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BOOK OF ABSTRACTS

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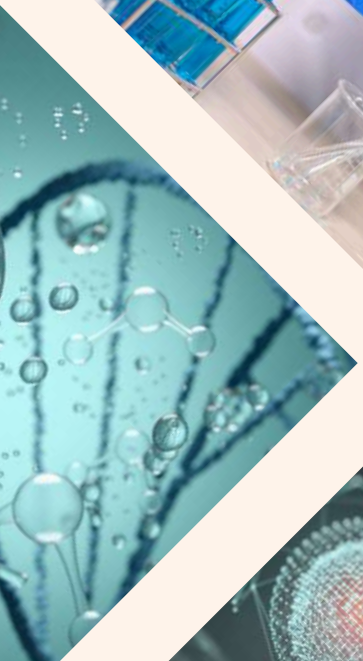

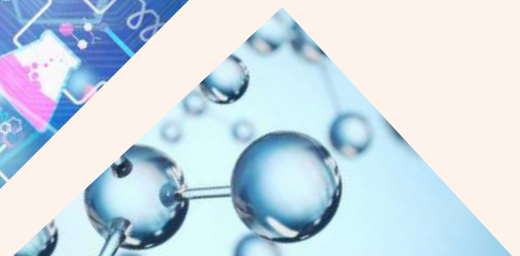

SPEAKER SECTION

SPEAKER: ANTONIO LOPALCO

Development of Midazolam/γ-Cyclodextrin Pediatric Orodispersible Films Using Direct Powder Extrusion 3D Printing

Antonio Lopalco[a], Giuseppe Francesco Racaniello[a], David Mathiron[b], Sebastien Rigaud[c], Florence Djedaini-Pilard[c], Nunzio Denora[a], Angela Assunta Lopedota[a]

[a]Department of Pharmacy – Pharmaceutical Sciences, University of Bari Aldo Moro, E. Orabona St., 70125 Bari (Italy); [b]PlateForme Analytique (PFA), Université de Picardie Jules Verne, Rue Dallery-Passage du Sourire d’Avril, 80000 Amiens (France); [c]Laboratoire de Glycochimie et des Agro-ressources d’Amiens (UR 7378 LG2A), Université de Picardie Jules Verne, Rue Baudelocque, 80000 Amiens (France)

Midazolam (MDZ) is a benzodiazepine administered via oral or sublingual routes in cases of antiepileptic treatment and surgical anesthesia but with limited bioavailability, low stability and an unpleasant taste. To overcome these limits 0.2% (w/v) MDZ oral solution containing γ-cyclodextrin (γ-CD)[1] have been developed for pediatric patients. However, solid forms adhering to the buccal mucosa and rapidly releasing MDZ would be beneficial. Orodispersible films (ODFs) are a potential solution, typically containing hydrophilic polymers that quickly dissolve in the buccal cavity, leading to rapid dissolution and drug delivery[2]. Direct printing of pharmaceutical powders allows the creation of personalized paediatric dosage forms, such as orodispersible films (ODFs)[3]. In this study, we present an optimized protocol to prepare midazolam (MDZ)/γ-cyclodextrin (γ-CD) inclusion complex-loaded ODFs using the innovative direct powder extrusion 3D printing technique (DPE). ODFs were formulated with a polymer blend consisting of polyethylene oxide and hydroxypropyl methylcellulose, in the presence or without γ-CD. An in-depth analytical investigation using NMR and LC-MS spectrometry demonstrated that MDZ/γ-CD inclusion complex could form in situ during the printing process. ODFs with the preformed inclusion complex and MDZ alone were also prepared and characterized in terms of drug loading, morphology, disintegration, drug release, and mucoadhesion. ODFs containing either the in situ-formed or preformed inclusion complex were equivalent and exhibited superior performance compared to films without γ-CD. The use of γ-CD was particularly advantageous in enhancing the film disintegration and MDZ dissolution. MDZ-loaded ODFs were successfully developed using DPE to produce thin, fast-dissolving films that are particularly suitable for paediatric populations. This approach facilitated the production of personalized dosage forms and enabled the creation of beneficial molecular interactions that would typically require additional pharmaceutical processes.

1. Mathiron, D. et al., “Benefits of methylated cyclodextrins in the development of midazolam pharmaceutical formulations”. *J. Pharm. Sci.*, 102: 2102-2111 (2013)
2. Scarpa M. et al., “Orodispersible films: Towards drug delivery in special populations”, *International Journal of Pharmaceutics*, Volume 523, Issue 1, Pages 327-335 (2017)

3. Racaniello, et al. “3D printed mucoadhesive orodispersible films manufactured by direct powder extrusion for personalized clobetasol propionate based paediatric therapies.” *International Journal of Pharmaceutics* vol. 643 (2023)

SPEAKER: SERENA BERTONI

Development of a new oral drug formulation for the treatment of Infantile Hemangioma in newborns.

Serena Bertoni[1], Eleonora De Renzis[1], Beatrice Albertini[1], Nadia Passerini[1]

1 – University of Bologna

The infantile hemangioma (IH) is the most common benign vascular tumor in the pediatric population. The first-line therapy for its treatment is oral propranolol, currently formulated as oral solution prepared extemporaneously in hospital pharmacy or available as concentrated solution (Hemangiol®). Recent studies have shown that a combination of oral propranolol and corticosteroids gives a faster response and significantly reduces the tumor volume in IH patients. However, there is currently no child-appropriate formulation available for administering a drug combination for IH treatment. In this study, solid lipid microparticles (MPs) were developed as a controlled and age-appropriate drug delivery system for the oral administration of a fixed-dose combination of propranolol hydrochloride and a corticosteroid, either prednisolone (combination I) or prednisolone acetate (combination II). The MPs were produced using spray congealing, a solvent-free technology that generates highly spherical and free-flowing particles. MPs were composed of an orally-approved lipid excipient (Compritol® 888 ATO), used alone as matrix-forming material (m-MPs) or combined with a hydrophilic polymer (polyethylenglycol, PEG) to obtain hybrid MPs (h-MPs). The produced formulations were characterized regarding drug loading amount, size, morphology and solid-state properties. Dissolution studies were conducted through an in vitro model specifically designed to simulates the gastrointestinal physiology (e.g. fluids volume and composition, digestion processes, etc.) of newborns. The obtained release profiles were compared considering the different fixed-dose combinations (I or II), type of MPs (matrix or hybrid) and administration vehicles (milk or apple juice). Spray congealed-MPs were successfully loaded with the two combinations with optimum production yields (about 70-80%) and satisfactory loading efficiencies (up to 90% considering a 1% w/w loading of each drug), indicating that this delivery system is suitable for administering two drugs, even with very different hydrophilic/hydrophobic properties, in the same dosage form. The morphological characterization showed spherical and non-aggregated particles with the crystalline drugs homogeneously distributed throughout the particle volume. Scanning electron microscopy images showed a homogeneous structure in case of m-MPs and a biphasic structure consisting in multiple PEG cores embedded in a lipid matrix in case of h-MPs. The in vitro release studies indicated that both types of MPs were able to control the release of propranolol and the corticosteroid drug for an extended period of time (about 3 hours) compared to free drugs. However, h-MPs guaranteed more consistent release profiles with less differences when varying drug combination or administration drink compared to m-MPs.

Overall, the proposed microparticle-based formulation represents a suitable dosage form for newborns and addresses the limitations of oral solutions used for IH treatment: the amount of MPs to be administered can be easily adjusted based on the patient's weight, enabling precise dosing and MPs can be dispersed in both baby-milk or apple juice, as recommended by the EMA to enhance compliance in newborns and infants. Based on the release profiles obtained, the h-MPs should help maintaining stable drug levels in the patient’s bloodstream, thus better therapeutic effect, by providing a sustained release over an extended period, as well as fewer

variations in the drug's absorption depending on the type of drink used for administration (milk or juice).

SPEAKER: SMITA SALUNKE

Accelerating Safer Administration of Medicines to Children in Low Resource Settings – Bridging Stakeholder Viewpoints.

Alka Mukne[1], Vandana Patravale[2], Pradeep Behera[3], K. Bangarurajan[4], Esmerald Hermans[5*], Jennifer Walsh[6*], Smita Salunke[7*]

1 – Indian Pharmaceutical Association (IPA), India; 2 – Society for Paediatric Medicines & Healthcare Initiative (PMHI), India; 3 – Thetabeta Analgorithms Pvt Ltd, India; 4 – JSS College of Pharmacy; Former Joint Drugs Controller, Drugs Standard Control Organization (CDSCO), India; 5 – Johnson and Johnson Innovative Medicine, Belgium; 6 – Jenny Walsh Consulting Ltd, UK; 7 – University College London School of Pharmacy, UK

*On behalf of European Paediatric Formulation Initiative (EuPFI)

Background: 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 and find solutions that accelerate the de-velopment and adoption of user-friendly administration devices. 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 featured a panel where researchers shared findings on paediatric medicine administration devices, followed by presentations on clinical and industry challenges. Participants then discussed procedural and operational issues and proposed solutions.

Results: The panel highlighted country-dependent use of devices for paediatric oral and inhaled medicines. Indian HCPs prioritize access, availability, and affordability, while European developers adhere to strict regulations on accuracy, dose markings, and labelling. In India, innovation is limited by lower regulatory reliance, with a focus on simplifying administration. The top-rated solutions, supported by all stakeholders, are device innovation and regulatory harmonization.

Conclusions: 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.

POSTER SECTION

A case report of a young patient with Beta Thalassaemia Major.

Manika Kreka[1], Bledi Kreka[1]

1 –UHCT Mother Terese, Albania Shahini University of Medicine, Tirana, Albania

Background: Haemoglobinopathies are very serious clinical conditions caused by genetic mutations, monogenic diseases. Among them, Beta Thalassaemia Major and Intermedia are very frequent diseases in Albania, with a high prevalence in our population. People with Beta Thalassaemia nowadays live longer and have a quite quality of life due to the quality of blood transfusions and a good iron chelation therapy compliance. From time to time there are a few side effects of general treatment and for this reason strict monitoring is needed. There is still more to do, in terms of permanent cure.

Aim: To report a difficult case of a 4 years old boy, suffering from Beta Thalasaemia Major who presented with abdominal discomfort and hematemesis.

Results: This patient was in treatment with blood transfusion (pure red blood cell) since the first year of life, once in three weeks. After 20 transfusions (when Ferritin level was above 1000 ng/ml) it was administered oral iron chelation therapy (Deferasirox) with a moderate dose per day (20 mg/kg/day). He was compliant and the ferritin level started to go down. 6 months after treatment he started to present with pale skin and complained from abdominal pain. It was excluded every abdominal pathology through ultrasound and laboratory examinations. Pain medications were administered from time to time.

One night he was admitted to Emergency Pediatric Ward with severe pain and hematemesis three times during the night. His Complete Blood Count showed severe anemia (nethertheless he was transfused two days ago) After some fast examinations and an urgent fibrogastroscopy, the boy was diagnosed with duodenal ulcer perforation (a very rare or uncommon in this age group, probably due to use of iron chelation therapy) and a surgery was underwent successfully.

Firstly, the patient was stabilized with blood transfusion and rehydration. In our opinion it was the effect of oral iron chelator drug, which causes this complication, unreported till now.

Discussion: A better understanding and awareness, a strictly monitoring of patients suffering from Thalassaemia and other haemoglobinopathies could help health professionals to act in the proper way and to save patients' lives. Better treatments are on the way, and we need to be optimistic.

Design of bilayered buccal films for azithromycin administration in pediatric population.

Giulia Bondi[1], Angela Abruzzo[1], Serena Bertoni[1], Federica Bigucci[1], Dritan Hasa[2], Cinzia Pagano[3], Luca Casettari[4]

1 – University of Bologna, Department of Pharmacy and Biotechnology; 2 – University of Trieste, Department of Chemical and Pharmaceutical Sciences; 3 – University of Perugia, Department of Pharmaceutical Sciences; 4 – University of Urbino Carlo Bo, Department of Biomolecular Sciences

Currently, azithromycin (AZT) represents one of the most prescribed drugs in pediatric population. It is generally administered through the oral route and employed for the treatment of different infectious diseases, such as acute bacterial sinus, otitis media, pharyngitis, tonsillitis, pneumonia, bronchitis, urogenital tract and skin infections. However, several drawbacks of AZT, like its low aqueous solubility, poor oral bioavailability and bitter taste, can affect the therapy efficacy and the children compliance. For this reason, alternative strategies useful to improve AZT administration should be investigated. In this context, buccal films can be considered as child-friendly promising formulations thanks to their thinness, flexibility, ease applicability and ability to ensure accurate dosing. Therefore, in this study we firstly aimed to obtain a mucoadhesive primary layer capable of establishing a closed and prolonged contact with mucosa and controlling AZT release. Secondly, a further layer was evaluated to be applied on the primary one, to assure a unidirectional absorption through the buccal mucosa and limit the drug bitter taste in the mouth. Specifically, for the primary layer preparation, solutions based on different selected mucoadhesive polymers (hydroxypropylmethylcellulose HPMC, sodium hyaluronate HYA, sodium alginate ALG, xanthan gum XG, carrageenan CAR and chitosan CH) were mixed with excipients able to increase drug solubility (Soluplus SOL and polyvinylpyrrolidone PVP, K25 or K90). The obtained solutions, loaded with AZT, were finally cast in a silicon mold and oven-dried at 70 °C for 7 h. After this, an ethylcellulose solution was sprayed on the primary polymeric layer and immediately oven-dried at 70 °C for 5 min, in order to obtain the second layer. Films were characterized in terms of thickness, weight, drug content, water uptake (WU) ability and in vitro release. The preliminary selection allowed us to formulate loaded films (theoretical amount of AZT equal to 9.9 mg/cm2) composed of CS/PVP (K25 and K90), CS/SOL, HYA/SOL and ALG/SOL. The obtained films were uniform, slightly opalescent, thin (thickness lower than 0.3 mm), and presented a drug content equal to 20-25 % w/w, also confirmed by X-ray analysis. Finally, WU ability and in vitro release depended on the polymeric composition of the film. Particularly, films based on CS/PVP and CS/SOL reached the maximum ability to hydrate after 2 hours, tended to solubilize and determined a quick drug release. On the other hand, HYA/SOL and ALG/SOL showed a more gradual hydration ability and sustained release, due to the high viscosity of the polymeric network in the gelled state. Interestingly, bilayered films allowed the release of a lower amount of drug with respect to the primary polymeric layer, thus demonstrating that they could limit drug release inside the buccal cavity. This latter finding is extremely important considering the need for limiting the bitter taste of AZT and minimizing the extent to which the drug is swallowed. Further investigations will be carried out in order to investigate the mucoadhesion properties of films and their ability to promote drug diffusion through a mucosa. Films with the selected compositions will be prepared through 3D printing technology (3DP), as innovative tool able to meet the demands of personalized therapy.

Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia: Improving Biochemical Control and Treatment Outcomes.

Federico Baronio[1], Michele Zagariello[1], Rita Ortolano[1], Daniele Zama[1,2], Marcello Lanari[1,2], Egidio Candela[1,2]

1 – Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna; 2 – Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna;

Background: Standard glucocorticoid therapy for congenital adrenal hyperplasia (CAH) often fails to adequately control androgen excess, leading to overtreatment with glucocorticoids and numerous adverse events. In Europe, two innovative modified-release hydrocortisone (MRHC) formulations are available: modified-release hydrocortisone tablets and capsules.

Modified-release tablets consist of an immediate-release outer layer and a prolonged-release core, allowing for once-daily dosing. However, this formulation does not replicate the physiological nocturnal cortisol rise, as cortisol levels increase only after the morning dose.

Modified-release capsules (MRHC, Efmody©, formerly Chronocort) provide delayed release and prolonged absorption, mimicking the natural circadian cortisol rhythm. MRHC is taken twice daily—two hours after dinner and one hour before breakfast—resulting in improved morning control of adrenal androgen markers in CAH patients and better disease management. Approved by AIFA (Determination 110/2021) for CAH patients ≥12 years, MRHC lacks clinical data in adolescents aged 12–18.

Objectives: We investigated whether modified-release hydrocortisone (MRHC), which mimics the circadian rhythm of cortisol, could improve disease control and evaluate its effectiveness, safety, and potential adverse effects

Methods: We conducted a 12-month prospective observational study on 18 CAH patients aged ≥12 who switched from conventional therapy to MRHC. Primary outcomes included reducing 17-hydroxyprogesterone (17OHP) levels below 1200 ng/dL, normalizing delta-4-androstenedione levels, reducing total hydrocortisone dose, and comparing adverse events and adrenal crises before and after the therapeutic switch. Secondary outcomes included ACTH, renin, testosterone levels, and metabolic profile parameters (BMI SDS, growth velocity SDS, and blood pressure).

Results: MRHC resulted in improved biochemical control, with a statistically significant morning 17OHP reduction observed after 3 months of MRHC therapy compared to conventional treatment ($p = 0.013$). However, at 6 months, the decrease was not statistically significant ($p = 0.116$). The percentage of patients with controlled 09:00h serum 17OHP (<1200 ng/dL) was 62.5% at 3 months and 45% at 6 months, compared to only 6% with standard therapy. The mean daily hydrocortisone dose was 15.4 mg/day at baseline and 15 mg/day at 6 months. No severe adverse events or adrenal crises were reported during MRHC therapy. Moreover, no laboratory, genetic, or clinical markers have been identified to predict which patients would benefit more from MRHC over standard treatment.

Conclusion: MRHC improved biochemical disease control in most patients, with a slight reduction in steroid dose over time and no severe adverse events or adrenal crises.

The Benefits of Glycosade and Maizena in the pediatric treatment of Glycogen Storage Diseases Type I, III, and IX: the experience of Emilia- Romagna.

Alice Rossi[3], Maria Giulia Regazzi[3], Rita Ortolano[1], Daniele Zama[1,2], Federico Baronio[1], Giacomo Biasucci[1,2], Marcello Lanari[1,2], Egidio Candela[1,2]

1 – Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna; 2 – Department of Medical and Surgical Sciences, Alma Mater Studiorum, University of Bologna; 3 – Clinical Nutrition and Metabolism Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna

Background: Glycogen storage diseases (GSDs) are inherited metabolic disorders causing abnormal glycogen metabolism, leading to hypoglycemia and hepatomegaly. GSD I, III, and IX require dietary management to prevent metabolic decompensation. Traditional therapy with raw cornstarch (Maizena) provides sustained glucose release but requires frequent intake, particularly at night, imposing a burden on patients and caregivers. Glycoside, a modified waxy cornstarch, offers extended glucose release, reducing administration frequency and improving metabolic stability. This study evaluates Glycosade's benefits in pediatric GSD patients at the Emilia-Romagna Regional Reference Center for metabolic disease and newborn screening.

Materials and Methods: A retrospective study was conducted on 7 pediatric patients with GSD I, III, and IX. 5/7 patients switched from traditional cornstarch to Glycoside, and metabolic control was assessed over six months. Clinical evaluations included fasting glucose, lactate, triglycerides, liver enzyme levels, and growth parameters. Primary endpoints were glucose stability, nocturnal hypoglycemia reduction, and liver function improvement. Secondary endpoints included gastrointestinal tolerance, treatment adherence, and patient well-being. Dietary intake data were recorded, including macronutrient distribution and cornstarch administration.

Results: Most of the patients showed improved metabolic control with Glycosade. Glycemic stability increased, reducing nocturnal carbohydrate needs. 5/7 patients maintained stable fasting glucose at three months, compared to two before switching. 1/7 patients with glycogenosis IXa take neither of the two compositions. Growth parameters remained stable, with 3 patients experiencing significant weight gain. Treatment adherence improved, reducing nighttime feedings and enhancing sleep quality. Gastrointestinal tolerance varied, with some patients tolerating Glycosade better than Maizena.

Discussion: Glycoside provided prolonged glucose release, minimizing hypoglycemia risk and improving adherence. Stabilized liver enzymes suggest reduced hepatic glycogen accumulation, enhancing long-term prognosis. Weight changes varied despite the known possibility of weight gain associated with these formulations. Glycosade's higher cost may limit accessibility, necessitating further cost-effectiveness studies. Expanding the study to a larger cohort will help validate these findings and determine optimal dosing regimens tailored to individual metabolic needs.

Investigation into user perspectives of minitablets for paediatric treatments in LMICs.

Soniya Notani[1], Elisa Alessandrini[1]

1 – UCL School of Pharmacy, United Kingdom

Background: Minitablets have been identified as a promising dosage form for the paediatric population. However, there is limited evidence-based data available on acceptability of minitablets, particularly handling aspects of minitablet. Additionally, there is insufficient information on whether there are differences in user opinions based on socio-economic status, health condition, or level of experience. 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. 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, administration methods, choice of packaging, ease/comfort of handling minitablets and willingness to use minitablets over conventional tablets.

Findings: 60 parents were recruited from schools and hospitals. 52% of the parents were classified as middle/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. Among all participants, 67% were willing to administer 1.5mm tablets (majority aged 2-8yrs), 26% were willing to administer 3mm tablets (majority aged 6-11yrs), and 7% were willing to administer 4mm tablets (majority aged 9-12yrs). 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. 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. 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. 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 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.

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. This pilot phase identified significant gaps in survey methodology, particularly in effectively correlating tablet characteristics with tablet number and size, association with socioeconomic status. 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.