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3D PRINTED POLYETHYLENE OXIDE ORAL DOSES WITH INNOVATIVE 'RADIATOR-LIKE' DESIGN: IMPACT OF MOLECULAR WEIGHT ON MECHANICAL AND RHEOLOGICAL PROPERTIES AND DRUG RELEASE

^{1,2}M Peak*, ³K Baj, ⁴A Isreb, ⁵M Wojsz, ⁶I Mohammad, ⁷M Albed Alhnan. ¹Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust, Liverpool; ²University of Central Lancashire, Preston, UK; ³Faculty of Pharmacy, Medical University of Lodz, Lodz, Poland; ⁴School of Pharmacy and Biomedical Sciences, University of Central Lancashire, Preston, UK; ⁵Faculty of Pharmacy with the Laboratory Medicine Division, Medical University of Warsaw, Warsaw, Poland; ⁶School of Pharmacy, University of Bradford, Bradford; ⁷King's College London, London, UK

10.1136/archdischild-2019-esdppp.22

Background Despite regulatory advances, lack of age-appropriate formulations (AAFs) remains a challenge in paediatric practice. 3D-printing of oral dosage forms (ODFs) offers potential for AAFs for children. Optimising drug release from 3D-printed ODFs is an important technological step. Despite the abundant use of polyethylene oxides (PEOs) and their extensive use as an excipient, there have been no previous reports of applying this thermoplastic polymer species alone to fused deposition modelling (FDM) 3D printing. We assessed the impact of polymer molecular weight (MW) on the mechanical properties of the resultant filaments and their rheological properties. In the FDM 3D printing process, we also tested the effect of an innovative radiator-like design of the ODF on the acceleration of drug release patterns.

Methods Blends of PEO (MW: 100K, 200K, 300K, 600K or 900K) with PEG 6K (plasticiser) and a model drug (theophylline) were prepared by hot-melt extrusion. The resultant filaments were used as a feed for a FDM 3D printer to fabricate innovative designs of ODFs in a radiator-like geometry with inter-connected paralleled plates and inter-plate spacing of either 0.5mm, 1mm, 1.5mm or 2mm.

Results Varying blends of PEO and PEG allowed formation of mechanically resistant filaments (maximum load at break of 357, 608, 649, 882, 781 N for filament produced with 100K, 200K, 300K, 600K or 900K, respectively). Filaments of PEO at a MW of 200K-600K were compatible with FDM 3D printing. Further increase in PEO MW resulted in elevated shear viscosity ($>10^4$ Pa.S) at the printing temperature and hindered material flow during FDM 3D printing. A minimum spacing (1 mm) between parallel plates of the radiator-like design was essential to boost drug release from the structure.

Conclusion These findings are essential in the development of next-generation personalised drug delivery doses using specialised polymer/polymer blends purposely optimised for FDM 3D printing.

Disclosure(s) Nothing to disclose

023

CAN CHILDREN SWALLOW TABLETS? OUTCOME DATA FROM A FEASIBILITY STUDY TO ASSESS THE SWALLOWABILITY AND ACCEPTABILITY OF DIFFERENT SIZED PLACEBO TABLETS IN CHILDREN AND YOUNG PEOPLE (CREATING ACCEPTABLE TABLETS – CAT)

¹L Bracken*, ¹E McDonough, ²S Ashleigh, ²F Wilson, ²U Ohia, ³P Mistry, ⁴H Jones, ⁴N Kanji, ⁵F Liu, ¹M Peak. ¹Paediatric Medicines Research Unit, Alder Hey Children's NHS Foundation Trust; ²NIHR Alder Hey Clinical Research Facility, Liverpool; ³Children's Cancer Trials Team, Cancer Research UK Clinical Trials Unit, Institute of Cancer and Genomic Sciences, University of Birmingham, Birmingham; ⁴Quotient Sciences, Nottingham; ⁵Department of Pharmacy, Pharmacology and Postgraduate Medicine, University of Hertfordshire, Hatfield, UK

10.1136/archdischild-2019-esdppp.23

Background It can be challenging to administer medicines to children and young people (CYP); due to the lack of available age-appropriate formulations. Developing medicines that are acceptable to CYP has the potential to improve treatment outcomes.¹ Acceptability has been defined as 'an overall ability of the patient and caregiver (defined as 'user') to use a medicinal product as intended'.² There is limited evidence for the acceptability of tablets in CYP. This feasibility study aimed to investigate the swallowability and acceptability of different sized placebo tablets in CYP aged 4–12.

Method Participants were asked to swallow three different sized placebo tablets; 6 mm, 8 mm and 10 mm, smallest to largest. Both healthy children and NHS patients were recruited. The researcher observed and recorded children's facial expressions as they swallowed each tablet.³ Following administration, an internal inspection of the mouth was conducted to identify any residue or non-swallowed tablet.⁴ Participants completed a questionnaire about the acceptability of each tablet. For analysis participants were stratified by age: 4–8 and 9–12 years.

Results 55 participants were recruited to the study. 30 children were in the younger group, of which 23% had taken a tablet before. 84% of the 25 older children had previously taken a tablet. 100% of participants attempted to swallow the 6mm tablet, with 67% of younger children and all older children successfully swallowing the tablet. All participants in the older group attempted to swallow the 8 mm and 10 mm tablet with 100% successfully swallowing the 8 mm and 96% successfully swallowing the 10 mm tablet. 77% of younger children attempted to swallow the 8 mm tablet, with 91% succeeding. 70% of younger children attempted the 10mm tablet, with 95% succeeding.

Conclusion This study demonstrates that tablets of 6mm, 8mm and 10mm are potentially an acceptable formulation for children aged 4–12 years.

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Disclosure(s) Nothing to disclose

024

IVERMECTIN IN CHILDREN: WHAT IS THE RIGHT DOSE TO ACHIEVE EQUIVALENT EXPOSURE COVERAGE IN CHILDREN AND ADULTS?

^{1,2,3}JM Brussee*, ^{1,4,5}JT Coulibaly, ^{1,2}J Keiser, ^{2,3,6}M Pfister. ¹Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute; ²University of Basel; ³UKBB, Pediatric Pharmacology and Pharmacometrics, University Children's Hospital Basel, Basel, Switzerland; ⁴Unité de Formation et de Recherche Biosciences, Université Félix Houphouët-Boigny; ⁵Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, Abidjan, Côte d'Ivoire; ⁶Certara LP, Princeton, NJ, USA

10.1136/archdischild-2019-esdppp.24

Background The broad-spectrum antiparasitic drug ivermectin is widely used in children, and its use in children weighing < 15 kg is off-label, as little data is available to inform the use of ivermectin in this young age group. Pediatric doses associated with consistent exposure across age are still unknown. Therefore, we aim to identify a dosing strategy for ivermectin treatment in both pre-school-aged children (2–5 years of age) and school-aged children (6–12 years of age) that achieves equivalent exposure coverage in children and adults.

Methods A population pharmacokinetic model for ivermectin was developed based on data collected in 80 pre-school-aged children (2–5 years), 120 school-aged children (6–12 years),¹ and eleven adults,² receiving an oral dose of 100–600 µg/kg ivermectin. Model-based simulations were performed to optimize pediatric dosing to achieve consistent exposure across various age groups.

Results Clearance per kilogram was higher in children than in adults, with a median (90% confidence interval) of 0.35 (0.12–0.73) L/h/kg in children compared to 0.20 (0.10–0.31) L/h/kg in adults. As a result, ivermectin exposure in children following a 200 µg/kg dose is ~30% lower than in adults. An increased dose of 250 and 300 µg/kg would be needed in school-aged children (6–12 years) and pre-school-aged children (2–5 years), respectively, to achieve equivalent exposure coverage in children and adults. Alternatively, we propose a height-based dosing schedule with a stepwise increase in number of administered 3-mg-tablets from 1 to 5 for children in sub-Saharan Africa with a height of 75–90 cm, 90–130 cm, 130–150 cm, 150–165 cm, and 165–175 cm.

Conclusion We report the first dosing strategy for the widely-used drug ivermectin that is associated with equivalent exposure coverage in children and adults. Further studies are necessary to establish the safety and efficacy of appropriate doses in the pediatric population.

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Disclosure(s) JMB declares no potential conflicts of interest. JDS declares no potential conflicts of interest. JTC declares no potential conflicts of interest. JK was financially supported by the Bill and Melinda Gates Foundation (OPP1153928) and an ERC grant (CoG 614739 A-HERO), and declares no other potential conflicts of interest. MP has a part-time employment with the consulting company Certara LP (USA), and declares no other potential conflicts of interest.

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CLAVULANATE STABILITY IN CHILD-APPROPRIATE FORMULATIONS IS INADEQUATE FOR USE IN TREATING YOUNG CHILDREN IN ASIA

¹I Mack*, ²M Sharland, ³S Rehm, ³K Rentsch, ⁴J Bielicki. ¹University Children's Hospital Basel (UKBB), Basel, Switzerland; ²St George's University of London, London, UK; ³University Hospital of Basel; ⁴University Children's Hospital Basel (UKBB), Basel, Switzerland

10.1136/archdischild-2019-esdppp.25

Background Amoxicillin-clavulanate (AMC) is among the most frequently used antibiotic for paediatric infections globally. AMC child-appropriate formulations are largely limited to dry powder suspensions, which have to be stored refrigerated once reconstituted due to stability limitations of clavulanate.

Methods Oral Amoxicillin (AMX) and AMC formulations were identified from IQVIA-MIDAS wholesale data, and 2015 antibiotic consumption in courses/1000 child-years was estimated in Bangladesh, India, Indonesia, Pakistan, Philippines and Vietnam with an assumed average treatment of 7 days. Costs per course in US-\$ standardised to 2015 were estimated from the same dataset. Nationally representative data on access to a refrigerator was extracted from the Demographic & Health Surveys Program. Degradation under different temperature conditions of two different AMC suspensions commercially available in Switzerland was tested. Average degradation (three bottles of each product) was measured during 8 days with ambient temperatures of 8°C versus 28°C.

Results In India and Pakistan more AMC than AMX courses were sold. In all countries AMC was at least twice and up to 10 times as expensive as AMX. Access to refrigeration was below 45%, even in countries with a high number of sold AMC courses (compared with AMX). In the evaluated co-formulated products, clavulanate showed a maximum degradation of 34% at 8°C, and 73% at 28°C after 8 days. AMX was largely stable at 8°C but 13% degraded at 28°C after 8 days.

Conclusions Oral amoxicillin-clavulanate suspensions are widely used in six Asian countries classified as middle-income countries by the World Bank. In reconstituted liquid AMC formulations, neither component is satisfactorily stable at room temperature. Storage conditions for stability are likely inadequate for AMC in many households in the six Asian countries of interest.

Disclosure(s) Nothing to disclose

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POPULATION PHARMACOKINETIC META-ANALYSIS OF INDIVIDUAL DATA TO DESIGN THE FIRST RANDOMIZED EFFICACY TRIAL OF VANCOMYCIN IN NEONATES AND YOUNG INFANTS

¹E Jacqz-Aigrain, ²S Leroux, ³AH Thomson, ⁴K Allegaert, ⁵EV Capparelli, ^{1V} Biran, ^{6N} Simon, ^{7B} Meibohm, ⁸Lo Y-L, ^{9R} Marqués, ^{10J-E} Peris, ^{11I} Lutsar, ^{12J} Saito, ^{12H} Nayamura, ^{13JN} van den Anker, ^{14M} Sharland, ^{15W} Zhao*. ¹Hôpital Robert Debré, Paris; ²CHU de Rennes, Rennes, France; ³University of Strathclyde, Glasgow, UK; ⁴Erasmus MC – Sophia Children's Hospital, Rotterdam, The Netherlands; ⁵University of California, San Diego, CA, USA; ⁶Hôpital de la Timone, Marseille, France; ⁷University of Tennessee Health Science Center, Memphis, TN, USA; ⁸University of Malaya, Malaysia, Malaysia; ⁹La Fe Hospital; ¹⁰University of Valencia, Valencia, Spain; ¹¹University of Tartu, Tartu, Estonia; ¹²National Children's Hospital National Center for Child Health and Development, Tokyo, Japan; ¹³University Children's Hospital Basel, Basel, Switzerland; ¹⁴St. George's Hospital, London, UK; ¹⁵Shandong University, Jinan, China

10.1136/archdischild-2019-esdppp.26

Background In the absence of consensus, the present meta-analysis was performed to determine an optimal dosing regimen of vancomycin for neonates.

Methods A 'meta-model' using NONMEM with 4894 concentrations from 1631 neonates was built and Monte Carlo simulations were performed to design an optimal intermittent infusion, aiming at reaching a target AUC₀₋₂₄ of 400 mg*h/L at steady state in at least 80% of neonates.