Formulation of odour-masked Cefixime:hydroxypropylβcyclodextrin-based chewable tablets for pediatric use

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INTRODUCTION: Formulating drugs intended for pediatric use is one of the main challenges for the pharmaceutical industry and regulatory agencies, due to growing needs.
Cefixime (CEF) is widely used in pediatrics, belonging to the antibiotics group of the WHO List of Essential Medicines for children[1]. Nevertheless, its unpleasant smell and taste can hinder the drug assumption, thus resulting in poor adherence to therapy. In order to reduce its unpleasant texture in the mouth, CEF-based ODTs quickly disintegrating in the oral cavity were specifically developed for 4-6 years-old children in our previous studies[2].

AIM OF THE WORK: to improve the smell and dissolution rate of Cefixime by manufacturing chewable tablets exploiting cyclodextrin (CD) complexation.

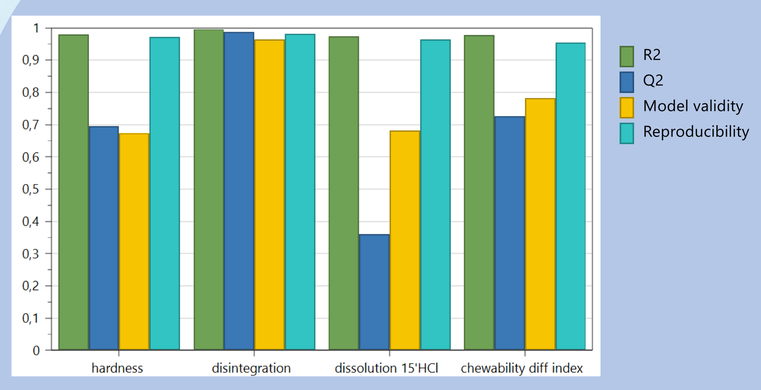
MATERIALS:
- Cefixime (CEF), Menarini
- Crospovidone (PVPP CL), HARKE Pharma
- Croscarmellose Sodium (AcDiSol®), Menarini
- GalenIQ™, Faravelli S.p.A.
- Magnesium stearate, Sigma-Aldrich
- Hydroxypropyl-β-cyclodextrin (HPβCD), Roquette

METHODS:
- Design of Experiments (DoE): full factorial design (3 factors-2 levels). Factors: compression force, compression time, type of superdisintegrant. Responses (critical attributes): hardness, disintegration time, % dissolution in 15', chewability index (CDI)
  $Y= \beta_0+\beta_1X_1+\beta_2X_2+ \beta_3X_3 + \beta_{12}X_1X_2+\beta_{13}X_1X_3+\beta_{23}X_2X_3+ \beta_{123}X_1X_2X_3$
- Co-grinding (GR) Cefixime:Hydroxypropyl-β-cyclodextrin (1:1 mol/mol), 24Hz, 60'
- Manufacturing (direct compression) of chewable tablets containing the drug "as is", as a physical mixture (PM CEF: HPβCD) and as co-ground (GR CEF: HPβCD), characterization (weight, diameter, thickness, hardness, chewability index), dissolution studies and stability studies (one month)
- Panel test of ten volunteers to evaluate the odour-masking effect of CD, using the Facial Affective Scale

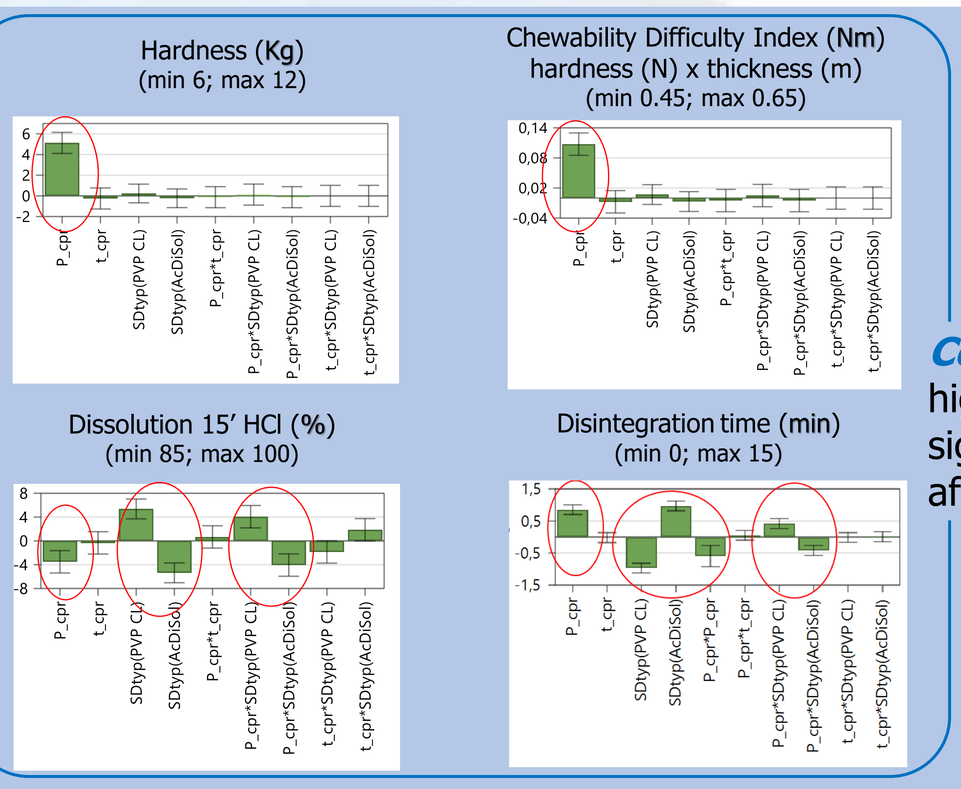
	Extremely good
	Very good
	Pleasant
	Odourless
	Unpleasant
	Very bad
	Extremely bad

RESULTS: DoE

Summary of fit



The model well fitted the results: R^2>0,95; Q^2>0,1 showed the significance of the model. The values of *model validity* and *reproducibility*, respectively >0,25 and >0,50 indicated that the model was valid and reproducible.

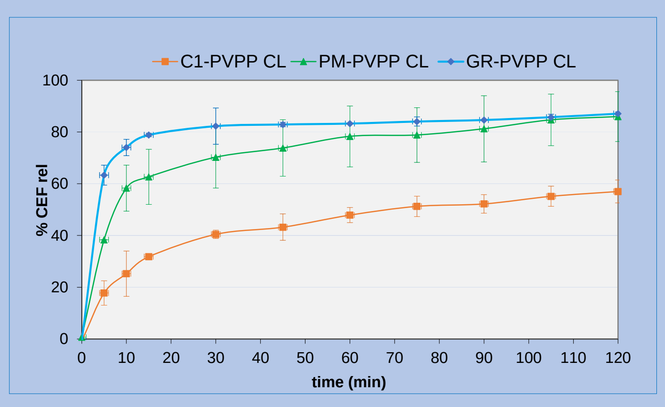


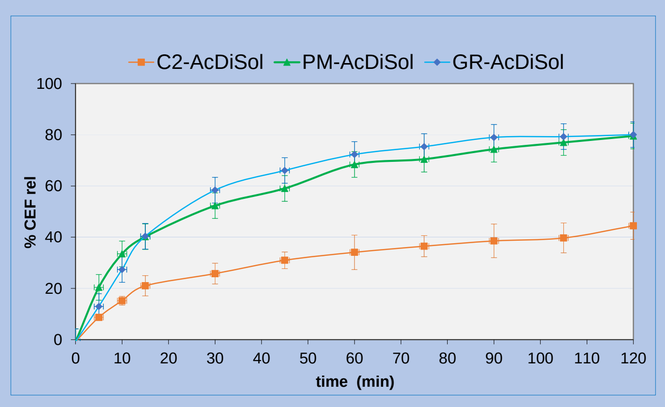
Coefficient plots highlighted the most significant parameters affecting each response

0,5 t x 30"
PVPP CL and AcDISol®

Dissolution test (pH 1.2, 2h)

An increased CEF release from the tablets containing both the binary systems CEF:HPβCD was observed, compared to the corresponding tablets containing the pure drug, achieving more than 80% CEF released.





Stability studies showed only a slight decrease in the CEF release profile, but still presenting an increasing trend.

Panel test

CONCLUSIONS:
- HPβCD has confirmed its odour-masking effect toward CEF and its positive effect in increasing its dissolution rate
- A safe, effective and odour-masked pediatric formulation has been developed

References:
[1] WHO (World Health Organization). WHO AWaRe Classification of Antibiotics. 2021. Available online: https://www.who.int/publications/i/item/2021-aware-classification (accessed on 15 April 2023).
[2] Cirri et al., Cefixime-based orally disintegrating tablets (ODTs) specifically developed for pediatric use, 62° Simposio AFI, Rimini, 2023