HEINRICH HEINE UNIVERSITÄT DÜSSELDORF

Oral paediatric formulations – problems, ideas and research

Warszawa, Poland
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PSSRC Pharmaceutical Solid State Research Cluster

Basic criteria for paediatric formulations

- Sufficient bioavailability
- Safe excipients
- Palatable and/or acceptable properties
- Acceptable dose uniformity
- Easy and safe administration
- Socio-cultural acceptability
- Precise and clear product information

J. Breitkreutz, J. Boos. Paediatric and geriatric drug delivery. Exp. Opin. Drug Deliv. 4: 37-45 (2007)

Draft guideline (2011 / 2013)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on Pharmaceutical Development of Medicines for Paediatric Use
Draft

Although any basic considerations regarding the use of a specific excipient in a medicinal product will not be different for adult and paediatric medicines, the inclusion of any excipient in a paediatric medicine requires additional concern in view of the potential risk of more pronounced safety implications. Overall, the following aspects are to be considered with respect to the selection of an appropriate excipient:

- the pharmaceutical technologic characteristics of the excipient and potential alternatives;
- the safety profile of the excipient for children all over the indicated target age groups on basis of single and daily exposure (and not the concentration or strength of the medicine);
- the expected duration of treatment i.e. short term versus long term;
- the criticality of the condition to be treated;
- the characteristics of the disease;
- manufacturability;
- allergies and sensitization.

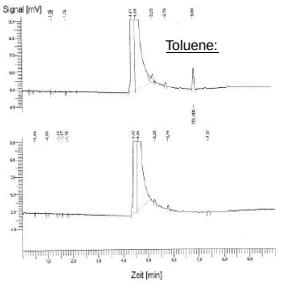
Undisclosed contaminants

1. Residual solvents
2. Pesticides
3. Heavy metals
4. Catalysts residuals
5. Plasticizers from packaging
6. Flavour components
7. Microbial burden
8. Contaminants from plant material

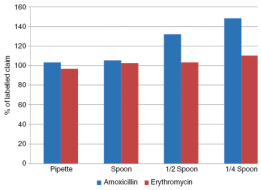
Case study: Sodium Benzoate

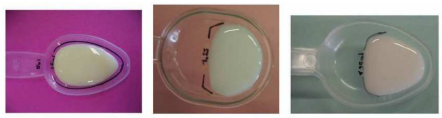
Synthesis:
Toluene ⟶
Benzoic acid ⟶
Sodium benzoate

Permitted Daily Exposure, PDE of Toluene = 8,9 mg/d (Ph.Eur./ICH), but related to woman, 50 kg b.w.



Drug administration / Dosing





K. Griessmann, J. Breitkreutz et al., Paed. Perin. Drug Ther. 8: 61-70 (2007)

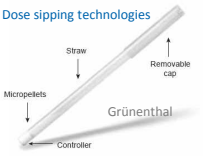
Drug administration / Dosing

Pulp spoons

Sandoz/Hexal

Egalet

Dose sipping technologies



Grünenthal

Bioglan

Pfizer

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Solid > liquid dosage forms

Advantages

- Nontoxic excipients
- Price
- Various opportunities for taste masking
- Modified release options
- Stability (storage & in-use & different climates)
- High content uniformity
- Easy administration

Disadvantages

- Dimensions: swallowing
- Requires liquid for swallowing
- Aspiration (safety)
- Difficult dose adaption
- Varying bioavailability

J. Breitkreutz, T. Wessel, J. Boos, Paed. Perin. Drug Ther. (1999)

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Administration Routes & Forms

Route / Dosage Form	Preterm newborn infants	Term newborn infants (0d-28d)	Infants and Toddlers (1m-2y)	Children (pre school) (2-5y)	Children (school) (6-11y)	Adolescents (12-16/18y)
Peroral						
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent DF*	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersable DF	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5
Nasal						
Solution	3	4	4	4	4	4
Semisolid DF	2	3	3	4	4	4
Rectal						
Suppositories	4	3	5	4	3	2
Rectal Enema	3	4	4	3	3	2
Rectal capsules	2	3	4	4	4	3

EMA Reflection Paper, Formulations of choice for the paediatric population (2006)

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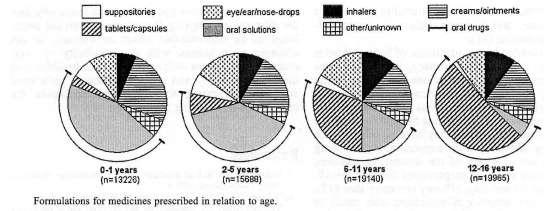
Suitability of dosage forms



Formulations for medicines prescribed in relation to age.

E. Schirm, H. Tobi, T.W. de Vries et al. Acta Paediatr. 92: 1486-1489 (2003)

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Suitability of dosage forms

Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children
WHO Headquarters, Geneva, Switzerland
15-16 December 2008

make medicines Child Size

Proposed recommendations

1. In general, the dosage forms of medicines that are likely to prove most 'suitable' particularly for developing countries are flexible solid dosage forms, such as tablets that are oro-dispersible and or that can be used for preparation of oral liquids (for example suspension or solution). These dosage forms could be used for many of the medicines that are necessary to treat the diseases that are the major causes of mortality and morbidity in under 5s (Lower respiratory tract infection, malaria, diarrheal diseases).
   Provided the product can be dispersed in breast milk from the mother, it could potentially be used in very young children (0-6 months). This type of product is feasible to manufacture in facilities that have conventional tableting facilities, but requires excipients that ensure stability and palatability. Examples of existing dispersible tablet products suggest that they can be more affordable than standard liquid dosage forms.

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Suitability of dosage forms

Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children
WHO Headquarters, Geneva, Switzerland
15-16 December 2008

make medicines Child Size

3. For oral medicines requiring precise dose measurement or titration, the most 'suitable' dosage form should be based on use of a solid platform technology (multi particulate solid, including those that could be dispersed to form a liquid dose), rather than oral liquids. This can allow production of 'tailored' doses and strengths as well as preparation as a range of dosage forms such as tablets or capsules. Examples of current forms are mini-tablets and spherical granules (pellets). In terms of feasibility for the manufacturer, these dosage forms can be manufactured from standard excipients including those that are pre-mixed and suitable for a range of actives, and they have potential flexibility for constructing appropriate FDCs.

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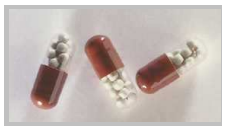
Flexible dosing with multiparticulates

Granules / Sprinkles / Pellets

Minitablets



Pankreatan (Novartis)
Cholspasminase (Merck)
Enzym-Lefax (Bayer)
Cotazym (UCB)

Flexible dosing with minitablets

Panzytrat OK, Abbott

Clyk, Balda Medical / Bayer

microDOSE®

J. Breitkreutz, L. Wazlawik

Suitability of mini-tablets

Mini-Tab Study 2
(confirmatory for Mini-Tab 1 study*)

- single-centre
- open
- randomised
- single dose
- three-way cross-over : coated MT, uncoated MT, glucose syrup
- 306 inhouse and outpatient paediatric patients, stratified in 6 age groups

  (0.5-1y, 1-2y, 2-3y, 3-4y, 4-5y, 5-6y → 51 patients/age group)

V. Klingmann, N. Spomer, C. Lerch, I. Stoltenberg, J. Bosse, J. Breitkreutz, T. Meissner, Eur. J. Pediatr., submitted

**N. Spomer, V. Klingmann , C. Lerch, I. Stoltenberg, T. Meissner, J. Breitkreutz Arch. Dis. Child. 97: 283-286 (2012)*

Suitability of mini-tablets

Evaluation criteria in Mini-Tab Study 1 & 2

Evaluation criteria for the outcome of mini-tablet or syrup administration

Criterion	Mini-tablet	Syrup
1	Swallowed: no chewing during deglutition and no solid residuals found during oral inspection	Everything swallowed: no liquid residuals found during oral inspection
2	Chewed: swallowed most of the tablet pieces, but small residuals found during oral inspection	Small runlet: liquid rinse or flowing out off the mouth
3	Spat out: no observed deglutition and no solid found during oral inspection	Spat out: no observed deglutition and the child disgorged the syrup directly
4	Choked on: the mini-tablet was inhaled or a cough was caused during swallowing	Choked on: some of the liquid was inhaled or a cough was caused during swallowing
5	Refused to take: all actions preventing the investigator placing the mini-tablet in the mouth	Refused to take: all actions preventing the investigator placing the dosing instrument into the mouth or intentionally closing the lips

N. Spomer, V. Klingmann , C. Lerch, I. Stoltenberg, T. Meissner, J. Breitkreutz Arch. Dis. Child. 97: 283-286 (2012)

Suitability of mini-tablets

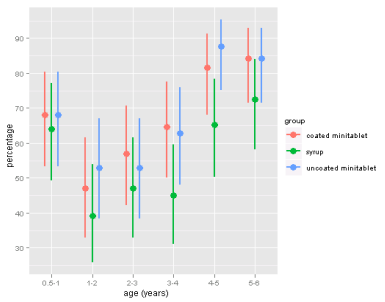
Capability to swallow:
uncoated minitablet > syrup
over all age groups
Difference 12,6 %
(95 % CI 5,7-19,6)
(p = 0.0007)

Capability to swallow:
coated minitablet > syrup
over all age groups
Difference 11,6 %
(95 % CI 4,6-18,6)
(p = 0.002)

Difference in acceptability and capability to swallow not significant between *uncoated* and *coated* minitablets

n=306

Capability to Swallow



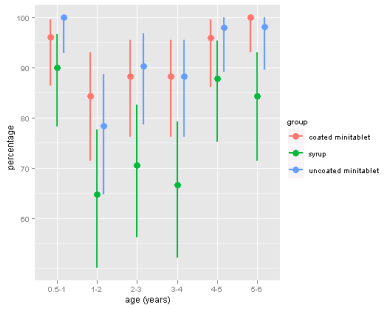
Suitability of mini-tablets

Acceptability:
uncoated minitablet
> syrup
over all age groups
Difference 15,0 %
(95 % CI 10,3-19,6)
p < 0.0001

Acceptability:
coated minitablet > syrup
over all age groups
Difference 14,9 %
(95 % CI 10,4-19,5)
p < 0.0001)

n=306

Acceptability



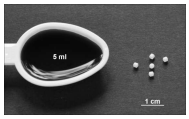
Suitability of mini-tablets

Safety

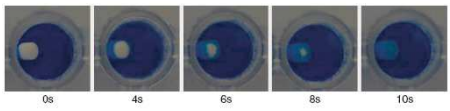
- All three galenic formulations were well tolerated
- None of the 306 children choked on the syrup
- None of the 306 children choked on the uncoated minitablet
- 2 of the 306 children (both in age group 0.5 - 1y) choked on the coated minitablet, both events without clinical relevance
- No. of subjects too small to evaluate safety of drug-free mini-tablets (follow-up study at least for <1 y children required)

V. Klingmann, N. Spomer, C. Lerch, I. Stoltenberg, J. Bosse, J. Breitkreutz, T. Meissner, Eur. J. Pharm., submitted

Orodispersible Mini-Tablets (ODMTs)



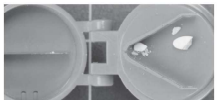
1,00 mg Hydrochlorothiazide



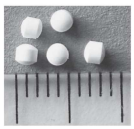
I. Stoltenberg, G. Winzenburg, J. Breitkreutz. J. Appl. Ther. Res. 7: 141-146 (2010)

Orodispersible Enalapril ODMTs

Xanef® cor 2,5 mg EM-Tabletten, von Hand geteilt



Xanef® cor 2,5 mg EM-Tabletten, inkorrekt geteilt mit Tablettenteiler



0,25 mg Enalapril maleate
1,00 mg Enalapril maleate

M. Hermes, Dissertation HHU Düsseldorf (2012)

Orodispersible Mini-Tablets (ODMTs)

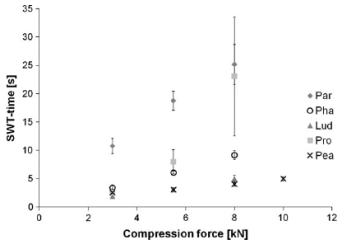


Fig. 3. Effect of compression force on simulated wetting test-time of mixtures of co-processed excipients, containing 3.5% (w/w) of sodium stearyl fumarate as lubricant; Parteck® ODT (Par), Pharmaburst® 500 (Phar), Ludiflash® (Lud), Prosolv® ODT (Pro), Pearlitol® Flash (Pea); mean ± standard deviation; $n = 10$.

I. Stoltenberg, J. Breitkreutz. Eur. J. Pharm. Biopharm. 78: 462-469 (2011)

Orodispersible Enalapril ODMTs

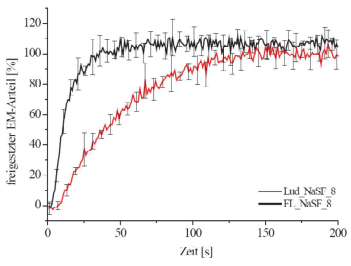


Abbildung 21: Freisetzungsprofile der Chargen Lud_NaSF_8 und FL_NaSF_8; je 5 ODMTs pro Messung; 200 g Wasser, 36 °C, Blattrührer 100 U/min; MW ± s; n=3

M. Hermes, Dissertation HHU Düsseldorf (2012)

New disintegration tester for ODMTs

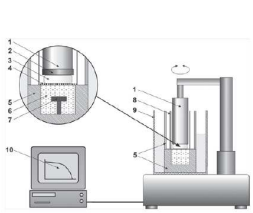
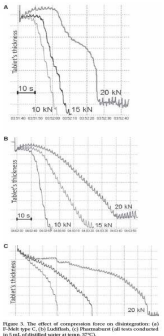
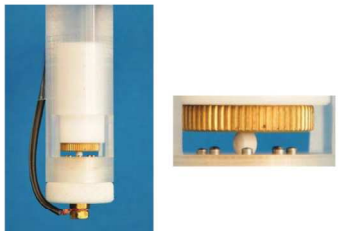


Figure 1. Construction of the Novel Apparatus: 1, rotating shaft; 2, magnetic field sensor; 3, tablet; 4, perforated plate; 5, outer chamber; 6, disintegration medium; 7, magnet ring; 8, inner chamber; 9, water bath; 10, computer with graph plotting software.

W. Brniak, R. Jachowicz et al., Pharm. Dev. Technol. (2012)

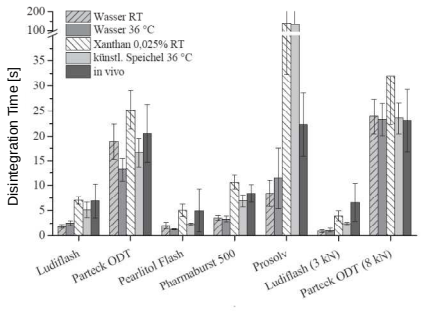


New disintegration tester for ODMTs



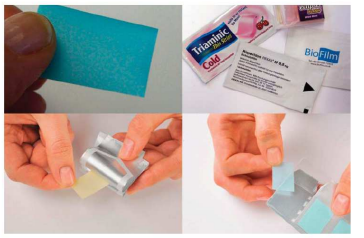
M. Hermes, Dissertation HHU Düsseldorf (2012)

New disintegration tester for ODMTs



M. Hermes, Dissertation HHU Düsseldorf (2012)

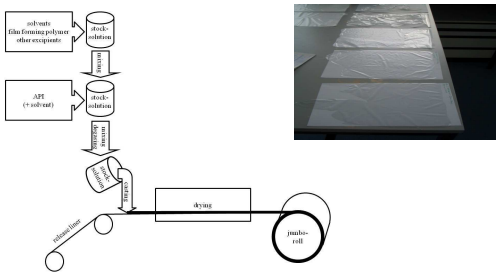
Orodispersible films



Examples for different marketed orodispersible films and packaging variants.

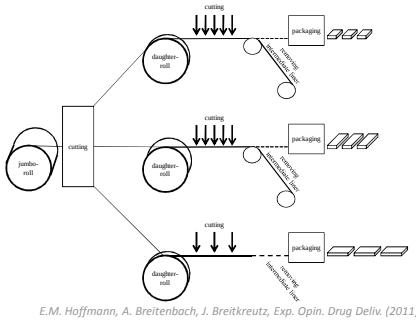
E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Exp. Opin. Drug Deliv. (2011)

Orodispersible films



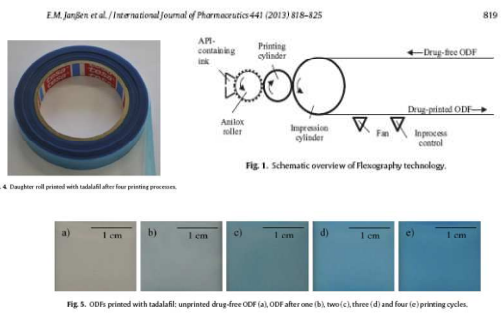
E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Exp. Opin. Drug Deliv. (2011)

Orodispersible films



E.M. Hoffmann, A. Breitenbach, J. Breitkreutz, Exp. Opin. Drug Deliv. (2011)

Printed orodispersible films



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J. Breitkreutz, J. Boos. Paediatric and geriatric drug delivery. Exp. Opin. Drug Deliv. 4: 37-45 (2007)

Thank you for your kind attention!

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