessandro Di Deo[2], Oscar Della Pasqua[2], Catherine Tuleu[1]

[1]UCL School of Pharmacy, London, UK & [2]Clinical Pharmacology & Therapeutics, University College London, UK
*email of corresponding author: elisa.alessandrini@ucl.ac.uk

INTRODUCTION

Medication adherence is the process by which patients take their medicines as prescribed. Nonadherence is very common and leads to significant public health issues. In children, adherence presents unique challenges compared to adults and patient acceptability plays a crucial role in affecting medication adherence, though its precise impact is hard to quantify. No studies have attempted to define acceptance limits based on the pharmacokinetic (PK) and pharmacodynamic (PD) response of a drug. However, it is well recognised that poor patient acceptability can lead to suboptimal adherence and potentially negative treatment outcomes.

Deferasirox is an oral iron-chelating agent used for the treatment of haemoglobinopathies. Its once daily administration makes it more appealing compared to the other oral iron-chelating agent deferiprone which has larger therapeutic effect but an inconvenient dosing schedule potentially negatively impacting adherence. However, deferasirox has an unpleasant taste which affects its acceptability and more generally, adherence particularly in young patients [1]. Using modelling and simulation methodologies, this study aims to quantify the potential negative effect of poor acceptability on treatment response to deferasirox in patients suffering from hemoglobinopathies.

METHODS

A nonlinear mixed-effects modelling approach has been used in NONMEM v.7.5.1. Firstly, a previously developed population PK model [2] was employed to derive relevant measures of drug exposure (i.e., area under the curve (AUC), steady-state concentration (C_{ss}) and maximum plasma concentration (C_{max})). Age and weight-related changes in the PK were described using allometric principles. Then, using an Emax model predicted ferritin levels have been derived to quantify the impact of varying adherence scenarios on treatment response. Different scenarios have been tested including random missingness: 20% and 50% of doses not taken, and partial intake:1/3 or 1/2 of the dose not taken for 20% or 50% of the time. A virtual paediatric population of 60 individuals, age range 2-18 years and weight range 12-60 Kg, was created and administered 20 mg/kg of deferasirox for a duration of 12 weeks.

RESULTS

All scenarios resulted in different drops of deferasirox plasma concentrations compared to perfect adherence. As expected, scenarios of random missingness led to worse reductions than those for partial intake. Moreover, the higher the percentage of missed or partially taken doses, the higher the reduction in AUC (% change) from perfect adherence, Table 1. However, deferasirox plasma concentrations alone are not predictive of therapeutic outcomes but the evaluation of change (reduction) in ferritin level is predictive of treatment response. Assuming comparable baseline ferritin levels and no dose variation, results from 12 weeks analysis showed a small increase of ferritin compared to perfect adherence for all the 6 scenarios evaluated. However, the lag in ferritin response would require a longer than 12 weeks evaluation to appreciate differences between adherence scenarios.

Table 1. Percentage of change for AUC compared to perfect adherence.

	Random missingness			**Partial intake**		
	SC1*	**SC2***	**SC3***	**SC4***	**SC5***	**SC6***
% Δ AUC^	-42.21	-64.36	-39.25	-40.70	-34.75	-45.29

^from perfect adherence. *SC1 and SC2: 20% and 50% of doses not taken. SC3 and 4: 1/3 of dose not taken 20% and 50% of times respectively. SC5 and 6: 1/2 of dose not taken 20% and 50% of times respectively.

CONCLUSIONS

Simulation scenarios can be used to explore clinical implications of nonadherence to treatments due to acceptability issues and help clinicians identifying high-risk patients who need targeted interventions to enhance adherence and optimise clinical outcomes. Our results indicate that missing one dose of deferasirox has an immediate effect on plasma concentrations but does not directly reflect on changes in ferritin levels, due to a lag in ferritin response. This delay between the start of treatment and achieving ferritin steady state means that clinical consequences of nonadherence may only become apparent in the long term, by which damages to internal organs from high iron levels may have become irreversible. As next step, we plan to evaluate ferritin levels at 6 and 12 months after treatment initiation and to apply the same scenarios of nonadherence to drugs with different PK and PD profiles to assess implications of a variable acceptability for different drugs.

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Children and parent views of 3D printed gummy bears as an alternative dosage form for children – an interim analysis

Louise Bracken[1]; Gabrielle Seddon[1], Rebecca Page[1], Andrea Gill[1]; Jennifer Duncan[1]; Nicola Vasey[2]; Sophie Dutta[2]; Touraj Ehtezzai[3]; Alice P. McCloskey[3]

1. Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust, Liverpool, UK. Contact louise.bracken@alderhey.nhs.uk
2. The Great North Children's Hospital, Royal Victoria Infirmary, Newcastle-upon-Tyne, NE1 4LP
3. School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, James Parsons Building, Byrom St, Liverpool, L3 3AF

INTRODUCTION

3D printing offers potential for personalised paediatric medicine[1-3] through its ability to incorporate tailored doses specific to patient needs, and characteristics such as colour and shape to meet patient preferences. Despite this exciting potential, there is limited work exploring what children and their parents/carers actually want, this work aims to address this.

METHODS

E-questionnaires were prepared using MSForms and distributed to parents of children aged 4-11 years at a local museum and at Alder Hey Children's Hospital. This short questionnaire (<5 mins) explored their experiences administering medicines to children including any difficulties, and their views on 3D printed gummy bears including comfort levels in administering these as a medicine, storage and safety requirements and manufacturing components. A second paper-based questionnaire was designed to capture the views of children aged 4-11 years on the acceptability of 3D printed gummy bears at pop-up stands located in Alder Hey. Children were asked to look, touch and smell a series of 3D printed gummy bears, a Haribo® gummy bear, and look at a picture of a 3D printed disc (Figure 1) and comment on their favourite shape, feel, colour, smell, and rank the most important characteristics of a medicine. The study will be repeated at the Great North Children's hospital and a local public space in the coming months. University ethics was sought and granted (UREC22/PBS/004 and amended UREC23/PBS/010).

RESULTS

73% of parents (n=30) reported they had struggled to administer a medicine to their child due to its taste or texture. Parents were happy to return to the pharmacy for ongoing supplies but would prefer if refrigeration of the gummy bears was not required. 25 children (mean age 4.2 years) provided feedback at Alder Hey with pink (54%) colour and strawberry flavours (64%) preferred. The children preferred the gummy bear shape but thought the round disc was acceptable. When asked to rank the most important characteristics of a medicine they put taste first, followed by smell. 84% of children said they would be willing to take the medicine everyday.

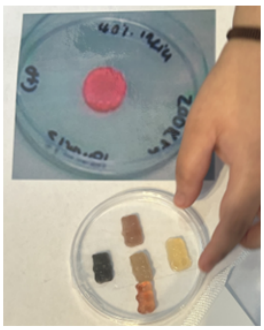

Figure 1. Photograph of 3D printed gummies, disc and Haribo® sweet used in the study

CONCLUSION

The work contributes to the growing body of evidence about 3D printed medicines particularly for children. It highlights that 3D gummies are acceptable as a dosage form, and that taste, colour and stability and room temperature are key areas for researchers to focus on to aid bench to bedside translation of these novel oral dosage forms.

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Abstract ID: 38

Design of taste-masked primaquine – ion exchange resin complex intended for pediatric formulations.

Thiago F. Guimarães[1]; Eduardo G. R. de Sousa[1]; Rosane A. S. San Gil[2]; Leandro B. Borré[2]; Alessandra L. Viçosa[1]; Valéria G. da Silva[3]; Diogo D. do Nascimento[1]; Laís B. da Fonseca[3].

[1] Fundação Oswaldo Cruz (FIOCRUZ), Instituto de Tecnologia em Fármacos (Farmanguinhos). Rua Sizenando Nabuco, 100 – Rio de Janeiro - RJ, Brazil, thiago.frances@fiocruz.br.

[2] Universidade Federal do Rio de Janeiro, Instituto de Química (UFRJ-IQ), Rio de Janeiro – RJ, Brazil.

[3] Fundação Oswaldo Cruz (FIOCRUZ), Serviço de Equivalência e Farmacocinética. Rio de Janeiro – RJ, Brazil.

Introduction

In recent years, the formation of complexes using antimalarial drugs and ion exchange resin (IER) has been investigated. It has proven to be an effective taste masking technique without compromising the bioavailability of these drugs[1, 2]. Primaquine diphosphate (PRQ) is also known for its unpleasant taste, which can lead to non-acceptance of the medicine among malaria patients under five years old, especially when it is given for a radical cure treatment of *P. vivax* and *P. ovale* over 14-day treatment[3]. This study aims to determine the feasibility of primaquine-resin complex formation and evaluate the taste masking efficiency of drug complexation with IER through an *in vitro* dissolution test using simulated saliva and fiber-optic UV for in-line determinations.

Method:

Primaquine-resin complexes were prepared in different drug-to-resin ratios (1:2, 1:1 and 2:1 (w/w)) using polacrilin potassium (PP) (Amberlite™ IRP88). The IER was suspended in PRQ solution (pH 5.0) and stirred at room temperature. After 180 minutes, the drug load efficiency (%) was determined by the difference in drug amount at the beginning and after the complexation reaction by UV-visible spectrophotometry at 260 nm. PRQ resinate complex was also characterized by differential scanning calorimetry (DSC) using sealed non-hermetic aluminum pans and was scanned at a heating rate of 10°C/min from 30 to 300°C under a dry nitrogen atmosphere (flow rate 50 mL/min). An optimized NMR spectrum of PRQ could be obtained at a recycle time of 15 s, a spinning rate of 10.0 kHz, and a contact time of 8 ms. Drug release from complexes was determined by adding complex equivalent to 15 mg of PRQ to 900 mL of HCl 0.1N, pH 1.2 and 37 ºC, using USP *apparatus* II at 100 rpm. Samples were collected at regular intervals and were assayed as mentioned before. The taste masking efficiency was evaluated *in vitro* using an in-line assessment. A fiber-optic UV sensor was used to determine the drug release during an adapted dissolution test using 500 mL of simulated salivary fluid at 37 ºC and pH 6.8 as dissolution medium, paddles at 50 rpm. The UV probes measured at 260 nm every 5 seconds for a total of 3 minutes.

Results

The drug-to-resin ratio of 1:1 (w:w) demonstrated high drug loading efficiency at 91% ± 1.03%. The other ratios resulted in excess PRQ or IER after 180 minutes. The PRQ resinate successfully achieved drug amorphization, which was confirmed by the absence of the endothermic event of the PRQ melting point (206ºC) when compared to the salt form of the drug. NMR analysis showed that all the carbon signals could be assigned, including those linked to the IER polacrilin potassium. A strong increase in the width of alkyl C4' and C2' carbons, and a decrease in T1rhoH values confirmed the interaction between PRQ and IER moieties. PRQ spectra were comparable with that published by Silva et al 2022. In the pH 1.2 dissolution test, the PRQ-complex exhibited a rapid drug release, with 94.5% ± 0.87% released in the first 5 minutes, suggesting no bioavailability issues in acidic conditions. Furthermore, in simulated saliva at pH 6.8, the resinate only released approximately 1.97% in 30 seconds, demonstrating effective taste masking due to the minimal amount of PRQ released in this condition.

Conclusion

The complexation of PRQ with IER presented a high drug loading efficiency and effectively reduced the drug's unpleasant taste, indicating that proceeding with the following development stages is feasible to create a new and palatable oral formulation of primaquine resinate for children.

Acknowledgment

Colorcon do Brasil kindly provided the ion exchange resin polacrilin potassium. This work was supported by Inova Fiocruz/VPCCB and CNPq (process number 440017/2022-0).

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Abstract ID: 39

Assessment of *in vivo* antimalarial activity of primaquine-ion exchange resin complex against *Plasmodium berghei* ANKA.

Mariana X. V. Passos[1]; Tatiana A. Pádua[1]; Eduardo G. R. de Sousa[1]; Renata R. Castro[1]; Elaine C. Rosas[1]; Thiago F. Guimarães[1]

[1] Fundação Oswaldo Cruz (FIOCRUZ), Instituto de Tecnologia em Fármacos (Farmanguinhos), Vice-diretoria de Educação, Pesquisa e Inovação. Rio de Janeiro – RJ, Brazil. thiago.frances@fiocruz.br

Introduction

Malaria remains the main parasitic disease in tropical countries. In 2022, this disease killed around 608,000 people, with 76% of these deaths being children under five years of age[1]. Formulation scientists face considerable challenges in creating age-appropriate dosage forms and concealing bitter-tasting drugs intended for oral administration to pediatric patients[2]. Primaquine (PRQ) is a bitter-tasting drug prescribed as a part of malaria treatment. Therefore, in the context of pharmaceutical formulation, the complexation of bitter-tasting drugs with ion-exchange resin represents a viable taste masking alternative[3, 4]. However, the complex must demonstrate equivalent effectiveness to the free drug and toxicological safety to be considered in future oral formulations. Considering that, this study aims to determine whether the primaquine resinate complex (PRQ-R) exhibits the same antimalarial activity as the drug primaquine diphosphate and evaluate possible toxic effects.

Method:

Primaquine-resin complexes were prepared in a 1:1 (w/w) drug-to-resin ratio using polacrilin potassium (PP) (Amberlite IRP88). The resin (R) was suspended in PRQ solution (pH 5.0) and stirred for 24 hours at room temperature. Resinate was filtrated and dried at 30 °C for 48 hours. The drug load efficiency (%) was calculated by the difference of drug amount at the initial and after complex formation by UV-visible spectrophotometry at 260 nm. To evaluate the compounds' in vivo antimalarial efficacy, male C57BL/6 mice were intraperitoneally (*i.p.)* inoculated with 1 x 10^6 *P. berghei* ANKA-parasitized red blood cells withdrawn from a previously infected mouse. Mice were treated daily up to day 4 after infection with PRQ, PRQ-R, or R (15,0 mg/kg primaquine base) when flow cytometry performed parasitemia determination. The results are expressed as drug activity[5] and were determined by the difference between the mean value of the control and experimental groups expressed as percent reduction. To assess the possible toxic effect of antimalarial substances, enzymatic activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AF) and the levels of total proteins, glucose, albumin, cholesterol, urea and uric acid were determined in plasma samples using specifics kits (Bioclin MG, Brasil). In addition, 5x10^5 Caco-2 cells/ml were cultured in DMEM medium for 24h. Afterward, the medium was replaced by fresh medium containing PRQ, PRQ-R, and R in a range of concentrations (n=3) and incubated for 48 hours at 37°C. Cell viability was determined by the MTT method, and absorbance was measured at 570 nm.

Results

The drug loading efficiency was about 89.36 ± 0.24%. Both PRQ and PRQ-R exhibited antimalarial activity with no statistically significant difference. The compounds PRQ and PRQ-R were able to reduce mice' parasitemia by more than 95%. The biochemical analysis showed that PRQ-R treatment increased AF levels by 71.2% and 56.7% after 24 and 48 hours, and PRQ treatment increased AF levels by 64% after 48 hours compared to non-treated mice. The samples did not exhibit cytotoxicity on Caco-2 cells.

Conclusion

These results indicate that the interaction between primaquine diphosphate and the ion exchange resin polacrilin potassium does not affect the effectiveness of primaquine resinate oral treatment. According to the results, primaquine resinate did not present any toxic effect, making it a potential candidate for future pediatric oral formulations.

Ethics

The animal experimental protocol was approved by the Animal Ethics Committee (CEUA/Fiocruz protocol number LW-37/22).

Acknowledgment

Colorcon do Brasil kindly provided the ion exchange resin polacrilin potassium. This work was supported by Inova Fiocruz/VPCCB and CNPq (process number 440017/2022-0). Authors would also like to thank Platform for Antitumoral Compound Screening (RPT11M), Technological Platforms Network FIOCRUZ, Oswaldo Cruz Foundation, for the analyses in Caco-2 cells culture.

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Abstract ID: 40

Accelerating Safer Administration of Medicines to Children in Low Resource Settings

Sifan Hu[a], Alka Mukne[b], Vandana Patravale[c], Pradeep Behera[d], K. Bangarurajan[e], Esmerald Hermans[f], Jenny Walsh[g], Smita Salunke[a,h]

[a] University College London School of Pharmacy, 29-39 Brunswick Square, London WC1N 1AX, United Kingdom
[b] Indian Pharmaceutical Association (IPA), India
[c] Society for Paediatric Medicines & Healthcare Initiative (PMHI), India
[d] Thetabeta Analgorithms Pvt Ltd, India
[e] Central Drugs Standard Control Organization (CDSCO), India
[f] Janssen Pharmaceutica NV, Belgium
[g] Jenny Walsh Consulting Ltd, East Midlands Chamber, 8 Experian Way, ng2 Business Park, Nottingham NG1 1EP, UK
[h] European Paediatric Formulation Initiative (EuPFI)

INTRODUCTION

Medication use in paediatric population is prone to dosing error as small dose volumes are required to be administered. Using safe and effective administration devices to prevent over-dosing and under-dosing is a key approach to secure paediatric medication safety. It is especially important to understand the pharmacotherapy needs of children living in resource-limited conditions for accurate dosing and find solutions that accelerate the development and adoption of administration devices with enhanced dosing accuracy. Hence, a workshop was held to understand the uptake of the already existing administration devices for oral and respiratory medicines in low- and middle-income countries, and to assess the level of awareness of issues associated with use of administration devices as well as the need of innovative devices.

METHOD

The workshop was organised in partnership with IPA, PMHI, TBA, at Scitech Centre in Mumbai, India on 4th March 2024. Experts from academia, industry, healthcare services and regulatory bodies were invited to attend [1]. The workshop consisted of a panel discussion where academic researchers shared findings of studies on the use of administration devices for paediatric medicines, followed by presentations on healthcare professionals (HCPs) and industry's perspectives on the challenges associated with the use and development of administration devices. Then, participants were divided into groups to discuss the procedural and operational challenges in relation to the administration of medicinal products to the paediatric population and propose constructive solutions. Participants' preferences for the proposed solutions were ascertained by voting. Lastly, an overview of regulatory guidance on administration devices was provided.

RESULTS

42 participants, including the speakers and organisers, attended the workshop. 80% of the participants were from India, and the rest from Belgium, China, Japan, Nigeria, UK and USA. 50% of the participants were academic researchers, 31% were from industry, 12% were healthcare professionals and 7% from regulatory agencies.

The panel discussion highlighted country-dependent usage of devices for administration of oral and inhaled paediatric medicines. From Indian HCPs' perspective, access, availability and affordability are the three main considerations for medication administration to children. From industry and regulator's perspectives, European device developers follow strict regulatory requirements surrounding accuracy, dose markings, and product labelling, whereas innovation of medical products in India is currently limited due to lower regulatory reliance and research priority is placed on simplifying the administration process. Overall, the highest scoring solutions are device innovation and regulation harmonisation, with votes from all stakeholder groups. However, academic representatives formed the largest voting group, and not all participants voted.

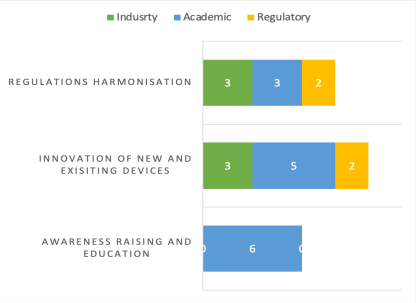

Figure 1. Scoring of potential solutions according to stakeholder group

CONCLUSION

Discussions and knowledge shared during this event showed the effectiveness of the workshop in fostering a deeper understanding of the issues regarding use and development of administration devices in low resource settings.

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