<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Poster title</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acceptance of drug-free minitablets in young children</td>
</tr>
<tr>
<td>2</td>
<td>A new chewing gum device suitable for children with enhanced bioavailability of herbal drug's active components</td>
</tr>
<tr>
<td>3</td>
<td>Compatibility of y-site administration of medications with a standard 3-in-1 parenteral nutrition admixture for paediatrics</td>
</tr>
<tr>
<td>4</td>
<td>Customizing the taste of medicine using the flavorx® flavoring system</td>
</tr>
<tr>
<td>5</td>
<td>Development and evaluation using electronic tongue of taste-masked drug for paediatric medicines</td>
</tr>
<tr>
<td>6</td>
<td>Development of an antiviral oral pediatric suspension</td>
</tr>
<tr>
<td>7</td>
<td>Development of antimalaric-antibiotic association in a fast dispersible tablet using rectal route</td>
</tr>
<tr>
<td>8</td>
<td>Development of new disintegration tests for orodispersible films</td>
</tr>
<tr>
<td>9</td>
<td>Development of orodispersible mini-patches for the treatment of vomiting and nausea</td>
</tr>
<tr>
<td>10</td>
<td>Development of clonidine hcl orodispersible film for paediatric population</td>
</tr>
<tr>
<td>11</td>
<td>Difficulties of administering drugs in a pediatric intensive care unit</td>
</tr>
<tr>
<td>12</td>
<td>Enteric coated microparticles for use in geriatric and paediatric patients</td>
</tr>
<tr>
<td>13</td>
<td>Evaluation of drug bitterness, masking and its effect on food taste quality using artificial lipid-</td>
</tr>
<tr>
<td>14</td>
<td>Evaluation of orally disintegrating tablets (odts) prepared with co-processed excipients</td>
</tr>
<tr>
<td>15</td>
<td>Extended release hpmc mini-tablets for paediatric delivery of hydrocortisone</td>
</tr>
<tr>
<td>16</td>
<td>Flavoring of commercial oral liquid pharmaceutical products</td>
</tr>
<tr>
<td>17</td>
<td>Hydroxypropyl cellulose films - the spoonful of sugar that helps the medicine go down?</td>
</tr>
<tr>
<td>18</td>
<td>Identifying the causes of off-flavor in generic tablets using electronic nose &amp; electronic tongue</td>
</tr>
<tr>
<td>19</td>
<td>In vitro performance of a dry powder inhaler using mouth-throat models of 4-5-year-old children</td>
</tr>
<tr>
<td>20</td>
<td>Innovative approach in formulating better medicine for children: stick pack oral melts</td>
</tr>
<tr>
<td>21</td>
<td>Instrumental method to reliably select the best flavour candidate for a stable masking of active principle bitterness over time</td>
</tr>
<tr>
<td>22</td>
<td>Interactive mixtures with high dose homogeneity ideal for mini-tablets</td>
</tr>
<tr>
<td>23</td>
<td>Investigation of processing parameters for orally disintegrating tablets</td>
</tr>
<tr>
<td>24</td>
<td>Minitablets with enalapril or ranitidine – production and methods of physical analysis</td>
</tr>
<tr>
<td>25</td>
<td>Oral dosage form suitability in paediatrics: healthcare professionals’ views after the EMA matrix</td>
</tr>
<tr>
<td>26</td>
<td>Odmts with taste-masked zinc sulphate as a child-appropriate dosage form for developing countries</td>
</tr>
<tr>
<td>27</td>
<td>Orodispersible minitablets as a child-appropriate dosage form with enalapril maleate: avoiding the</td>
</tr>
<tr>
<td>28</td>
<td>Paediatric drug forms and pharmacy education in Bulgaria</td>
</tr>
<tr>
<td>29</td>
<td>Paediatric extemporaneous formulations: an audit in the secondary care setting</td>
</tr>
<tr>
<td>30</td>
<td>Pediatric treatment development for helminthiasis able to be used by who in campaigns of prevention</td>
</tr>
<tr>
<td>31</td>
<td>Selecting the food matrix with the highest masking power for delivering recommendations for children</td>
</tr>
<tr>
<td>32</td>
<td>Sensory analysis of paediatric formulations of abacavir and lamivudine for hiv</td>
</tr>
<tr>
<td>33</td>
<td>Steady state pharmacokinetics of the novel azt/3tc fdc tablets in hiv-infected children</td>
</tr>
<tr>
<td></td>
<td>Study on solid self-emulsifying formulations with ibuprofen</td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>37</td>
<td>Taste assessment of orodispersible mini-patches by an electronic taste sensing system</td>
</tr>
<tr>
<td>38</td>
<td>Taste masking of an amodiaquine hcl granular formulation and its evaluation by a human taste panel</td>
</tr>
<tr>
<td>39</td>
<td>Taste masking of bitter apis by using hot-melt extrusion (hme)</td>
</tr>
<tr>
<td>40</td>
<td>Taste masking of hot-melt extruded bitter apis: an astree e-tongue evaluation</td>
</tr>
<tr>
<td>41</td>
<td>Taste masking evaluation of hot melt extruded paracetamol using an electronic tongue</td>
</tr>
</tbody>
</table>
Acceptance of drug-free minitablets in young children
Spomer Natalie¹, Klingmann Viviane¹, Stoltenberg Ines², Lerch Christian³, Meissner Thomas¹, Breitkreutz Jörg²
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Objective: To determine the applicability and capability to swallow small-sized solid dosage forms (minitablets, 2 mm diameter) in young children. Up to now there is no reliable scientific data available. While WHO recommends the use of solid multiparticulates, EMA doubts about their applicability in paediatrics. This clinical study was aimed at generating scientific data on the acceptability of uncoated and coated drug-free minitablets in children < 6 y.

Methods: The trial was performed in a randomised cross-over design with 2 mm minitablets (film-coated or uncoated) and 3 ml glucose syrup 15% as a reference. 306 children (0.5 to 5 y) were included in the prospective study. The study was performed adhering to all regulations including ethical and informed consent and registered in the German Register for Clinical Studies. Hospitalized children matching the inclusion criteria were tested according to the predefined randomisation scheme. Children received either the minitablet with a beverage of their choice or 3 ml of the glucose-syrup. Deglutition and swallowing were assessed. Subsequently, the procedure was repeated with the other formulations. Evaluation criteria for minitablets were: swallowed, chewed, spat out, choked on, refused to take; for the syrup: completely swallowed, small runlet, spat out, choked on, refused to take.

Results: In all age groups the acceptance (swallowed or chewed/swallowed) of the uncoated minitablet was higher or equal to the syrup (95% CI). Capability to swallow the uncoated or coated minitablets showed differences between the age groups: very young children were fully capable to swallow without chewing. Surprisingly, even the youngest children accepted the minitablet better than the syrup which is in clear contradiction to EMA/CHMP’s present opinion. Some children between 2 to 4 y chewed the minitablets, which might be a problem for coated dosage forms with funtionalized films, but still accepted them well.

Conclusion: Minitablets are a promising and safe alternative to liquid drug formulations, also for young children from 6 m to 6 y. EMA should reconsider their recommendations regarding the applicability of solid dosage forms for children.

A new chewing gum device suitable for children with enhanced bioavailability of herbal drug’s active components
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Formulating Better Medicines for Children
Objective: The aim of the research is to develop a new device suitable for delivering in children active principles derived from herbal drugs. Since most herbal drugs suffer from poor oral bioavailability a further aim to be accomplished is to enhance the bioavailability of the active ingredients. Silybum Marianum dry extract was selected in this research as a poorly bioavailable phytocomplex model.

Design and methods: Two kind of 3 layers chewing gums were produced: System 1 containing the pure Silybum Marianum dry extract (91.7% of Silybin A+B) and System 2 containing dry extract mechanochemically activated with sodium croscarmellose. A schematic representation of the gum, including the phytocomplex content in each layer, is depicted in the Figure.

The ingredients of the core and external layers of a chewing gum were: (inner core) phytocomplex, talc, magnesium stearate, colloidal sylicon dioxide, Mint aroma, aspartame, and (external layer) gum base, maltodextrins, talc, colloidal sylicon dioxide, Mint aroma, aspartame. Each formulation was chewed for 40 min by a panel of 15 healthy volunteers and the content of the main Silybum Marianum flavolignans (free Silybin A and B) in plasma was determined.

Results: A very fast and pronounced absorption of Silybin A and B was obtained from the 3 layers gums containing the mechanochemically activated dry extract, whilst the plasma concentrations after administration of System 1 were under the sensitivity of the HLPC-MS method. A comparison of the AUC of System 2 with an oral formulation (capsule) reported in literature, the 3 layers gums revealed an improvement of 3 and 7 times for free Silybin A and B, respectively.

Conclusions: This study demonstrates a great bioavailability enhancement of the chewing gum, with the advantage of a device having patient compliance, no risk of accidental overdosing and easy production with commonly used apparatus and excipients.
Compatibility of y-site administration of medications with a Standard 3-in-1 parenteral nutrition admixture for paediatrics

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Compatibility studies are mainly conducted for TPN standard bags and doses relevant for adults.¹ There is a lack of documented information for paediatric patients. There are two main compatibility problems, precipitation and destabilisation of the fat emulsion. The aim was to conduct preliminary examinations of the compatibility of TPN standard bags suitable for children and selected drugs relevant for co-administration in children. Olimel® N5E (Baxter, UK) was chosen as TPN (3-in-1) admixture. The volume of TPN required to meet the ESPGHAN/ESPEN guidelines,²³ was identified for children between 10–50 kg. The drugs tested were: Fosphenytoin, furosemide, paracetamol, ondansetron, dexamethasone, acyclovir, ampicillin, metronidazole, fluconazole, clindamycin and ceftazidime. Relevant dose and dilution was identified.²⁻⁵ For simulation of the Y-site administrations, drug and TPN admixture were combined in centrifugation tubes in three different mixing ratios. The amount of TPN (ml/h) meeting the drug (ml/h) in the line was calculated. The mixing ratio 1:1 was always tested, in addition two mixing ratios representing highest and lowest amount of drug probable to meet TPN in the infusion line. Physical compatibility was examined immediately and after 4h. The samples were examined under microscope to check for changes in droplet size. Zeta potential and pH were measured. The aqueous phase, collected after centrifugation, was examined for particles using a Tyndall beam and reduced transmission.

Acyclovir, the positive control, gave precipitation after mixing with TPN. Preliminary results indicate that the other investigated drugs seem to be compatible with Olimel N5E at doses relevant for children between 10-50 kg. Acknowledgements: The financial support from the "Norwegian Medicines for Children Network" is greatly appreciated, so is also the support and guidance from the several hospital pharmacies, paediatric wards and TPN admixture manufacturers (Baxter, Norway, and Fresenius Kabi, Norway) who all have generously shared their experience and expertise.

Customizing the taste of medicine using the flavorx® flavoring system – a unique approach to improving medication compliance
Amos Stuart, Baker Chad, Cielewich Chris, Gueye Yaye.

Objective: To determine which pediatric liquid medications are commonly re-flavored in the U.S. pharmacy setting and which flavors are preferred by consumers.

Design & Methods: The FLAVORx Online Formulary provides detailed re-flavoring instructions for commercially prepared pediatric medications and over-the-counter drugs. This guide is one of several references a pharmacist can consult when a patient requests flavoring or when a physician or pharmacist recommends flavoring to improve compliance. By investigating 2010 usage data from the FLAVORx Online Formulary, medications were ranked according to how often they were re-flavored in the pharmacy. The data also identifies the most commonly chosen flavors for improving the palatability of pediatric liquid medications. Over 2 million flavorings were analyzed. Brand and generic versions of medications were consolidated and listed as the brand name.

Results: The 20 most commonly re-flavored medications are detailed in Figure 1. Figure 2 shows the most popular flavor choices from the selection of FLAVORx flavors.

Figure 1: Commonly Re-Flavored Liquid Medications

Figure 2: Popular Flavors for Improving the Palatability of Liquid Medications
Conclusions: The FLAVORx Flavoring System is used to improve palatability for a wide-range of pediatric medications. Antibiotics are shown to have flavoring requested by patients and added by pharmacists quite often. Five flavors (grape, bubblegum, strawberry, watermelon and cherry) dominate the preferred flavor choice of the U.S. consumer. However, no single flavor was preferred by a majority of people.

**Development and evaluation using electronic tongue of taste-masked drug for paediatric medicines**

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**Objective:** The aim of this study is to develop effective taste-masked drugs by selecting safe and acceptable excipients for paediatric population.

**Methods:** Taste-masking of acetaminophen is achieved by encapsulating inside a skin former based on sodium caseinate and lecithin through spray-drying process. A 24 full factorial design is set up to estimate the effect of different variables on taste-masking efficiency. Taste assessment is carried out by two methods: in vitro drug release study using the syringe pump and bio-mimetic taste evaluation using the Astree e-tongue.

**Results:** In the first two minutes, only 7% to 17% of drug is released from 16 formulations in comparison of about 30% from pure drug. The model of experimental design reveals the predominant effect of sodium caseinate and especially of lecithin in retarding the drug release within first 10 min. The evaluation of taste in function of time is realized by Astree e-tongue with solutions equivalent to 0.4% of drug in water. Two formulations are analyzed including run 2.1 (ratio caseinate:lecithin 1:0.5) and 2.13 (5:1.5) for comparison. Within first two
minutes, these two formulations represent a better masking effect rather than reference. Interestingly, the masking efficiency is shown more important and stable throughout 10 minutes without agitation in the case of the run 2.13.

**Conclusions:** Through spray-drying process, acetaminophen seems encapsulated within the skin former composed of sodium caseinate and lecithin. This coating delays the release of drug in the early time, therefore is able to mask the drug bitterness upon administration into the mouth.

**Development of an antiviral oral pediatric suspension**

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An age-appropriate suspension for children between the ages of 3 and 6 years was developed for an antiviral BCS class 2 compound. A screening study was performed to select a wetting agent and a buffer. The drug substance was difficult to wet and hydroxypropylcellulose gave the best results. Citric acid was selected as buffer. Because of its thixotropic behavior, Avicel RC591 was chosen as the suspending agent. Combinations of various sweeteners and flavors at different concentrations were screened to mask the bitterness. However, this was not successful. By an additional increase of the drug substance particle size, an acceptable taste was obtained as was confirmed by a clinical pediatric study. Since the drug substance particle size is the main factor that influences physical stability (sedimentation, resuspendability), the taste and the dissolution of the suspension, a particle size that satisfies all three important product characteristics was selected. Optimal chemical stability was obtained in the pH range 6.0-7.0. In this pH area the parabens are the best preservatives for use in children. Since propylparaben precipitated into the formulations, suspensions with only methylparaben were screened for their antimicrobial efficacy. Sodium methylparaben at 3.43 mg/mL was selected for the formulation as the sodium salt is more water soluble and requires no heating during the production process. Target pH was set at pH 6.4 with pH limits of 6.0 and 6.8. The formulation has been shown to be chemically and physically stable and a shelf life of 24 months at room temperature has been defined.

**Development of antimalaric-antibiotic association in a fast dispersible tablet using rectal route.**

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**Objective:** We develop an emergency symptomatic treatment for children in developing countries who suffer from high fever, far from hospital and/or Health center, involving transfer to these centers. The most frequent causes are either malaria or/and bacterial infection. According with WHO, we choose an antimalaric-antibiotic association, Azytromicyn and Artemether.
**Design & Methods:** Health status frequently doesn’t avoid oral administration, and as the treatment has to be delivered at home, we choose rectal route. The form containing 300mg Artemether and 400mg Azytromicyn, is an oblong and scored tablet. It must be fast dispersable in rectal ampulla, easy to administrate, of low cost production and easily transposable in developing countries.

**Results:** Interaction between both API was tested with DSC, Crystallography and HPLC. We choose direct compression. Excipients are justified (compatibility, quantity, acceptability in pediatric treatment), and controls are performed at every step of the process. The critical point is disintegration time (2ml water only). We create tests to optimize excipients and to appreciate swelling: the use of a chamois leather capillarity moistened allows the choice of lubricants. Dissolution time is optimized by the choice of Lutrol®, and best % is obtained by testing 3 percentages, U-test Mann and Whitney pvalue=0.04). Content uniformity measured (HPLC method) shows acceptable results (between 85% and 115% of the mean, 10 tablets tested).

**Conclusions:** The characteristics of this form are compatible with rectal route; it can be use even in very emergency cases. Bioavailability studies are actually performed on rabbits. Collaboration: P. Millet HÔPITAL ST-ANDRÉ, Bordeaux, P. Oliero, WHO Genève and T. Kauss, Université Bordeaux Segalen

**Development of new disintegration tests for orodispersible films**

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**Objective:** Orodispersible films are intended to disintegrate within seconds on the tongue. They are a promising new dosage form especially for children. No official disintegration test has been published yet. Using the pharmacopoeial disintegration apparatus the endpoint determination is almost impossible. Alternative methods described in literature lack of the mechanical stress performed by the human tongue. New simple tests mimicking the physiological conditions should be developed in the present paper.

**Methods:** Test 1: The pharmacopoeial disintegration apparatus was equipped with a newly developed sample holder. 300 ml phosphate buffer pH 7.4 at 37 °C were used as medium. Test 2: One edge of a special film specimen according to DIN EN ISO 527-3 is fixed, on the other edge a magnetic mass is attached, revealing a vertically positioned specimen. A paint roller impregnated with water rotates at the film surface. The endpoint is determined by the time-point the mass falls down. Both methods were tested with five placebo preparations based on different polymers.

**Results:** The disintegration times of both tests were in the range of typical in vivo disintegration times (10 to 59 s respective 11 to 65 s). Equipment handling and endpoint determination were easy. Using the improved pharmacopoeial disintegration test the mechanical stress is simulated
by the movement through the medium. The roller method deals with a smaller, more realistic volume, but is difficult to be adjusted correctly.

**Conclusion:** The pharmacopoeial disintegration apparatus modified with the new sample holder is the most suitable disintegration test system for orodispensible films.

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**Development of clonidine hcl orodispensible film for paediatric population**

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**Introduction:** The lack of age-appropriate formulation of Clonidine HCl limits its use in infants for postoperative pain management and sedation.

**Objectives:** Formulation of acceptable low dose clonidine HCl films. Exploration of characterization methods of orodispensible films especially discriminative dissolution test.

**Design and Method:** Clonidine HCl films (90mcg/2cm\(^2\)) were prepared either by solvent casting (SC) or thermal injection (TIJ) method [1] based on a polymer blend of Lycoat NG 73\(^\circledR\) (Roquette) a novel hydroxypropyl pea starch and carboxymethyl cellulose. They were assessed in terms of thickness, mechanical properties, morphology, drug uniformity and disintegration time. Two dissolution methods were attempted (small Petri dish versus Franz diffusion cell containing 5ml of pH=6.0 phosphate buffer at 37\(^\circ\)C). Drug release was measured by a validated HPLC method.

**Results:** Optimum thin films (77+/-.5.5µm) were obtained with ideal mechanical properties (high strain, high tensile strength, low Young's modulus), fast disintegration time (39+/-.1 seconds). Drug polymers compatibility was demonstrated by microscopy. Drug was homogeneously dispersed in SC and TIJ films. Drug release was completed within 3 minutes similarly with both methods.

**Conclusion:** Clonidine HCl orodispensible films are promising dosage forms for the younger age group of paediatric intensive care patients. Franz cell and Petri dish method seems promising to evaluate films dissolution test.

Development of orodispersible mini-patches for the treatment of vomiting and nausea
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Objective: The aim of the study was to develop an orodispersible mini-patch (ODMP) containing dimenhydrinate that offers an alternative to syrups or suppositories for the treatment of vomiting and nausea in the paediatric population.

Methods: Patches consisting of the modified starch polymer Roquette’s Lycoat RS 720, glycerol, ethanol, water, coloring agent Sicovit E122 and dimenhydrinate were prepared and modified by adding hydroxypropyl-ß-cyclodextrin (HP-ß-CD) and sodium saccharin as taste masking agents. Patches were cut into rectangular pieces (2cmx1.5cm) after drying. Weight, thickness, disintegration time, adhesion force, drug release and API content were determined.

Results: Patches containing HP-ß-CD were completely transparent, whereas the other formulations appeared cloudy after drying. HP-ß-CD improved the solubility of dimenhydrinate in the formulation and prevented the precipitation of the drug after evaporation of water and the co-solvent ethanol. The content uniformity test according to the European Pharmacopoeia (2.9.40) for an API dose under 25 mg was successfully performed. Adhesion testings showed that the patch became sticky and viscous within seconds after having contact to a small amount of fluid. The drug release started immediately while the patch disintegrated in the same range of time as in typical in vivo disintegration time testings for placebo (15 to 29s).

Conclusion: Due to their adhesion to wetted mucosa and their fast disintegration, danger of swallowing, aspirating or inhaling an ODMP is minimized. This dosage form offers a novel innovative approach that could be beneficial to dimenhydrinate suppositories, dragees and syrups already available on market.

Difficulties of administering drugs in a pediatric intensive care unit
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Objective(s): Regulation No. 1901/2006 issued by the European Parliament stresses the need “to improve the information available on the use of medicinal products in the various paediatric populations”. The objective of this work is to identify the difficulties of drug administration in children hospitalized in a pediatric intensive care unit.

Design & Methods: This study was conducted from May 2009 to June 2010 in the pediatric intensive care unit of University Hospital of Caen (12 beds). A questionnaire was distributed to medical and paramedical staff of the unit to learn about the difficulties encountered in administrating drugs to children and the conduct required to address those difficulties.
**Results:** Thirty-two observations were performed in children who are between 8 months and 16 years old. They report that unpleasant taste is the main problem (Pristinamycin, paracetamol). The enquiry reveals that many of professionals mix these drugs with food, although its compatibility with the drugs is unknown. Residue remains when enteral feeding is required for dispersible tablets (amoxicillin, lansoprazole). Frequently there is a total absence of appropriate dosage, (warfarin) or of adapted forms (patches of scopolamine). These problems generate risks of ineffective treatments because of underdosing or poor kinetics.

**Conclusion:** This study identifies drugs whose administration is difficult in children and risks to the patients due to the absence of specialities tailored to children. The significant number of statement due to Pristinamycin lead us to engage a feasibility study to formulate pristinamycin-cyclodextrin-inclusion complex to solve its tasting problem

**Enteric coated microparticles for use in geriatric and paediatric patients**

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**Objectives:** Children and the elderly have difficulties in taking conventional modified release (gastric-resistant or sustained-release) dosage forms due to swallowing difficulties. The aim of this project is to develop gastric-resistant microparticles using industrial adapted fluidised bed coating.

**Materials and methods:** Prednisolone was layered onto MCC microspheres (100 - 200 µm) and further coated with Eudragit® L30D-55, containing 5, 10 or 15% w/w glycerol monostearate (GMS) in a fluidised bed coater (MP-micro). The equipment was modified by the addition of swirl vanes and a filter mesh to aid air flow and prevent product loss. The enteric coated microparticles (weight gain 30 and 40%) were subjected to dissolution tests in 0.1 M HCl for 2 h and subsequently pH 6.8 phosphate buffer using USPⅡ apparatus.

**Results and discussions:** Coating process using formulations containing 5 and 10% GMS were discontinued due to particle agglomeration. No agglomeration was observed using 15% GMS and the resultant coating showed smooth surfaces and high yields (90.4 and 90.7% for the 30 and 40% weight gain respectively). Weight gain at 30% was not sufficient to provide gastric resistance (25% release in 0.1 M HCl). At 40% weight gain, less than 5% prednisolone was released in 0.1 M HCl in 2 h followed by immediate release in buffer, indicating good gastric-resistance.

**Conclusions:** Drug-loaded microparticles were successfully coated with an aqueous enteric formulation using fluidised bed coating and gastric-resistance was achieved. Future work will focus on the effect of drug solubility on acid-resistance, and the application on sustained release microparticles.
**Evaluation of drug bitterness, masking and its effect on food taste quality using artificial lipid-based membrane taste sensor**

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²Kyushu University

**Objectives:** Oral drug administration frequently causes patients, especially pediatric patients, to refuse medication because of drug bitterness, resulting in decreased therapeutic benefit. Consequently, we need a method to reduce or mask bitterness, as well as objective measurements of bitterness. This study describes visualization of bitterness intensity and estimates the effect on food taste quality with co-existing bitterness-masking drugs. We propose a way to evaluate easy-to-take drugs for pediatric patients using an artificial-lipid based taste sensor.

**Methods:** A Taste Sensing System (TS-5000Z, Intelligent Sensor Technology, Inc., Japan) with multichannel lipid/polymer membranes was used to measure the bitterness of sample solutions. The membrane potential induced by drug adsorption at the membrane surface is converted to taste information (taste intensity and quality). To estimate the bitterness intensity of unknown drugs, taste-sensor measurements and sensory evaluation scores were performed against a quinine-hydrochloride sample. Hydrochloride drugs as well as promising bitterness-masking materials and their effects on food taste quality were measured to evaluate sensitivity and bitterness-suppression effect.

**Results:** Quinine taste intensities were highly correlated with sensory-evaluation scores. Drug bitterness intensity was estimated based on the sensor output regression line. Addition of bitterness-masking materials significantly masked bitterness. The potency of co-existing masking drugs on food taste quality is also described.

**Evaluation of orally disintegrating tablets (odts) prepared with co-processed excipients**

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**Objectives:** One of the problems limiting therapy with solid oral dosage forms in pediatric population is difficulty with swallowing. Orodispersible tablets (ODTs) were developed to overcome that issue since they dissolve or disperse in saliva quickly after administration. In this
study three co-processed excipients for direct compression of orodispersible tablets were evaluated.

**Design & Methods:** Placebo tablets composed of F-Melt type C, Ludiflash or Pharmaburst and sodium stearyl fumarate as a lubricant were directly compressed with single punch tablet press with compression force 10 - 30 kN. Their mechanical properties (hardness and friability) were evaluated. The disintegration time was measured in standard pharmacopeial disintegration apparatus and with rotating shaft apparatus constructed in our department (based on proposition of Narazaki et al.). In order to obtain additional data on disintegration process of prepared formulations magnetic resonance imaging (MRI) technique and wetting test with visual observations were applied. The results were compared with disintegration time in the oral cavity.

**Results:** All tablets disintegrated in less than 3 minutes. The implemented computer software allowed observation of changes in tablet’s thickness during disintegration, due to swelling or erosion. Application of magnetic resonance imaging method allowed the better understanding of disintegration process. Solvent penetration inside the tablet, wetting of tablet mass, swelling, and erosion were observed.

**Conclusions:** The results have shown that all evaluated excipients can successfully be used for formulation of ODTs.
This work was supported by the Polish Ministry of Science and Higher Education, grant no. N N405 024439, which is gratefully acknowledged.

**Extended release hpmc mini-tablets for paediatric delivery of hydrocortisone**

Faiezah¹, Roberts Matthew¹, Seton Linda¹, Ford James¹, Levina Marina², Rajabi-Siahboomi Ali²

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²Colorcon Ltd, Dartford, UK

**Objectives:** Mini-tablets are dosage forms with potential for paediatric drug delivery. Extending drug release helps to prolong therapeutic action and enhance patient compliance. The aims of this study were to develop extended release (ER) mini-tablets and to evaluate the influence of hydroxypropyl methylcellulose (HPMC) concentration on hydrocortisone release from differently sized minitablets.

**Methods:** Formulations including 16.67 %w/w hydrocortisone and 30, 40, 50 or 60 %w/w HPMC (METHOCEL™ K15M) were used to manufacture 2 or 3 mm mini-tablets and 4 or 7 mm tablets (hydrocortisone doses of 0.67, 2.50, 6.67 and 33.34 mg/tablet respectively) on a Stylcam®100R rotary press simulator. Drug release was evaluated using a Varian VK 7000 dissolution tester and UV spectrophotometry at 248 nm.

**Results:** Robust ER hydrocortisone mini-tablets were successfully produced. Increasing HPMC concentration and tablet size reduced drug release rate. At 30 %w/w HPMC rapid hydrocortisone release from all studied mini-tablets was observed, indicating the need for
higher polymer concentrations. At higher HPMC levels (> 40%) a thick and turbid gel layer formed, which was resistant to erosion and diffusion, resulting in a reduced drug release rate. In comparison to 7mm tablets, mini-tablets demonstrated faster hydrocortisone release rates at all HPMC concentrations.

**Conclusions:** This work has demonstrated the feasibility of producing ER mini-tablets to prolong the release of hydrocortisone, thus allowing dose flexibility for paediatric patients. Drug release rate can be tailored by altering the mini-tablet size and/or the concentration of HPMC.

**FLAVORING OF COMMERCIAL ORAL LIQUID PHARMACEUTICAL PRODUCTS**

Roger Embrechts, Albertina Arien, Janssen R&D, Janssen Pharmaceutica, Beerse

A literature survey was performed to evaluate which flavors are used in marketed oral liquid pharmaceutical products. Databases describing the composition of pharmaceutical products on the market in the US, Germany and UK were consulted. In addition, literature concerning flavor preferences was reviewed. The information was grouped per market and divided in 4 age classes: a) less than 2 years, b) 2 to 5 years, c) 6 to 11 years and d) above 12 years. Moreover data was classified according to the therapeutic area in which the product is used. Results indicate that cherry flavor is most frequently used in US pediatric and adult formulations, while strawberry flavor is the preferred flavor in German and UK pediatric formulations. Though, peppermint is most frequently used in adult formulations. Some flavors like grape and bubble gum are mainly used on the US market. When taking the three countries together the most often used flavor in the <2 year group is strawberry, in the 2-5 year group it is cherry, in the 6-11 year group grape and in the ~12 year group it is cherry. In the analgesic group the most often used flavor is cherry, in the anti-allergic group grape, in the anti-infective group strawberry, in the broncho group menthol, in the cardiovascular group orange, in the CNS group mint, in the deficiency group lemon and in the gastro-intestinal group peppermint.

**Hydroxypropyl cellulose films - the spoonful of sugar that helps the medicine go down?**

Ernest Terry¹, Martini Luigi¹, Roberts Matthew², Ford James²

¹Glaxo SmithK line.
²Liverpool John Moores University

**Objective:** Films designed to dissolve in the oral cavity have potential for administering medicines to paediatric patients. This work identifies a potential application for Hydroxypropyl cellulose (HPC) films to improve paediatric patient compliance by overcoming swallowing difficulties commonly associated with solid oral dosage forms and also palatability commonly associated with liquid oral dosage forms.
Methods: Aqueous HPC EF (Klucel® (Aqualon)) solutions (5 %w/w) containing paracetamol at concentrations of 5, 10 or 15 mg/g and a placebo solution were prepared. Films were cast and dried in a vacuum oven for 6 hours at 40°C, 3 hours at 60°C or 2 hours at 80°C. Film weight and thickness were determined. Disintegration testing in 25ml of purified water at 37°C and dissolution testing using USPII apparatus in 900mL of purified water at 37°C were performed. Paracetamol content was determined using a HP UV Spectrophotometer at a wavelength of 274nm.

Results: Disintegration times of HPC films increased as paracetamol content increased. Drying conditions did not affect films containing paracetamol.

Conclusion: HPC films are able to retard dissolution rate of paracetamol and therefore may have application for administering drug substance to paediatric patients by overcoming swallowing difficulties and also potentially providing taste masking and aiding oral cavity absorption.

Films containing 5 and 15 mg/g of paracetamol had slower dissolution rate than the drug alone, indicating HPC modifies drug release for a period after disintegration of the film thus potentially preventing the taste concentration threshold of paracetamol being reached and aiding absorption from the oral cavity.

Identifying the causes of off-flavor in generic tablets using electronic nose & electronic tongue
Attila Aranyos, Sylvain Morel, Hervé Lechat, Fatma Ayouni, Marion Bonnefille
Alpha MOS
**Purpose:** This study is aimed at evaluating the possible cause of off-flavors in generic tablets and also their sensory stability over time.

**Method:** The odor analysis was conducted with HERACLES flash gas chromatography based Electronic Nose (Alpha MOS) equipped with 2 columns (DB5/DB1701, 2m of length and 100µm of diameter) and HS100 autosampler (CTC Analytics). The taste analysis was performed with ASTREE electronic tongue (Alpha MOS) based on potentiometric measurement between a ChemFET sensor array and a reference electrode. Data acquisition and processing was carried out with the Alphasoft software. The set of samples included the brand medicine, a generic, four samples of the generic for which different claims were received and three aged batches of the generic tablets.

**Results:** Both the odor and taste maps built after Principal Components Analysis of the e-nose and e-tongue measurements respectively, showed a clear differentiation of the group of aged tablets on one side and the group of tablets subject to a claim on the other side. The taste and odour of the brand and generic products were also significantly different. Using Kovats index method, it could be observed that the complaints on the bad tablets could be due to an important presence of acetic acid and maltol compared with other tablets.

**Conclusion:** Using the e-tongue and e-noses it was possible to rapidly compare the odor and taste profile of various tablets and to identify the cause of defect in some products, without incurring health risks linked with human testing.

**In vitro performance of a dry powder inhaler using mouth-throat models of 4-5-year-old children**

Below Antje, Bickmann Deborah, Breitkreutz Jörg.
Heinrich-Heine University, Institute of Pharmaceutics and Biopharmaceutics, Duesseldorf
Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein

The efficiency of aerosol delivery to children is mainly influenced by the low inhalation flow rate and the small inhaled volume. By simulating inhalation profiles and different pediatric mouth-throat models the salbutamol sulphate delivery from a multidose dry powder inhaler (Novolizer®) was investigated. The experimental setup consisted of a next generation impactor (NGI), an idealized or realistic mouth-throat model and an electronic lung. The electronic lung simulated the time-varying profiles in the upper airway models. To determine the fine particle fraction (FPF) in the NGI, a steady flow rate of 60 l/min was applied. Two inhalation profiles generated by a 4-year-old child showed peak inspiratory flow rates of 24 and 42 l/min and inhaled volumes of 300 and 520 ml. The deposited mass was collected and determined by HPLC. Deposition measurements with the idealized upper airway model revealed up to 70 % of labeled claim deposited mass in the model and a fine particle fraction of 4 - 5% at both profiles.
There are no significant differences in the amount and site of deposition by using the different profiles. In comparison to measurements with constant flow rates less FPF, especially less deposited particles on NGI cups 4 to 6 (2.82 – 0.55 µm) are observed. The FPF at steady flow was 8% (including 6% on cups 4 - 6). The investigated device has shown a FPF of 4 - 5% under simulated in vivo conditions. A difference in performance by using either an idealized or realistic mouth-throat model with simulated profiles was not observed.

**Innovative approach in formulating better medicine for children: Stick Pack Oral Melts**
A. Arzhavitina
Losan Pharma GmbH, Neuenburg, Germany

Developing paediatric drug products we at Losan are risen to a challenge to combine a child acceptable dosage form being perfectly taste masked so that a child would probably not take it only once with a necessity to assure a child resistant packaging solution. Stick Pack Oral Melts is one of the examples of our innovative approach to meet this challenge. A coating applied directly on the API crystals assures on one hand a perfect taste masking and on the other hand improves the swallowing performance and mouth feel of this dosage form allowing a direct application without water. Filled in a stick pack together with a flavour blend this singe dosage form replaces the potentially inaccurate preparation of suspensions or syrups from powders. Containing no solvents, co-solvents and preservatives no irritation of oral mucosa can occur during application. Another advantage as compared to dry syrups is no problems with open package stability. AUC equivalence of this dosage form taken without water compared to a reference tablet taken with water was shown (e.g. Paracetamol Stick Pack).

**Instrumental method to reliably select the best flavour candidate for a stable masking of active principle bitterness over time**
Attila Aranyos, Sylvain Morel, Hervé Lechat, Fatma Ayouni, Marion Bonnefille
Alpha MOS

**Purpose:** This study is aimed at optimizing the masking of active principle bitterness in a liquid oral form by selecting among 4 candidates (strawberry, pineapple, fruit mix 1, fruit mix 2), the flavor that offers the best combination of masking efficiency and sensory stability over time.

**Method:** The method consists of taste and aroma assessment. To quantify the taste masking power, several active formulations and corresponding placebo were analyzed. Taste analysis was performed with an electronic tongue. To evaluate flavors stability over time, the different formulations were analyzed right after preparation and after one month of storage under stressed conditions. Both taste and aroma stability were quantified using respectively the electronic tongue and 2 electronic noses: one based on Gas Sensor technology for overall aroma profiling, the other based on flash gas chromatography that gave additional information on the chemical composition thanks to Kovats index characterization.
Results: In terms of taste masking, the two fruit mixes showed the highest masking power. The taste of strawberry flavor changed significantly over one month compared with the three others. Conversely, strawberry aroma was the most stable and fruit mix 1 the least stable. But GC-based enose measurements showed that, in strawberry, new chemical components appeared over time whereas the change of aroma of the other flavors mainly corresponded to a loss of intensity.

Conclusion: Using the e-tongue and e-noses it was possible to rapidly screen various formulations and reliably select the flavor (fruit mix 2) that efficiently and durably masked the medicine bitterness.

Interactive mixtures with high dose homogeneity ideal for mini-tablets

Fredrik Sandberg Løding¹, Sofia Mattsson², Ingunn Tho¹
¹University of Tromsø, Dept. of Pharmacy, Drug Transport and Delivery Group, N-9037 Tromsø, Norway
² Umeå University, Dept. of Clinical Pharmacology, SE-90187 Umeå, Sweden

Studies have shown that the homogeneity is higher in interactive mixtures compared to random mixtures¹⁻³, thus interactive mixtures should be particularly suitable for mini-tablets. The aim of this study was to study the homogeneity of interactive mixtures prepared using different carrier particle size and mini-tablets prepared from the mixtures. Granulated mannitol, Pearlitol® 200SD, 300 DC, 400DC and 500DC (Roquette, France), was used as carrier material and sodium salicylate (Sigma-Aldrich, Germany) as fine particulate drug. The carriers were fractionated into size fractions: 180-250μm, 250-355μm, 355-500μm. Apparent particle density, particle size and external surface area of materials were determined. Micronized drug (1% w/w) was mixed with the carriers in a Turbula mixer for 24 h and 48 h (n=2). Homogeneity was investigated by taking 30 samples (20 mg) random were quantified, and the drug content was normalised by division with the theoretical content². Homogeneity was expressed as the relative standard deviation of the normalised values. Prior to compression magnesium stearate (1% w/w) was added.2 mm mini-tablets were directly compressed, compression force 8 N determined. All combinations resulted in interactive mixtures with high dose homogeneity after 48 h of mixing. For the smallest carrier size fractions, high homogeneity was obtained after 24 h, whereas for the largest size fraction 48 h was necessary. High dose homogeneity was proven also in mini-tablets. As the production of mini-tablets is highly dependant on homogenous powder mixtures, interactive mixtures seem like an ideal solution.

REFERENCES

Investigation of processing parameters for Orally Disintegrating Tablets

Grachet Maud, Morris Vicky, Bajwa Gurjit
Pfizer
ODTs are routinely utilised as a platform technology for delivery of drugs to paediatric patients. To date, the majority of formulation development studies focussed on excipient characterisation rather than manufacturing process development. The aim of this study was therefore to determine the optimal mechanical properties of an ODT placebo formulation, and to define a robust manufacturing process characterised by the solid fraction to achieve disintegration time and friability under 30 s and 1 % respectively. A placebo formulation consisting mainly of Pearlitol 200SD, xylitol and crospovidone was prepared at 200 g scale via direct compression (blend-screen-blend manufacturing process with magnesium stearate added as lubricant prior to compression). Force/ hardness profiles were determined using different standard concave tooling on a singlestation compaction simulator and on a hand press. Tablets were compressed to a target weight ranging from 100 to 500 mg (defined as the weight limit by the FDA) and evaluated as per USP. Due to crospovidone properties, the solid fraction (up to 0.85) did not significantly impact disintegration time when tablet weight and diameter were fixed. However, results indicated that a 1:1 ratio of volume to surface area for a 0.75 solid fraction could produce ODTs with good mechanical properties. To match these specifications, a 500 mg tablet should be manufactured at a diameter over 14 mm which would prevent paediatric administration. Furthermore, a lower ratio would challenge the manufacturing design space since lamination and capping were observed over a 0.80 solid fraction.

Minitablets with enalapril or ranitidine—production and methods of physical analysis
Anna Madanecka¹, Malgorzata Sznirowska²

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²Department of Pharmaceutical Technology, Medical University of Gdańsk, Gdansk, Poland

Objectives: To investigate the minitableting process and physical parameters of minitablets (2-3 mm in diameter), when they are produced from tablet mass prepared for compressing standard tablets.

Design & Methods: Enalapril minitablets were produced by granulation and ranitidine minitablets—by direct compression (Korsch XL 100, with spherical punches). Impact of the main compression pressure on: hardness, friability and disintegration time was studied.

Results: The uniformity mass of the prepared minitablets was confirmed. The correlation between main compression pressure and hardness, disintegration time or friability were similar for standard (7 mm) tablets and for minitablets. Hardness measurement of minitablets is problematic and time-consuming. It was impossible to test all minitablets with one equipment: Autotest 4 was suitable for 3 mm minitablets while it was impossible to conduct the measurements for 2 mm (low and high hardness) and 2.5 mm minitablets (low hardness). These were finally tested by Texture analyser TA.XT Plus, which was not appropriate, however, for minitablets with high hardness. Easier and more reliable verification of minitablet’s resistance was friability test performed in a pharmacopoeial apparatus. Disintegration test for
2.5 or 2.0 mm minitablets was not reliable because the product goesthrough 2 mm mesh of the basket sieve. Use of smaller sieve apertures was proposed.

**Conclusions:** Minitablets were produced sucessfully from the tablet mass prepared for standard tablet production. Tests for tablet hardness and disintegration time require special equipment when 2.5 or 2.0 mm minitablets are considered. Pharmacopoeial friability test appears suitable even for the smallest units.

**Oral dosage form suitability in paediatrics: healthcare professionals’ views after the EMA matrix**

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\textsuperscript{c}Department of Practice and Policy, The School of Pharmacy, University of London

**Background:** There is limited clinical evidence from literature on the effects of pharmaceutical technology aspects of paediatric oral medicines (e.g. dosage form type) on patient-related outcomes (e.g. preference, adherence).\textsuperscript{1} The EMA reflection paper\textsuperscript{2} remains a strong point of reference when determining dosage form suitability. Other stakeholders, including healthcare professionals, might influence medicines choice and use in practice, and their views should also be considered.

**Objectives:** To broadly determine paediatric-specific requirements and perceived suitability of oral dosage forms among healthcare professionals, in comparison with the preferences of adolescents (as per a previous study with healthy 17 year olds) and suitability as presented in the ‘formulations of choice’ reflection paper matrix\textsuperscript{2}.

**Design and Methods:** Self-completion questionnaires were administered to a convenience sample (n=22) of healthcare professionals at a large UK NHS trust.

**Results:** For suitability in relation to age, responses varied widely among respondents and in comparison with the EMA matrix, possibly due to lack of familiarity with less traditional dosage forms. Taste and size were regarded as the most important properties. No specific preferences had been observed among the adolescent respondents.

**Conclusions:** There was little consensus among healthcare professionals regarding dosage form suitability for paediatric patients. This reinforces the need for evidence-based research in the areas of acceptability from children themselves, rather than simply relying on proxy reports from adults. This pilot study showed that there was much support from respondents advocating this type of research, which will be extended in the CALF (Children’s Acceptability of Oral Formulations) Medicines Survey.

**References:**


**Odmts with taste-masked zinc sulphate as a child-appropriate dosage form for developing countries**

Stoltenberg Ines, Breitkreutz Jörg
University of Düsseldorf

**Objectives:** Zinc sulphate is an essential medicine for children in developing countries suffering from diarrhoea. Since it shows a strong metallic taste, a sufficient taste-masking is urgently needed. The aim of this study was the development of a taste-masked child-appropriate dosage form.

**Methods:** Orally disintegrating mini-tablets (ODMTs) containing 1mg zinc sulphate were compressed with a standard rotary press. Ludiflash® and Pearlitol® Flash were used as ready-to-use excipients. The influences of additional sweeteners (sodium cyclamate, saccharine sodium) as well as the use of sodium chloride (NaCl) as bitter blocker were investigated. Therefore, an experimental design was used to evaluate crushing strength and simulated wetting test-time (SWT). A second experimental design provided the assessment of taste by taste sensing system (TSS) and human taste panel (HTP).

**Results:** ODMTs with Pearlitol® Flash showed a shorter SWT-time (8.7s-23.3s) and a lower crushing strength (approx. 5N) than ODMTs containing Ludiflash®. The sweeteners and NaCl did not influence SWT and crushing strength significantly. The taste assessments showed an improvement of taste by both sweeteners, whereas sodium cyclamate had a greater impact on taste. NaCl did not influence the taste significantly. However the formulation containing the largest amounts of sweeteners and NaCl obtained the best values with both test methods. Based on these results a suitable formulation, containing Pearlitol® Flash, 16.8% sodium cyclamate, 1.6% saccharine sodium and 9.8% NaCl, was developed.

**Conclusion:** ODMTs containing 1mg zinc sulphate per tablet as a child-appropriate dosage form for developing countries could be developed. The inexpensive approach of adding suitable sweeteners resulted in successful taste-masking.

**Orodispersible minitablets as a child-appropriate dosage form With enalapril maleate: Avoiding the problems of extemporaneous formulations?**

Hermes Martin, Breitkreutz Jörg
Heinrich-Heine-University, Düsseldorf, Germany

**Objective:** Drug therapy of children suffering from renal disease, heart failure or hypertension is often based on ACE-inhibitors like enalapril maleate (EM). However, these drugs are not available in child-appropriate dosage forms within the EU. The aim was to develop a dosage
form which allows individual, accurate dosing and circumvents the disadvantages of liquid extemporaneous formulations.

**Design & Methods:** Three dosage forms were compared regarding uniformity of dosage units, dosing accuracy, and stability:
1. Orodispersible minitablets (ODMT) produced on an IMA/Kilian Pressima rotary press equipped with 2 mm punches
2. Xanef cor®2.5 mg EM tablets (MSD) divided in halves using a pill splitter
3. a suspension prepared from 25 Xanef cor®2.5 mg EM tablets and 250 ml distilled water; withdrawal by dosage syringe

Samples were stored at 40°C/75%rh, the suspension additionally at 7°C and 25°C and tested before storage and after 2, 10 and 43 days. The ODMTs contain EM, FlowLac®, Kollidon®CL-SF and PRUV® or magnesium stearate. The EM-content was determined by HPLC (VWR/Hitachi, 250/4mm C-18 column (Machery-Nagel), λ=215 nm).

**Result:** ODMTs provide longer shelf life than the suspension and dosing was found to be more accurate compared with halved tablets. They disintegrate within 5 s and can easily be swallowed.

<table>
<thead>
<tr>
<th></th>
<th>ODMT</th>
<th>½ Xanef cor®</th>
<th>Xanef cor® Susp.</th>
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<tbody>
<tr>
<td>1.25 mg</td>
<td>3.93</td>
<td>12.86</td>
<td>40.03 ± 2.52</td>
</tr>
<tr>
<td>0.5 mg</td>
<td>10.68</td>
<td>1.53</td>
<td>72.34 ± 3.46 at 25°C</td>
</tr>
<tr>
<td>0.25 mg</td>
<td>12.68</td>
<td>6.35</td>
<td>93.02 ± 6.94 at 7°C</td>
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</tbody>
</table>

EM [%] after 43 days at 40°C/75%rh

89.86 ± 10.72
Conclusions: Presuming correct handling, the suspension allows the most accurate dosing. By comparison, ODMTs provide a child-appropriate, stable and easy to dose alternative to extemporaneous formulations.

**Paediatric drug forms and pharmacy education in Bulgaria**
Valentina Petkova, Milen Dimotrov, Nikolai Lambov
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The aim of this issue is to describe the changes in the pharmaceutical sphere, concerning the paediatric drug forms and especially those that led to introduction of a new discipline in the curriculum of the Faculty of Pharmacy - Sofia, Bulgaria. The first Bulgarian Law of the drugs and pharmacies in the human medicine was introduced in 1995 and that was the first attempt to harmonize the Bulgarian drug regulation with that of the European Union. All these circumstances, together with the new drug discoveries, new drug technologies and new methodologies constantly challenge us to reconsider our roles as pharmacists in the health care system. The most contemporary direction is the creation of the new discipline on paediatric drug forms. In the beginning of 2010 a new course in “Paediatric drug forms” was introduced as free eligible subject in two departments of the Faculty – Department of Pharmaceutical technology and Department of Social pharmacy. The lectures and seminars of this subject are led during the first semester of the fifth year of the studies. The experience in this course shows that there
is a great interest among the students on all the topics of the course. The initial outcomes from this new discipline are described.

**Paediatric extemporaneous formulations: an audit in the secondary care setting**
McCague Paul¹, Donnelly Ryan¹, McFarland Margaret², Wells Brian², Burns Anne², McElnay James¹
¹QUB
²BHSCT

**Objective(s):** For children who cannot take adult dosage forms, a number of medicines have to be prepared extemporaneously. There has not been a published systematic study to investigate the extent and type of extemporaneous production in the pharmacies of paediatric hospitals in XXXX. Therefore, we conducted this audit to investigate the above aspects.

**Design & Methods:** After obtaining audit approval, data collection was carried out at the hospital dispensary. A pro-forma was used to collect necessary information from extemporaneous formulation records. Data were collected for formulations prepared over a two-month period in early 2011 for patients in paediatric wards.

**Results:** Over the two-month period, over 170 items were extemporaneously prepared. On average, the hospital dispensary prepared 4.6 items per day in this manner. All products were oral solutions or suspensions. Three main methods were employed to manufacture the products. These included manufacture from raw materials (41%), from crushed tablets (33%) or using the contents of capsules (26%). The most common extemporaneously prepared formulations were for electrolyte imbalances and disorders of the blood (41%) and cardiovascular disease (22%).

**Conclusions:** The results show a considerable number of extemporaneous preparations are prepared for paediatric patients on a daily basis (an average of 4.6 items daily), particularly for disorders of the GI tract, blood, cardiovascular system and nutritional deficiencies. As a result of the audit, health care providers are now more aware of the extent of extemporaneously prepared medicines prescribed for children in the hospital.

**Paediatric treatment development for helminthiasis able to be used by Who in campaigns of prevention.**
D.Larrouette¹, F.Doz¹, O.Massé¹, C.Michenet¹, G.Lemagnen¹, P.Gueroult¹
¹LTPIB Université Bordeaux Segalen, France

**Objective(s):** Helminthiasis, parasitic, chronic and debilitating diseases caused by worms (helminths) is the second word endemic infection. Praziquantel (tablets divisible in 4 parts: Biltricide®) was selected and used by WHO in campaigns of prevention for children. Scored tablet induce a loss of product, bad taste and may cause gulp irritation. Moreover, dosage
adjustment is difficult for children (6 months to 6 years). So, we develop a pharmaceutical form suitable for children from 6 month to 14 years old, 40mg/kg as dose.

**Design & Methods:** According to WHO, we choose a water dispersible tablet able to be divided in two parts, containing 600mg of Praziquantel. Time of dispersion in water have to be less than 3mn, taste have to be acceptable, and process have to be as simple as possible.

**Results:** We choose wet granulation process (Praziquantel has bad rheological properties). Excipients chosen are justified (compatibility, quantity, acceptability in pediatric treatment), and controls are performed at every step of the process. Content uniformity measured (HPLC method) shows acceptable results (between 85% and 115% of the mean, 10 tablets tested. Dispersion time, reliable to hardness: 1.9mn (mean of 6 tablets). Compression cycle was optimized with STYLCAM® (compression simulator). Our tablets show better dissolution profile than Biltricide® (test U Mann-Whitney, pvalue=0.08) Flavor coffee chosen (according to clinicians’ recommendations) induces acceptable taste.

**Conclusions:** These dispersible tablets are in keeping with the WHO’s specifications. The next steps will be stability study, % of PZQ in every part when scored.

Collaboration: P.Millet HÔPITAL ST-ANDRÉ, Bordeaux, P.Oliero, WHO Genève and C.Larraya, SYNVEC, Bordeaux

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**Selecting the food matrix with the highest masking power for delivering**

**Recommendations for children intake**

Sylvain Morel, Attila Aranyos, Hervé Lechat, Fatma Ayouni, Marion Bonnefille

E-mail: bonnefille@alpha-mos.com

Affiliation: Alpha MOS

**Purpose:**

In pediatric oral forms, the drug formulation can mask the bad taste to a certain extent. But sometimes it can also be necessary to mix the drug with food to mask its taste and thus facilitate its absorption by children. This study is aimed at selecting among various food products the one that will best mask the bad taste of granulates.

**Method:** The method employed consists of taste assessment using an electronic tongue (ASTREE, Alpha MOS), equipped with ChemFET sensors and a reference electrode. Sensors acquisition was processed thanks to multivariate statistics (AlphaSoft software). A fixed mass of granulates was mixed in 6 food products (water, soda, orange juice, apple juice, 2 flavored yoghurts) at 3 quantities for each one. The pure food products were analyzed for reference.

**Results:** E-tongue measurements were processed on a Principal Components Analysis to visualize taste similarities and differences. To quantify the masking effect, the Euclidean distance between the food with and without the drug was calculated. The lower the distance, the better the masking power. Water showed a very low masking efficiency compared to food
matrices. The soda and yoghurts had the highest masking power. The quantity of yoghurt added to the drug had a significant impact on global taste.

**Conclusion:** Thanks to e-tongue measurement, it could be advised to patients to mix the granulated drug with a glass of soda (250mL) or with 2 table spoons (30g) of flavored yoghurt in order to efficiently mask the bad taste of the medicine.

**Sensory Analysis of paediatric formulations of abacavir and lamivudine for HIV**
David Sarah, Wang Xiaolei, ernest terry
GSK

**Objective:** To conduct an open label sensory analysis study to determine the taste characteristics of solutions of Abacavir and Lamivudine with and without excipients in healthy adults as a substitute for infants.

**Introduction:** By the end of 2006 only 15% of HIV-infected children needing treatment were receiving it. Major challenges for delivering treatment for such children include: a lack of paediatric formulations that can be easily dosed in small children and limited studies evaluating the safety and efficacy of existing antiretroviral formulations. Fixed-dose combination antiretroviral drugs have been developed to increase compliance and efficacy and to reduce dosing complexity; however, most commonly adult products are modified to be administered to children, with limited success. Also studies have highlighted that nucleoside analogues are bitter and foul tasting which would lead to reduced compliance, therefore, taste is an important attribute to characterise and try and mask. Formulations of abacavir and lamivudine were prepared, suitable for infants i.e. powder for oral solution (PfoS) and fast disintegrating tablets (FTD). The product performance was evaluated by adult human volunteers filling in a response form using a Visual Analogue Scale (VAS). The study used 2-4 volunteers. Based on the small number of volunteers the result was not statistically valid but gave an indication whether the formulations ameliorate the taste of the API and whether flavour would be required in a future formulation. The WHO recommends paediatric dosing based on abacavir (ABC) 60mg and lamivudine (3TC) 30mg tablets; therefore, this was used in the current study.

**Materials and methods:** A risk assessment was conducted to determine the safety of abacavir and lamivudine if used in a rinse and spit test. The assessment concluded it was safe to conduct the test, with certain precautions. Four formulations containing abacavir and lamivudine were prepared (Table 1). A bulk blend containing the powder ingredients was prepared and each individual dose was subdispensed from the bulk into a 45cc HDPE bottle. 10 ml of potable water was added prior to dosing. The study was set up in two sessions; Session 1 characterised the taste of each test solution/ dispersion (1 to 4) and in Session 2 volunteers were asked to compare a formulated product (2 to 4) to the APIs (1). Volunteers were requested to take a 10ml sample, swill in their mouth for around 20 seconds and then spit out the sample and fill in a response form after tasting (figure 1). All materials were clinical grade and each oral
solutions/suspensions were prepared on the day of tasting to GMP although no analytical testing was performed on the sample prior to use.

**Table 1 Composition and quantitative formula for the formulations to be tested**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>1</th>
<th>2</th>
<th>3</th>
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<tr>
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<td>PfoS</td>
<td>PfoS</td>
<td>FDT</td>
</tr>
<tr>
<td>Abacavir Sulphate</td>
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<td>70.2mg</td>
<td>70.2mg</td>
<td>70.2mg</td>
</tr>
<tr>
<td>Lamivudine</td>
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<td>30.0mg</td>
<td>30.0mg</td>
</tr>
<tr>
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<td>70.0mg</td>
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</tr>
<tr>
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<td>38.65</td>
</tr>
<tr>
<td>Sodium Stearyl Fumarate</td>
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<td>0</td>
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</tr>
<tr>
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<td>100.2g</td>
<td>400.00mg</td>
<td>400.00mg</td>
<td>250.00mg</td>
</tr>
</tbody>
</table>

**Results and discussion:** Abacavir and lamivudine are bitter and salty tasting. Abacavir and lamivudine have an intense flavour and last a long time (1.5 min). Volunteers did not feel significant grittiness with Formulation 4.

**Figure 1 Example response form with VAS**

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**Conclusions:** No sample was acceptable to taste. Formulations 2, 3 and 4 did not improve the flavour or taste of abacavir and lamivudine alone. More work is required to flavour and sweeten abacavir and lamivudine to make it palatable to children. Definitive taste studies will be required in the target population, when ethical, before registration.

**Acknowledgments:** Thanks to my team at GSK for their analytical support

**References**

**STEADY STATE PHARMACOKINETICS OF THE NOVEL AZT/3TC FDC TABLETS IN HIV-INFECTED CHILDREN**

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\(^2\)National University of Rwanda, Faculty of Medicine, P.O Box 117 Butare/Rwanda

**Introduction:** The treatment of paediatric population requires individualized drug dosing (according to body weight or body surface) necessitating the availability of different concentrations and different dosage forms of the same drug due to different ability of paediatric patients to handle liquid or solid dosage forms. Mostly, liquid and solid dosage forms are necessary to satisfy the needs for all age-range of paediatrics. However, on the market, there is a lack of appropriate dosage forms for paediatric patients.

In previous studies, the innovative tablets were developed with breakable in multiple subunits design allowing sufficient flexibility in dosing and were fast disintegrating allowing drug administration as liquid (after dispersion in small amount of water) or as solid depending on child’s ability of swallowing.

These innovative tablets were suitable for different paediatric age groups and allowing to obtain doses related to body weight or body surface area, and their application has been demonstrated for 2 specific applications which were relevant for treatment of children in developing countries (in view of HIV/AIDS and malaria burden in these areas)\(^{(1)}\)\(^{(2)}\).

After study of bioavailability of AZT and 3TC in healthy adult volunteers which showed that the novel FDC tablet (containing 300 mg zidovudine and 160 mg lamivudine) developed for
paediatric applications presented similar pharmacokinetic parameters with marketed tablets “Duovir”, in vivo study should be performed in children living with HIV. The objective of this study was to determine the steady state pharmacokinetics of zidovudine (AZT) and lamivudine (3TC) following administration of the novel FDC tablet (containing 300 mg zidovudine and 160 mg lamivudine) to children HIV positive.

**Experimental methods:** 36 children living with HIV were recruited in this study. The children were randomly divided in two groups of 18 children: a) control group which continued their usual AZT/3TC treatment (i.e. using Duovir or Duovir N tablets), and b) trial group treated with the experimental FDC tablets. During the 10-day study period, all children received the same dose as before entering in the study, which was calculated according to the current therapeutic standard guideline (i.e. twice daily 7.5 mg AZT and 4 mg 3TC per kg body weight) (3).

Tablet pieces corresponding to calculated doses were obtained by breaking marketed tablets using bistouries and by manual breaking of novel FDC tablets. All children maintained their usual drug administration schedule, only the tablet dosage design was different between both groups. Since all children were in ambulatory care, specific instructions and a demonstration on how to use the novel FDC tablets were given to parents/guardians of the children and the children returned to the hospital for blood sampling.

A blood sample was taken prior to the start of the study (i.e. day 0) to monitor the steady state plasma concentration of lamivudine and zidovudine due to the regular treatment with Duovir or Duovir N tablets. On day 3, 7 and 10 of the study, several plasma samples were taken over an 8-hour period: 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 h after the first daily drug administration. The concentration of AZT and 3TC were analysed from plasma samples using a validated LC-MS method.

**Results and discussion:** The pharmacokinetic parameters of lamivudine and zidovudine after administration of Duovir® or Duovir® N tablets (control group) were similar to those obtained when treating the children with the novel FDC tablets (trial group). There were not significant difference between the average $C_{\text{max}}$ and $AUC_{ss-8h}$ ($p > 0.005$) of the trial and control groups. The relative bioavailability ($F_{rel}$) was 97.3% for zidovudine and 93.5% for lamivudine.

**Conclusion:** Substituting the conventional HIV treatment with commercially available 3TC/AZT tablets (Duovir® or Duovir® N) during 10 days by the novel FDC tablets containing AZT and 3TC, did not significantly change the pharmacokinetic parameters of both drugs in children (4) (5).

**References:**

Study on solid self-emulsifying formulations with ibuprofen
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Department of Pharmaceutical Technology and Biopharmaceutics, Faculty of Pharmacy, Medical College

Objective: Ibuprofen belongs to BCS class 2 drugs due to its low solubility and high permeability. This drug is used in paediatrics in the treatment of mild to moderate pain, inflammation and fever. It is known that immediate release of the drug is preferred in paediatrics. The medicines should be prepared using appropriate excipients in minimal quantities. Therefore the aim of the study was to improve solubility of the drug by preparing solid self-emulsifying formulations with a minimal amount of excipients to obtain the immediate release of the drug.

Design & Methods: To prepare solid self-emulsifying systems containing ibuprofen, Labrasol was used as a surfactant. Ibuprofen was dissolved in Labrasol. The solution was solidified using adsorbentssuch as Neusilin US2 or Neusilin SG2. Dissolution studies were performed to evaluate the properties of the formulations.

Results: Results of dissolution studies showed that the presence of Labrasol and the carrier influenced the amount of the drug dissolved. It was stated that Neusilin US2 and Neusilin SG2 had beneficial effect on drug dissolution. The application of Neusilin US2 was more effective than the use of Neusilin SG2. Transmittance analysis showed that thanks to self-emulsifying properties of Labrasol, microemulsion may be formed after dispersing the solid formulation in water. The solid formulation obtained may be used to prepare minitablets, pellets, capsules or suppositories as a paediatric dosage form.

Conclusions: Results of the present study revealed that it was possible to obtain solid self-emulsifying formulations with ibuprofen. Proper choice of the formulation components enabled to improve the solubility of ibuprofen.

Taste assessment of orodispersible mini-patches by an electronic taste sensing system
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Institute of Pharmaceutics and Biopharmaceutics, Heinrich Heine University of Duesseldorf, Germany

Objective: An orodispersible mini-patch (ODMP) is a new and alternative dosage form for children, since there is no need of swallowing a high amount of fluid. Convenient taste of the drug formulation is extremely important. Therefore, the aim of this study was to mask the unpleasant taste of dimenhydrinate incorporated in ODMPs by the use of pharmaceutical excipients.
Method: Taste assessment measurements were performed using the taste sensing system SA402B (Insent, Atujo-Chi, Japan) equipped with seven lipid membrane sensors. ODMPs and reference substances were dissolved in demineralized water before measurement.

Results: A molecular interaction between hydroxypropyl-ß-cyclodextrin (HP-ß-CD) and dimenhydrinate could be accurately monitored by the electronic taste sensing system. Whereas two sensors for bitter cationic molecules could detect the reduction of the free diphenhydramine part of dimenhydrinate, another sensor for anionic molecules still detected chlorotheophylline, the counterion. Therefore, a reduction of 32.09% of the free diphenhydramine by complexation could be predicted by means of multivariate data analysis. By adding sodium saccharin to the HP-ß-CD formulation an additional taste masking effect could be detected by one sensor, but not quantified due to the underlying taste masking technique.

Conclusion: The electronic taste sensing system’s bitter sensors were capable to verify the improved taste of ODMPs containing dimenhydrinate. Taste masking effects by reduction of the free amount of drug could be reliably quantified by the electronic taste sensing system whereas effects obtained by sodium saccharin covering the bitter taste by enhanced sweetness could be verified but not quantified.

Taste masking of an amodiaquine hcl granular formulation and its evaluation by a human taste panel

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2Institute of Pharmaceutical Innovation, University of Bradford, Richmond Rd, Bradford

Objective(s): This study aimed to assess the ability of a range of flavour and sweetener combinations to mask the bitter taste of the well established anti-malaria active pharmaceutical ingredient (amodiaquine hydrochloride) presented in a granular form suitable for paediatric use.

Design & Methods: A paediatric formulation of amodiaquine hydrochloride was prepared in the form of fast disintegrating granules. The bitter taste of the drug was masked using aspartame alongside a range of different flavours. The five (5) - point Hedonic scale was employed to evaluate the effectiveness of these taste masking strategies, which were compared with that of a sweet-tasting commercial paediatric product.

Results: It was observed that the presence of aspartame sufficiently masked the bitter taste of the drug even in the absence of flavourings. For the strawberry flavoured granules, the percentage sweet response was observed to decrease with increased concentration of this flavouring, while for vanilla flavoured granules, the degree of sweetness increased with higher levels of the flavouring in the formulation. For similar levels of flavourings, it appeared that the magnitude of sweetness observed for vanilla flavoured granules was greater than that perceived for the strawberry flavoured granules, although the differences were not statistically significant.
(p-values of the student T test for the volumes of 0.25 and 0.50ml were 0.93 and 0.30 respectively). The commercially available product was rated highest in terms of the degree of sweetness.

**Conclusions:** It is therefore evident that the bitter taste of amodiaquine hydrochloride can be masked satisfactorily using the simple approach of adding sweeteners and flavours.

**Taste masking of bitter apis by using hot-melt extrusion (hme)**

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1 The University of Greenwich, Central Avenue, Chatham Maritime, Chatham, Kent, ME4 4TB
M.Maniruzzaman@greenwich.ac.uk

**Design and method :** Cetirizine HCl-CTZ, Propanolol HCl-PRP, Verapamil HCl-VRP, and Diphenhydramine HCl-DPD and polymers were mixed according to Table 1, in 100g batches. Extrusion was performed using a Randcastle single-screw extruder (RCP0625). The extrudates were milled by a ball milling (400 rpm, 5mins). The resulting granules were characterized by XRPD, DSC, SEM, XPS and dissolution studies. The taste masking efficiency was evaluated in vivo with six volunteers by using the bitterness intensity scale from 1 to 5 where 1 indicates no and 5 indicates strong.

**Table 1:** Composition and processing conditions of HME formulations-

<table>
<thead>
<tr>
<th>Polymers</th>
<th>CTZ (%)</th>
<th>DPD (%)</th>
<th>PRP (%)</th>
<th>VRP (%)</th>
</tr>
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<tbody>
<tr>
<td>Eudragit®S100</td>
<td>20</td>
<td>20</td>
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<td>20</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Eudragit®L100</td>
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<td>20</td>
<td>10-20</td>
<td>20</td>
</tr>
<tr>
<td>Zone Temperature (°C)</td>
<td>132/140/145/150/155</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acryl EZE®</td>
<td>20</td>
<td>20</td>
<td>10-20</td>
<td>20</td>
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<td>Zone Temperature (°C)</td>
<td>100/110/110/113/115</td>
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</table>

**Results** All formulations showed the presence of APIs in amorphous state with some showing only one glass transition (Tg), indicating molecularly dispersed APIs. The in vivo study for taste masking of the extrudates showed [Fig. 1(a)] influence of the polymeric carriers. The experimental findings from XPS elucidated intermolecular ionic interactions between oppositely charged drug-polymers. Dissolution studies of the HME granules showed rapid release [Fig. 1(b)] for all APIs.
Conclusions
The appropriate selection of drug-polymer combinations can achieve significant taste masking effect by HME.

Fig. 1: (a) Taste scores of extrudates (b) Dissolution profiles of extrudates.
**Taste Masking of Hot-Melt Extruded Bitter APIs: An Astree E-Tongue Evaluation**

**Objective:** To investigate the potential of HME for masking the taste of bitter APIs when incorporated into different polymer formulations.

**Design and Method:** Cetirizine HCl-CTZ, Propanolol HCl-PRP, Verapamil HCl-VRP, and Diphenhydramine HCl-DPD and polymers were mixed according to Table 1, in 100g batches. Extrusion was performed using a Randcastle single-screw extruder (RCP0625). The extrudates were milled by a ball milling (400 rpm, 5mins). The resulting granules were characterized by XRPD, DSC, SEM, XPS and dissolution studies. The taste masking efficiency was evaluated *in vivo* with six volunteers by using the bitterness intensity scale from 1 to 5 where 1 indicates no and 5 indicates strong. Additionally an Astree electronic Tongue equipped with a seven specific sensors was used for *in vitro* taste evaluation.

**Results:** All formulations showed the presence of APIs in amorphous state with some showing only one glass transition (Tg) (data not shown), indicating molecularly dispersed APIs. The *in vivo* study for taste masking of the extrudates showed (Fig. 1) influence of the polymeric carriers. The experimental findings from XRD and DSC elucidated molecularly dispersed drug granules into the polymer matrix and therefore amorphous extrudates showed rapid drug release for all formulations.
### Table

<table>
<thead>
<tr>
<th>Polymers</th>
<th>CTZ (%)</th>
<th>DPD (%)</th>
<th>PRP (%)</th>
<th>VRP (%)</th>
</tr>
</thead>
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<tr>
<td>Eudragit®S100</td>
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<td>10-20</td>
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---

**Fig. 1:** Taste scores of extrudates.

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Formulating Better Medicines for Children
The taste map shows significant discrimination between placebo and active solutions of CTZ (Fig. 2). Liquid sensors are able to detect the presence of the drug in the coated formulations. Focusing on pure drug in water the complex with Eudragit polymer at 90% shows a better taste improvement compared to Acryl EZE coating (Fig. 3). The distance proximity with placebo is about four times less important. Drug/polymer ratio at 10/90% for all formulations gave the best taste improvement with Eudragit L100 compared to Acryl EZE, which correlated with sensory data. The masking efficiency of Eudragit polymer is about 72% was observed as an improvement for all four APIs. PLS models show a good correlation for all formulations with the taste results of panelists whereas the PLS highlights the same conclusions: sensory panel was sensible to taste perception with Eudragit.

**Conclusions:** The appropriate selection of drug-polymer combinations can achieve significant taste masking effect by HME and thus HME has been successfully employed for taste masking of four cationic bitter drugs evaluated by an Astree electronic tongue and in vivo studies. Eudragit L100 showed substantial masking improvement compared to Acryl EZE while the results of the electronic tongue support the in vivo panellist’s taste results.

**Taste Masking Evaluation of Hot Melt Extruded Paracetamol using an Electronic Tongue**

**Objective:** The purpose of this study was to evaluate the masking efficiency of hot melt extruded paracetamol formulations by using an electronic tongue.

**Design and Methods:** Extruded granules containing 30%, 40% and 50% paracetamol (PCM) in Eudragit EPO® or Kollidon® VA64 were prepared by HME. The temperature profile used for all formulations was 100°C/113°C/113°C/113°C/115°C (feeding zone → Die). The produced extrudates were milled to obtain granules (<500μm). Grinding by ball milling carried out with a rotational speed of 400 rpm for 5mins each. The taste masking effect of the process formulation was evaluated in vivo by a panel of six healthy human volunteers. In addition, in vitro evaluation carried out by an Astree E-Tongue equipped with a seven specific sensors.
Results: Control solutions (100% PCM) and placebo polymers (VA64 & EPO) were well separated on the taste maps (Fig. 1). The taste maps showed significant discrimination between placebo and extruded formulations. The three drug-polymer solutions were close and far from PCM indicating a significant taste evolution and a masking improvement towards pure PCM. Despite a lowest distance from pure active to placebo formulation as VA64 solutions, the same conclusions were observed for EPO polymer.

Table 1: Sample used for taste masking analysis

<table>
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<tr>
<th>Level</th>
<th>Code</th>
<th>Drug (%)</th>
<th>Placebo (%)</th>
<th>Drug (mg)</th>
<th>Placebo (mg)</th>
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Figure 1: Signal comparison between active and placebo formulations with Kollidon VA64
Formulating Better Medicines for Children

Table 2: Sensory scores for polymers and paracetamol solutions by 6 human volunteers

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<tr>
<th>Code</th>
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</table>

Figure 2: Distance and discrimination comparison of 100% PCM and polymer formulation on Astree E-tongue (after 60s).

The distance between the pure active and the polymer formulations are indicative of taste masking power of each polymer. Increased distance suggests that taste is farther than pure PCM. Significant taste improvement was observed for each of formulation compared to polymer alone (DI>80%). An improved taste was observed with VA64 in which the highest average distance obtained for 30% drug loading. Although EPO showed the closest distance and lowest DI to pure PCM the masking is not significantly different from that of VA64 but the optimum result was achieved with 50% PCM/EPO loading. In addition, the in vivo results are in a good agreement with electronic tongue evaluation.

Conclusions: HME has been successfully employed for taste masking of PCM evaluated by an Astree electronic tongue and in vivo studies. Both polymers showed substantial masking improvement even at high drug loading while the results of the electronic tongue were similar to those obtained in the in vivo comparative studies.