UNIVERSITÀ DEGLI STUDI DI MILANO
DIPARTIMENTO DI
SCIENZE FARMACEUTICHE
Sezione di Tecnologia e Legislazione Farmaceutiche Maria Edvige Sangalli

Paediatric-Medicine Development in a Nutshell

Associazione Farmaceutici Industria
Società Scientifica

Children Orosensory Perception and Taste Masking of Paediatric Formulations

Paolo Gatti, PhD
Research Fellow and Manager Formulation

Milano, November 5th 2014

Taste Masking: Why ?

Palatability (pleasant mouthfeel) of oral dosage forms influences **patients adherence** to therapeutic regimen.

Clinical Efficacy → Patient Healing

"My diabetic research shows that test subjects are 98% more likely to take their diabetic pills if the pills are covered in chocolate."

Clinical Efficacy ← Patient Compliance

Taste Masking: Why ?

Palatability has particular impact in case of **pediatric patients**

Taste Masking

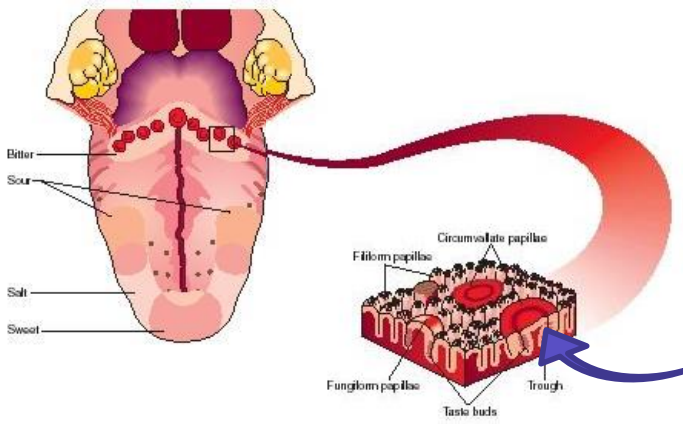
Taste Masking: Key Facts

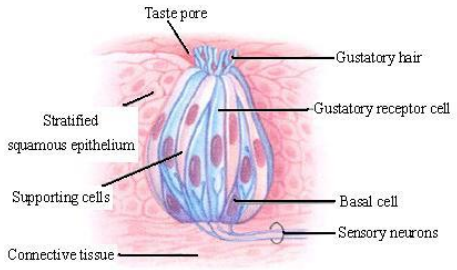
Mouthfeel

Chemical interaction: Flavour

→ Smell, **Taste**

Drug





smoothness, roughness,…

→ viscosity, volume, slipperiness, grittiness,

Physical interaction: Texture

Dosage form

Pediatric Taste Masking

Developing pediatric medicines is a challenging work

Children are not simply "*small adults*"

also from a palatability achievement perspective

Pediatric Taste Masking: Challenges

- **Taste perception**
  - Well known physiology → tongue taste bud stimulated by chemicals
  - It has been shown **differing between adult and children:**
    - Children seems more sensitive to bitter taste than adults
    - Children like significantly more than adults food and beverages tasting sweet
      - This preference remains during childhood and starts to decline to adult level during adolescence
      - In a panel test 50% of child and adolescent but only 25% of adults chosen as their favourite a solution containing double amount of sugar than a standard cola
      - *Mennella J.A. et Al. Clin.Ther., 2013; 35(8), 1225-46 -- Mennella J.A. et Al. Clin.Ther., 2008; 30(11), 2120-32 -- Schiffman S.S., 2007; Proc.Nutr.Soc. 66, 331-45*

Pediatric Taste Masking: Challenges

- **Taste assessement**
  - Standard definition of *acceptable taste* does not exist
  - *In vivo* testing is still more reliable than in *vitro*
    - Lack of *in vitro – in vivo* correlation (IVIVC)
  - Ethical concern for taste study with healthy children
    - Regulatory authorities do not allow children enrollment in study that can be conducted with adults
    - “Swill and Spit” approach is allowed, depending on drug safety profile
    - Better embedding taste assessment in clinical studies with ill children
  - Concern about design and outcomes of studies with children
    - Questionnaire set-up, children communication skills
    - Answers reliability
  - Adult sensory Panels could requires specific sensitivity and training to provide reliable assessment of children taste response

Taste Masking: Evaluation

In Vivo Tests

Human panel

(Atcual taste physio-/psychological process)

Bull Frog

Receptor → tongue, taste buds

Transmission→glossopharyngeal nerve+AC amplifier

Perception→current peak analysis

In Vitro Tests

Drug release in solution

(Only for some taste masking methods)

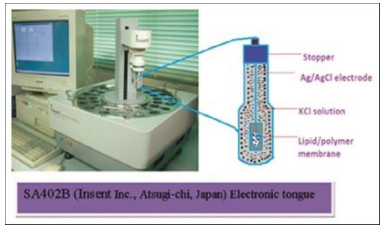
Perception→larger the amount of drug released at a certain time, poorer the effect of taste masking

"Electronic Tongue"

Receptor → membrane probes

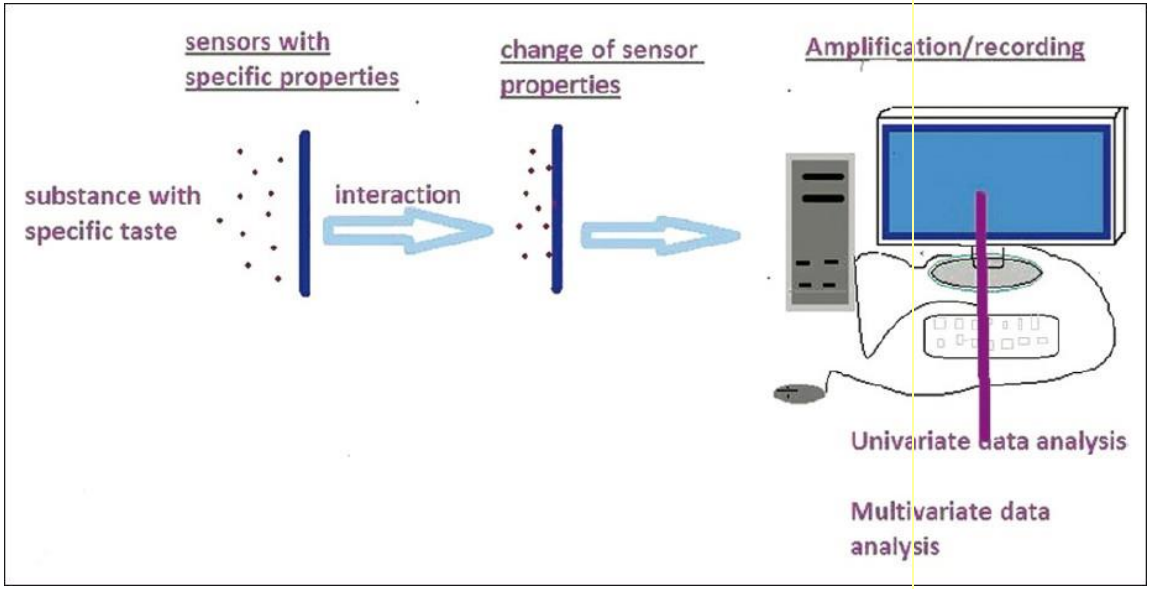
Transmission→electronic circuit

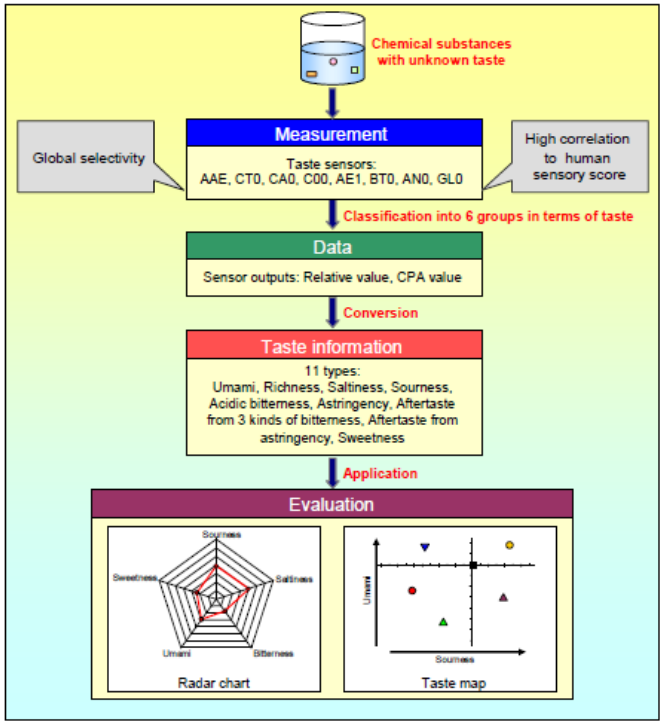
Perception→statistical analysis software



Taste Masking:Evaluation

E-Tongue concepts





Major cons

Artificial sensors → In vitro – In vivo correlation to be confirmed, especially for taste inhibitors

Pediatric Taste Masking: Challenges

- **Drug and oral dosage form development**
  - Drug taste not usually considered as screening factor during lead selection process
    - Focus on pre-clinical safety, tolerability and efficacy and on physico-chemical properties
    - Tablets and capsules, the most used adults dosage forms can be easily taste masked
    - Early taste evaluation of compound with limited toxicity data available suffer of a lack of robust techniques
  - *Pediatric Investigation Plan (PIP)* approach (EMEA)
    - Usually must be agreed with EMEA's Pediatric Committee during early clinical development stage (i.e. Phase I) → sufficient data to guide pediatric formulation development (i.e. pediatric dose, taste, etc.) could not be available
    - Very likely pediatric clinical development is initiated with *enabling dosage form* that could require taste optimization at a later stage → bridging PK study is required in this case
  - **Liquid dosage form preference**
    - Solid dosage forms are accepted by older children and adolescent, but younger children and their carers prefer liquid formulations
      - Highly soluble drugs are difficult to formulate as suspensions → taste masking difficulties
      - Strongly bitter compounds could be difficult to taste mask even in case they are poorly soluble → limited amount going into solution could be sufficient to overcome bitterness threshol

Pediatric Taste Masking Challenges

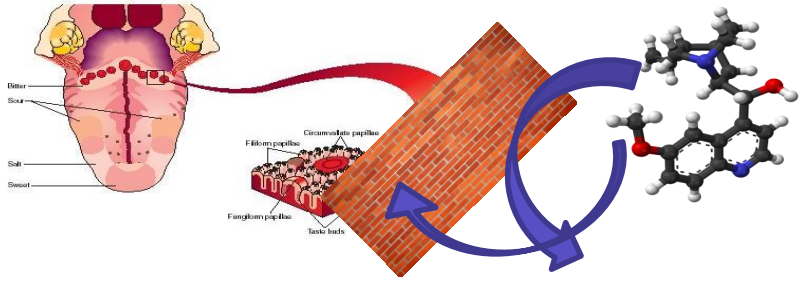
Pediatric Age Preferred Oral Dosage Forms

	New born (0-4 weeks)	Infants and toddlers (1 m – 2 y)	Child pre-school (2-5 y)	Child School (6-11 y)	Adolescent (12-18 y)
Drops	++++	+++++	+++++	+++	++
Liquid	++	++++++	+++++	+++	++
Fast dispersing tablet	+	++++	++++	+++++	+++++
Multiparticulate (included minitbt)	++	++	++++	++++	+++++
Tablet (larger than 3 mm)	Not Applicable	+	+++	++++	+++++
Chewable tablet	Not Applicable	+	+++	+++++	+++++

Modified From: Nunn T., EMA Workshop on Pediatric Formulations, November 2011

Taste Masking: How to Achieve

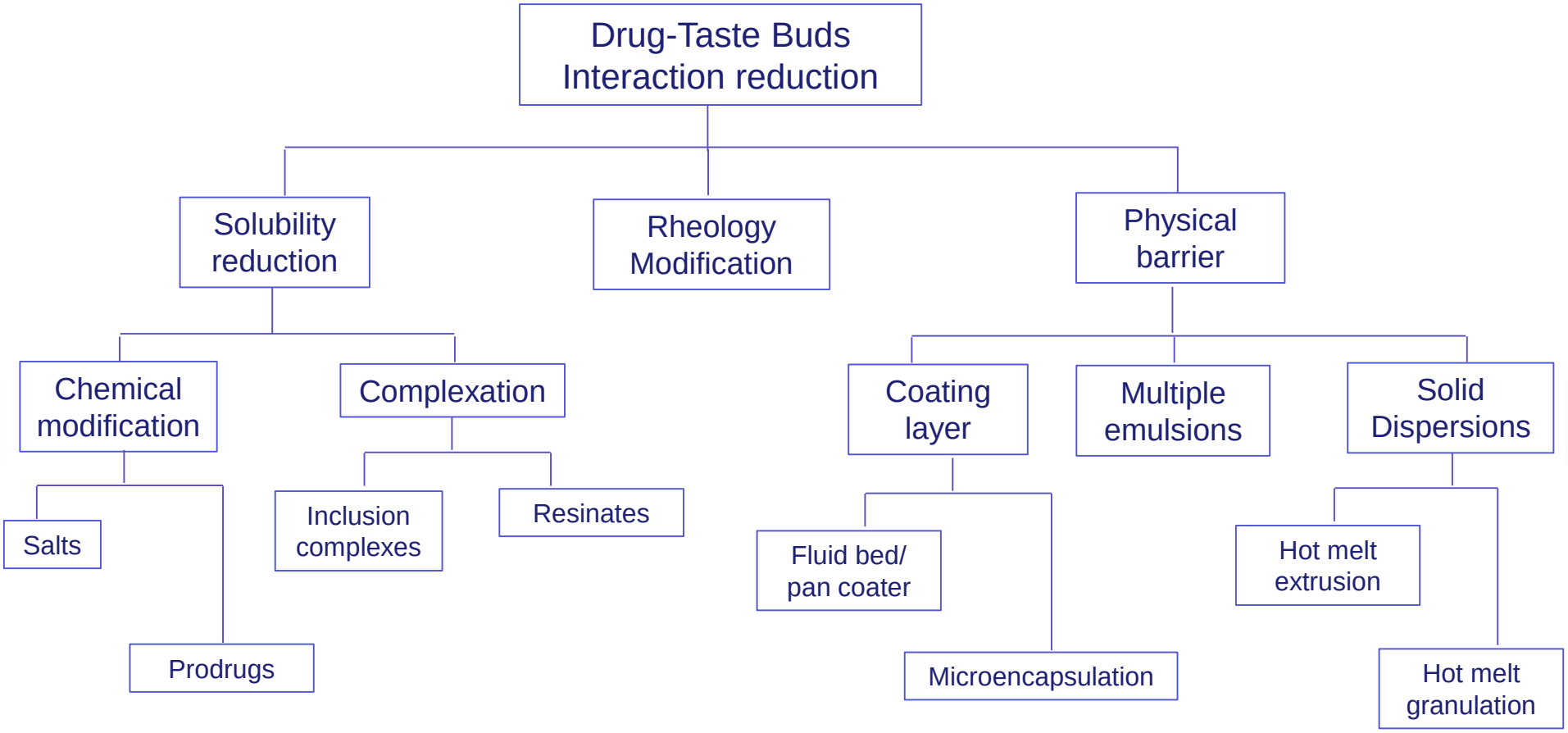
- **Prevent/reduce direct contact between drug and taste buds**
  - Solubility reduction
  - Physical barrier
    - Around dosage form
    - Around drug particles



- **Create pleasant taste stimulation "cancelling" that of drug**
  - Sweeteners, flavors and combination thereof
  - Enhancers

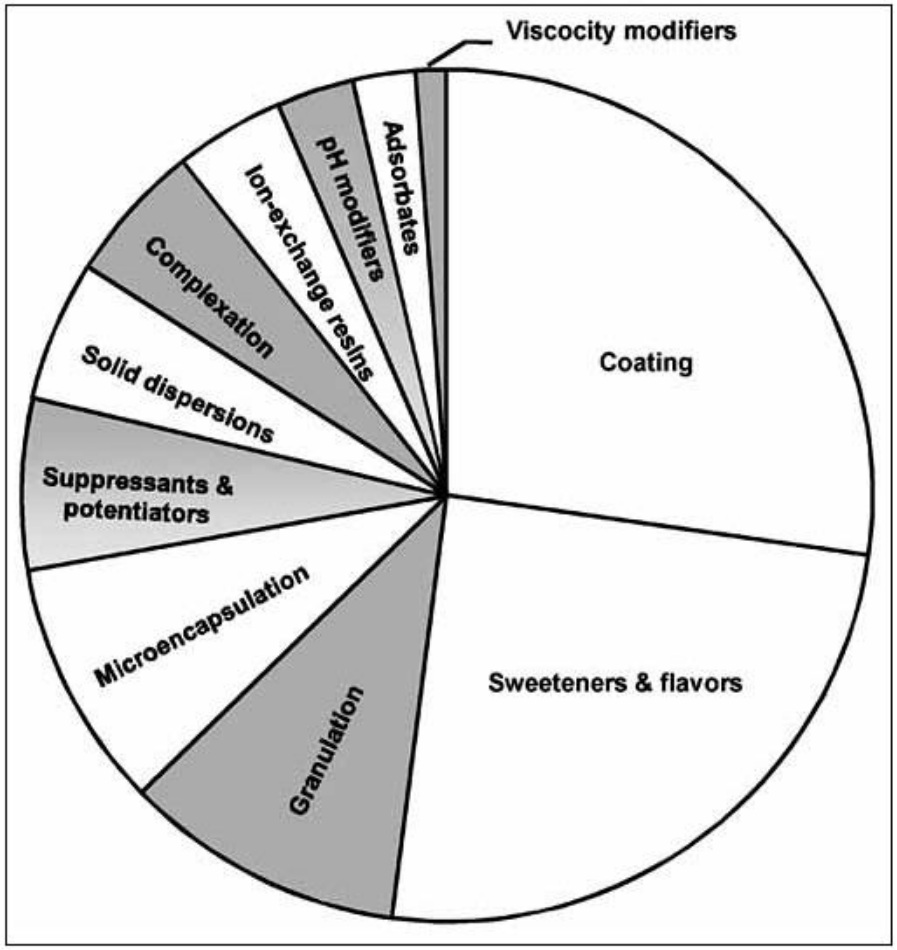
- **Suppress taste bud response to drug stimulation**
  - Substances competing with drug at taste bud receptor sites
  - Usually specific for each drug → Unlike to have "Universal suppressant"

Taste Masking: How to Achieve



Taste Masking: How to Achieve

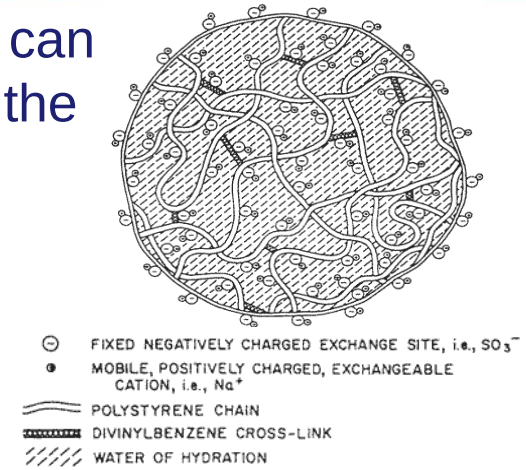
Filed patent 1997-2007 for taste masking approaches



From: J.P.Reo International Journal of Pharmaceutics 367 (2009) 65.72.

Taste Masking Technologies – Solubility Reduction
Complexation with ion-exchange resins

- *Ion exchange resin* ← Insoluble ionic materials that can exchange their mobile ions of equal charge with the surrounding medium
  - Structural portion: polymer matrix
    - i.e Styrene crosslinked with divinylbenzene
  - Functional portion: ion active group

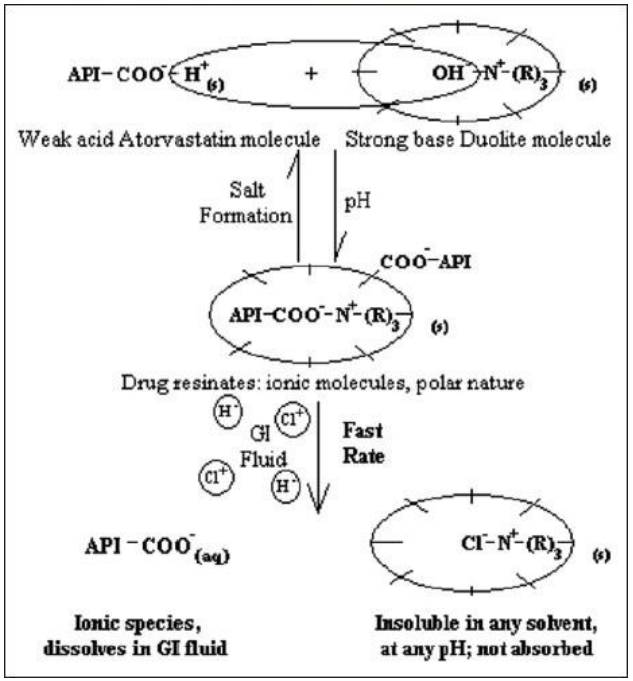


	Positively charged (Anion exchanger)	**Negatively charged (Cation exchanger)**
Strong exchanger	**Quaternary ammonium** *Duolite AP143 (USP-NF, EP, JP)*	**Sulfonic acid, Phosphonic acid** *Amberlite IRP69 (USP-NF, EP, JP)*
Weak exchanger	Tertiary amines *Dowex 2, Amberlite IR 4B*	Carboxylic acid *Amberlite IRP 88 (USP/NF)*
Counter ion	Chloride	Sodium, potassium, ammonium

- Ion active group interacting with drug → *Drug Resinate*
  - Only drugs bearing acidic or basic functional group
  - Original counter ion displaced by the inonized drug in an equilibrium reaction

Taste Masking Technologies – Solubility Reduction Complexation with ion-exchange resins

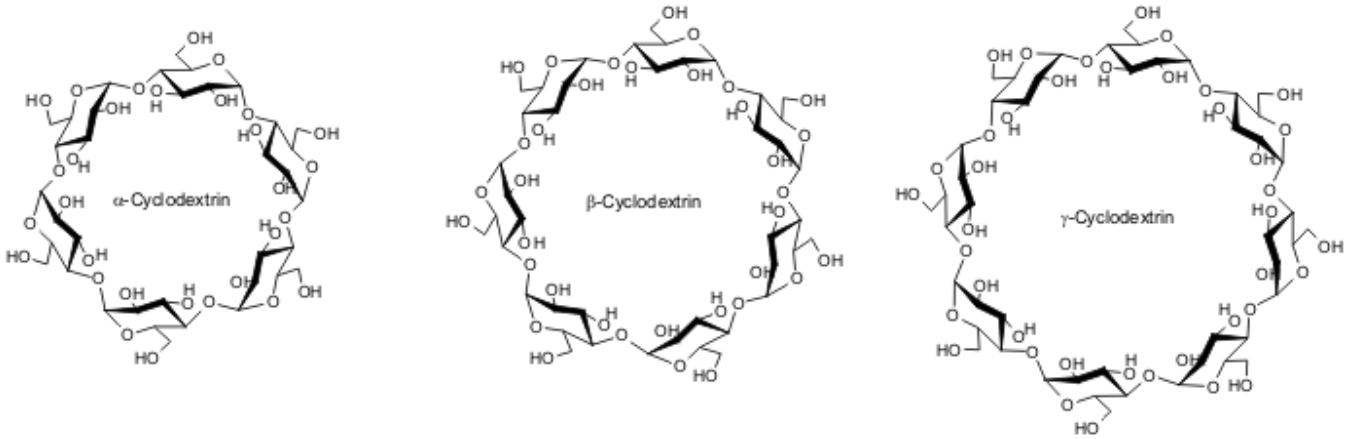
- *Drug resinate → Slow elution of drug from resinate in the mouth fluid reduces bitterness and nausea associated with bitter drugs*
  - Complex is stable at average pH and ion concentration of saliva
  - Complex quickly broken down interacting with ions available in GI tract



- *Drug resinate → solid or liquid dosage form taste masking*
  - Resinates are prepared suspending and stirring the resin solid particles in concentrated drug solution; washing to remove unbound drug, drying the resinate suspension if solid product is required
  - Drug load up to 50% can be achieved
    - Larger the drug molecule, lower the drug load because of steric restrictions

Taste Masking Technologies: Inclusion Complexes

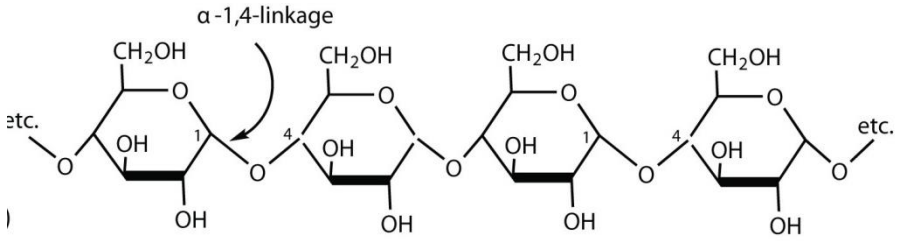
- Cyclodextrines
  - Bucket shaped oligosaccharides that owing peculiar structure can entrap geust molecule in their internal cavity

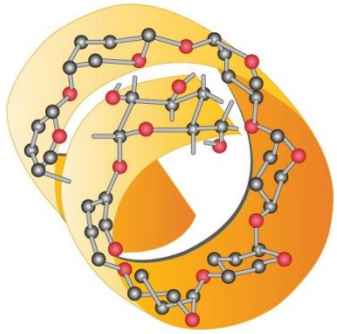


  - β-cyclodextrin and Hydroxypropyl- β-cyclodextrin (i.e. Kleptose® Roquette)
  - Possible regulatory restrictions for pediatric applications

Taste Masking Technologies: Inclusion Complexes

- Maltodextrines
  - Starch derivatives containing soluble amylose fraction
  - Amylose is linear chain of α-D-glucose units joined together by α-1,4-glycosidic bonds. Because of hydrogen bonding, amylose acquires a spiral structure that contains six glucose units per turn.





  - Amylose helical structure bears hydrophilic external surface and hydrophobic internal cavity that allows inclusion of drugs
  - No significant regulatory restrictions even for pediatric applications
  - Kleptose® Linecaps (Roquette) pea starch maltodextrine

Taste Masking Technologies: Inclusion Complexes Case Study Kleptose® versus Kleptose® Linecaps

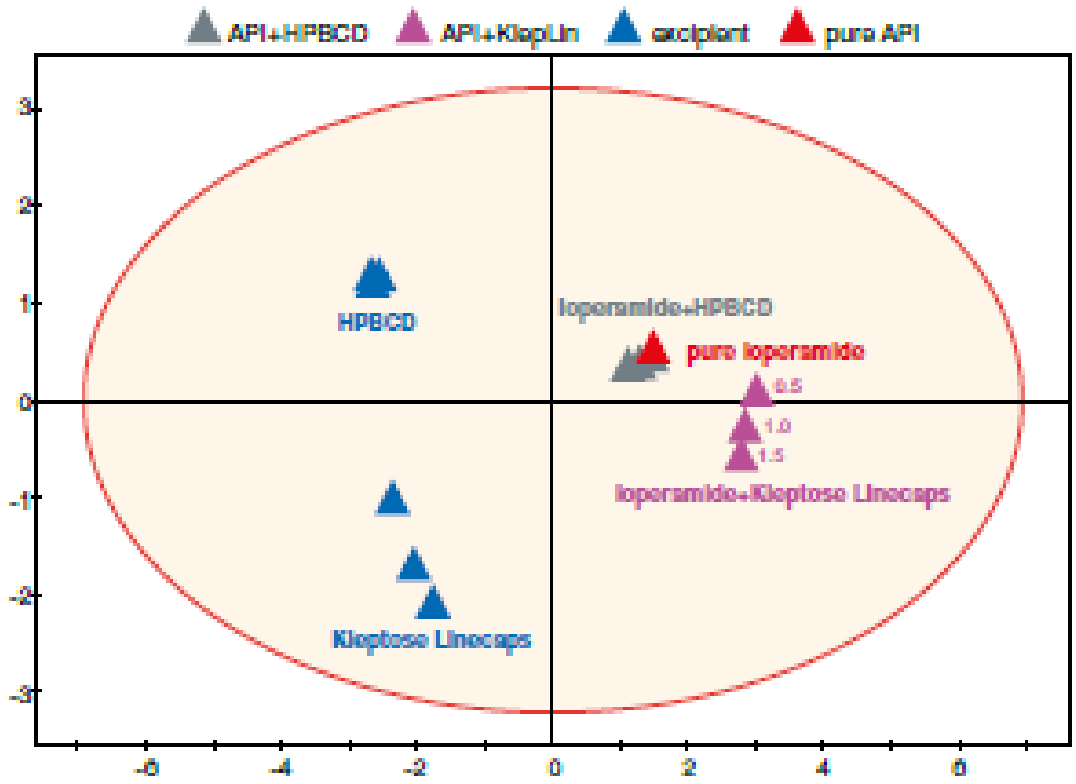


Figure: Principal component analysis (PCA map) of pure loperamide hydrochloride (red), mixtures with hydroxypropyl-ß-cyclodextrin (grey), mixtures with KLEPTOSE® Linecaps 17 (purple) and pure excipients (blue). Testing system SA 402B, Insent Inc., Japan. All seven sensors displayed (R^2 values: PC-1: 0.79; PC-2: 0.17)

From Kleptose® Linecaps Technical Documentation (Roquette)
www.roquette.com

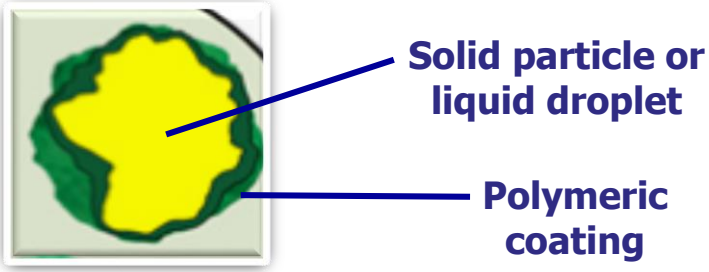
- Loperamide target drug
- In vitro taste assessment with Insient e-Tongue
- Maltodextrine complex taste masked better than HP-β-CDX

Taste Masking Technologies
Coating by Microencapsulation

Microencapsulation by coacervation → **Microcaps®***

Microencapsulation

The coverage of a solid particle or liquid droplet by means of a polymeric coating



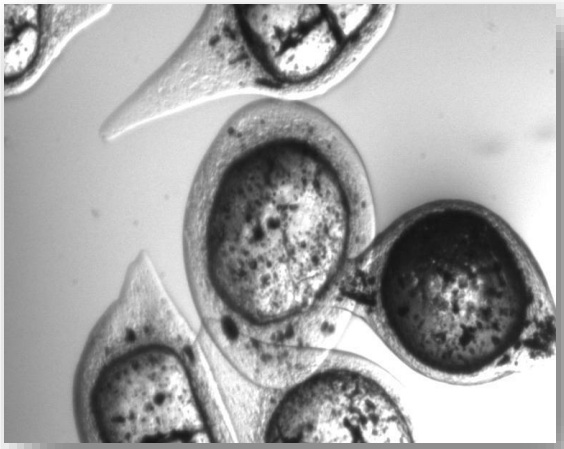


Fig. A KCl during the microencapsulation process with ethycellulose

Fig. B Example of liquid microencapsulation

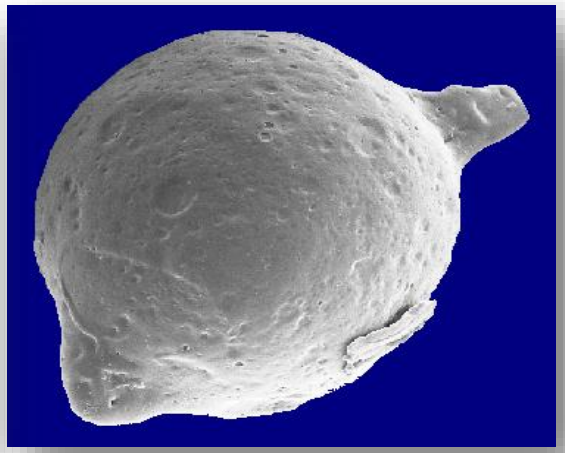
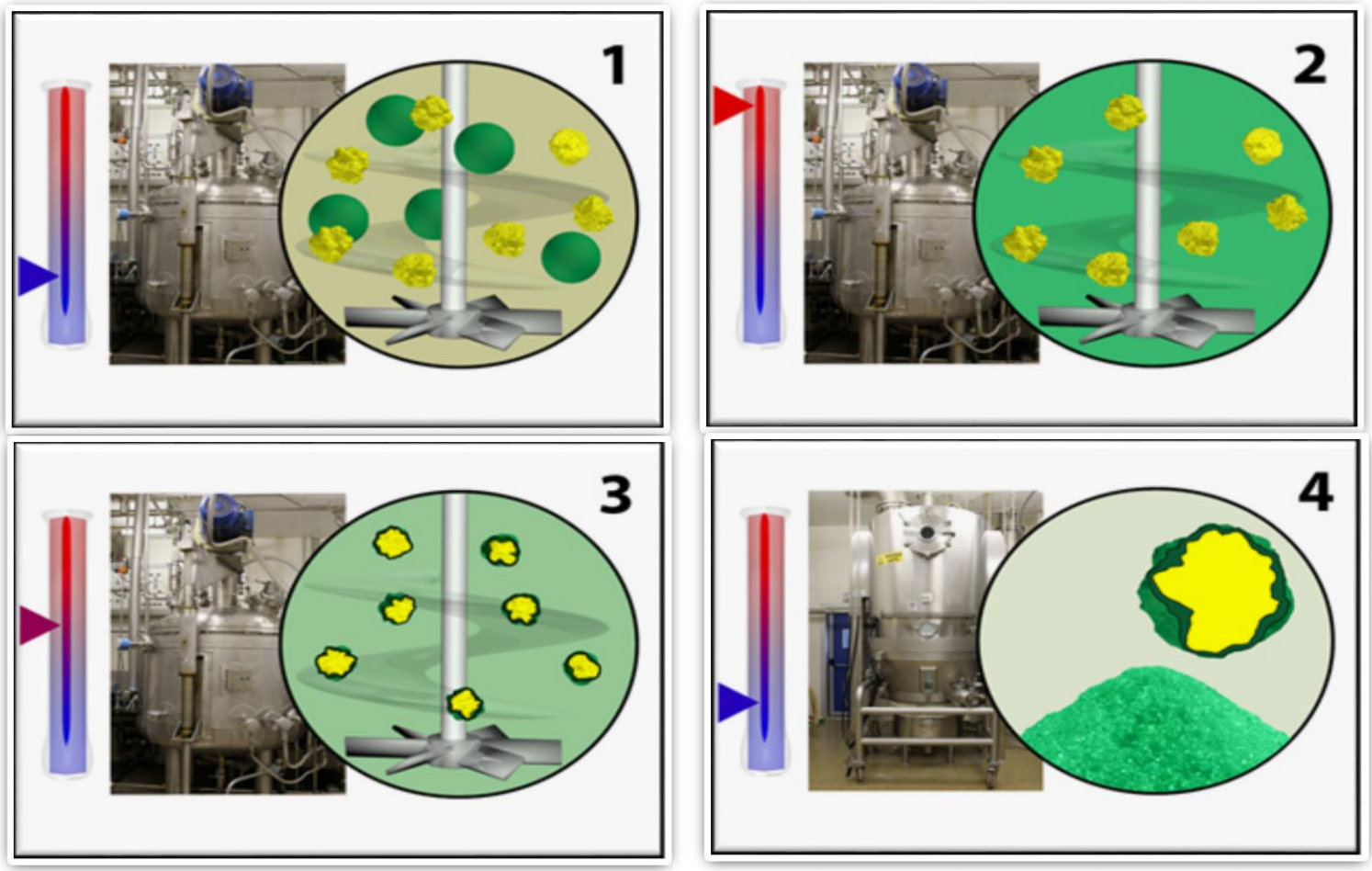


Fig. C Final KCl microcapsule after drying step

*Microcaps is a registered trademark of Aptalis Pharma S.r.l.

Taste Masking Technologies: Microencapsulation by coacervation



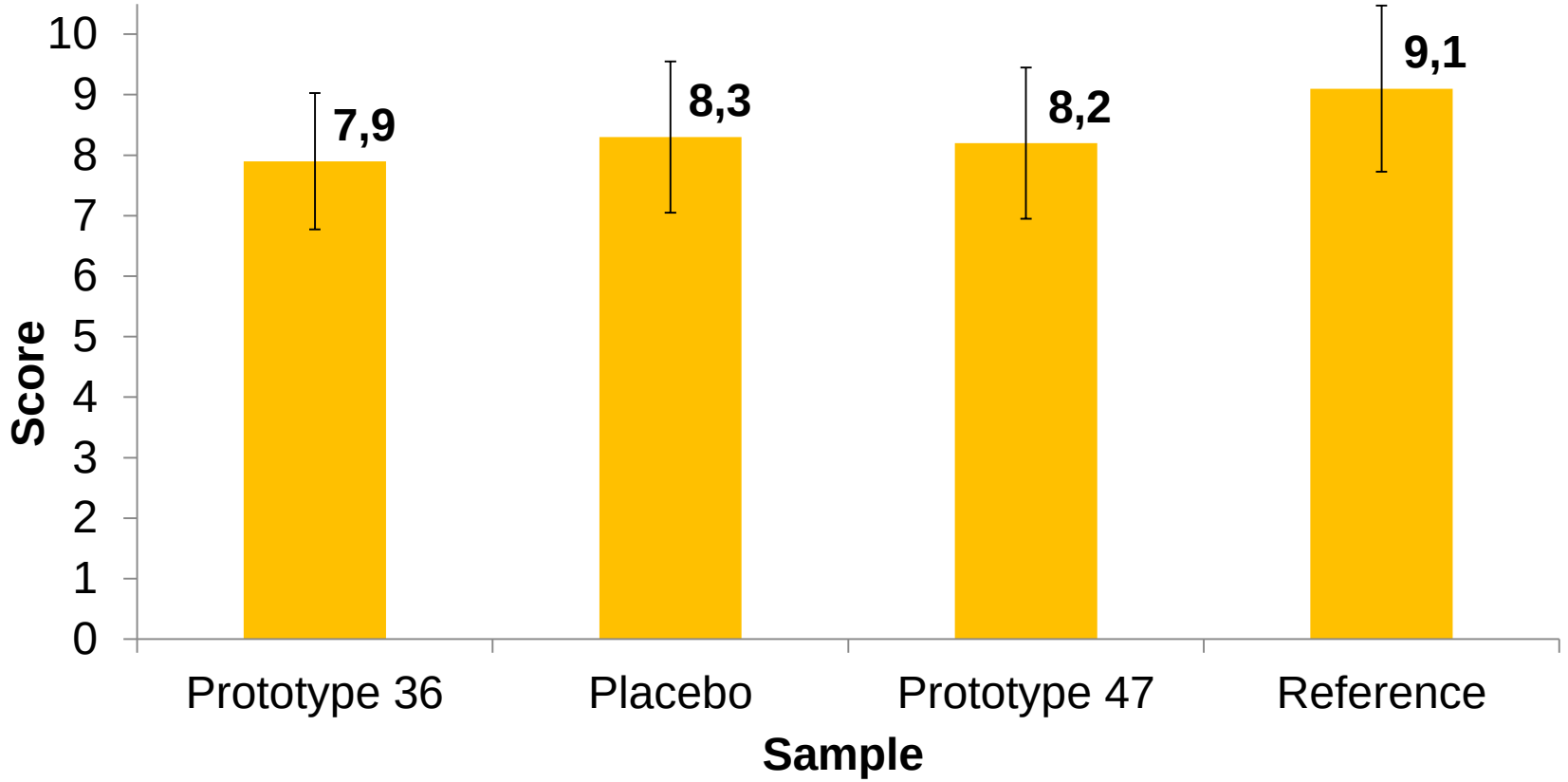
Although spherical particles are shown (yellow), the Microcaps® coacervation process can be used for varying particle shapes, including needle-shaped, platelets, spheroid, etc.

Microencapsulation Case Study
Fexofenadine HCl for Pediatric Patients

DRUG	• **Fexofenadine HCl**, 15 and 30 mg dosages, indicated for the relief of symptoms associated with seasonal allergic rhinitis, and for the treatment of uncomplicated skin manifestations of chronic idiopathic urticaria
NEED	• Provide an alternative delivery system to the Allegra® tablets* for easy administration in the form of a dry syrup / oro-dispersible granulate† • Taste-mask a bitter API • Suitable to be administered: ✓ in 50ml of water ✓ onto a tablespoon with few ml of water ✓ directly in the mouth avoiding water intake
SOLUTION(S)	• Use **Microcaps® taste masking technology** to develop an oral powder formulation • Granulation of Microcaps® with part of the excipients • Commercial presentation 300/600mg sachet

*ALLEGRA is a registered trademark of Aventisub II Inc.
†The formulation is particularly beneficial for pediatric use.

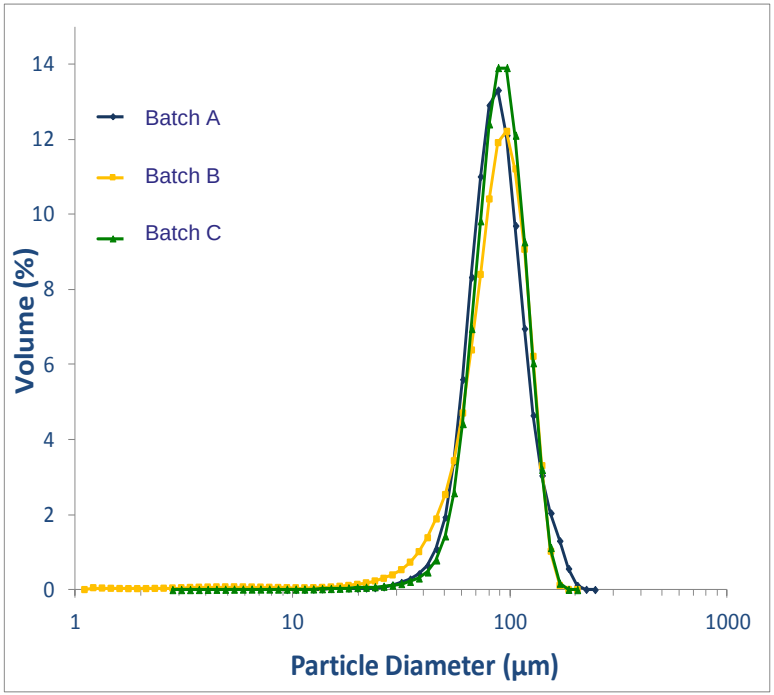
Fexofenadine Case Study
Results of Taste Masking Study by Partner

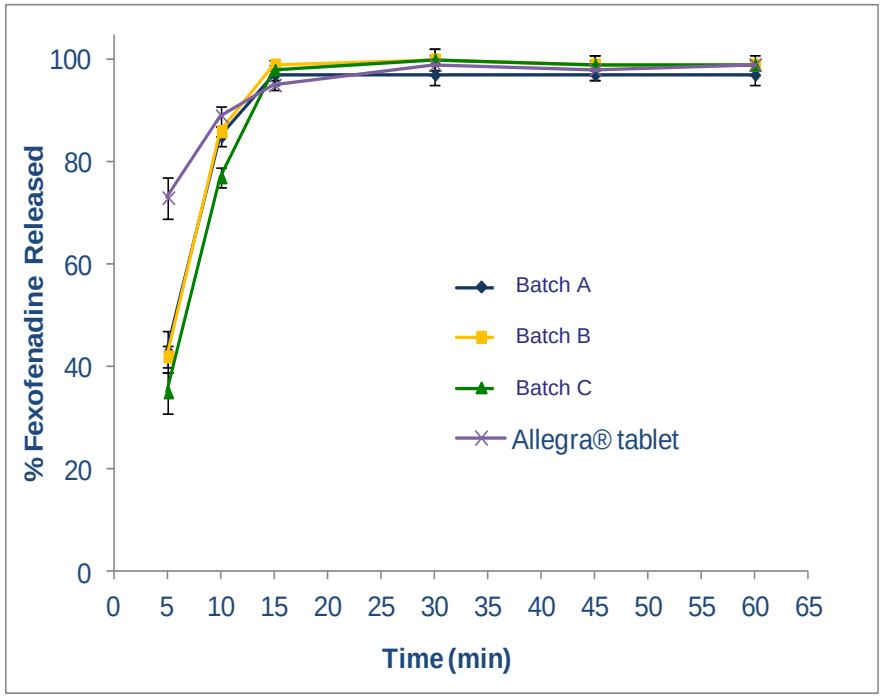


Overall taste masking acceptability rating of two different batches of Fexofenadine HCl microcapsules combined with sucrose/xanthan gum granulate (sample Prototype 36 and Prototype 47) vs placebo (composed only by sucrose/xanthan gum granulate) and vs Reference sachet product selected by Sanofi.

Fexofenadine Case Study
Microencapsulation of the API

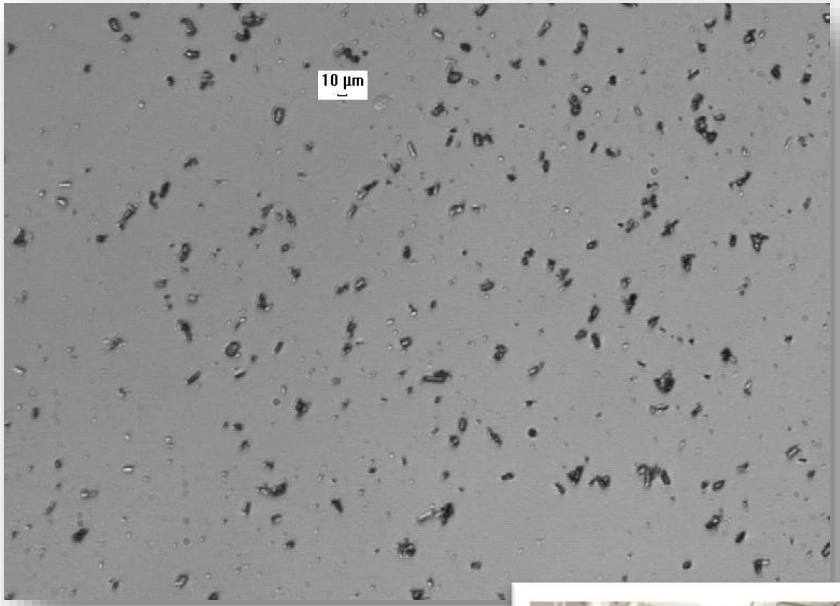
- ✓ Coating level 15% w/w ethylcellulose
- ✓ The PSD of the microcapsules was basically below 100 µm
- ✓ The assay was close to the theoretical value 850 mg/g (99-98%)
- ✓ DRT comparable to the Allegra® tablets (buffer pH 3.0 0.001M)
- ✓ Manufacturing of first clinical prototype to evaluate bioavailability and bioequivalence (Microcaps® prototype vs. Allegra® tablets) in healthy volunteers



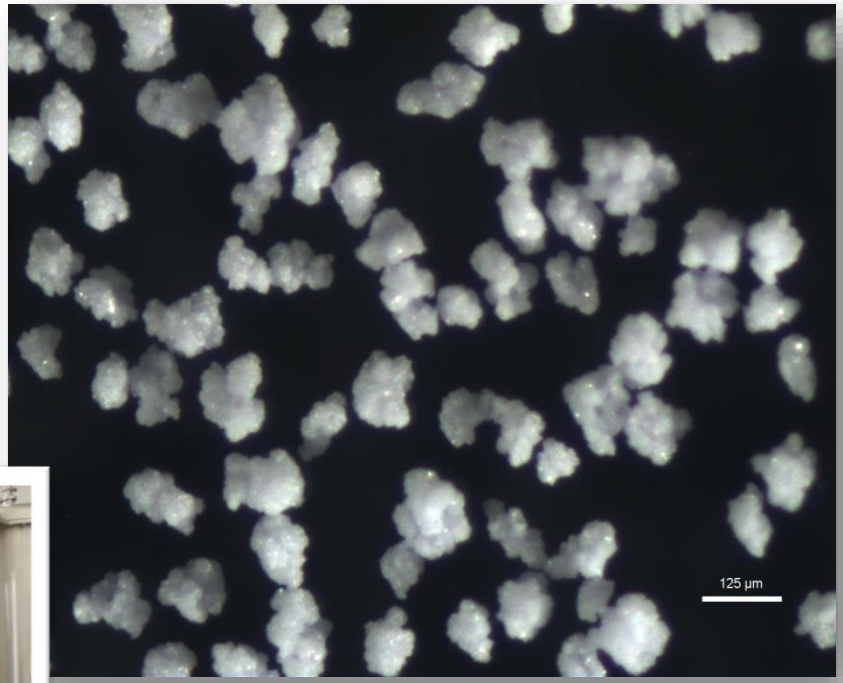


Fexofenadine Case Study
Scale Up Production Protocol

Fexofenadine HCl bulk



Fexofenadine HCl Mic



80 gal reactor coupled with fluid bed dryer

Fexofenadine Case Study
Scale Up Protocol

Microcapsules directly mixed with sucrose/xanthan gum granulate, encompassed one scale mixture.

Blend homogeneity of this mixture that was likely, in part, a consequence of:

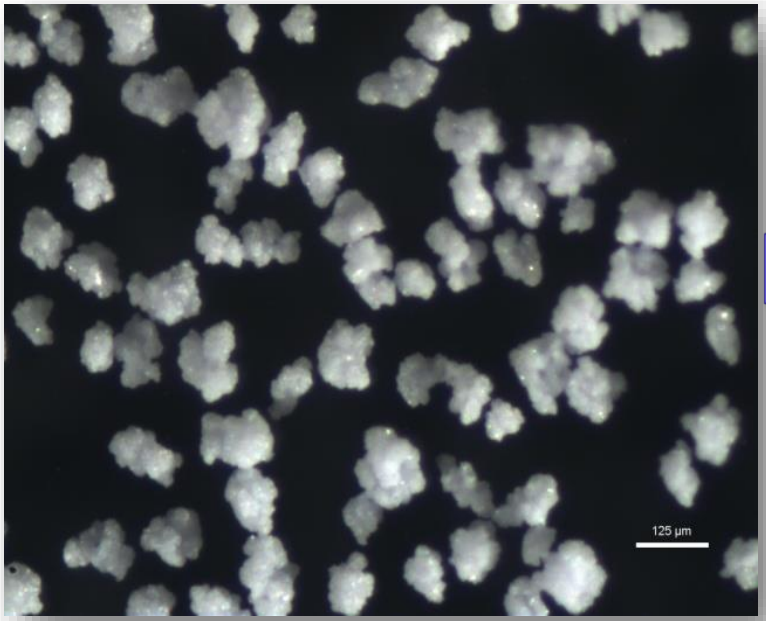
- High dilution (ratio microcapsules-sucrose/xanthan gum granulate 1:16.5)
- Significant difference in particle size between microcapsules (d_{90} = 125µm) and granulate (mean diameter = 400µm)
- The electrostatic charge of microcapsules

The mixing process was enhanced by:

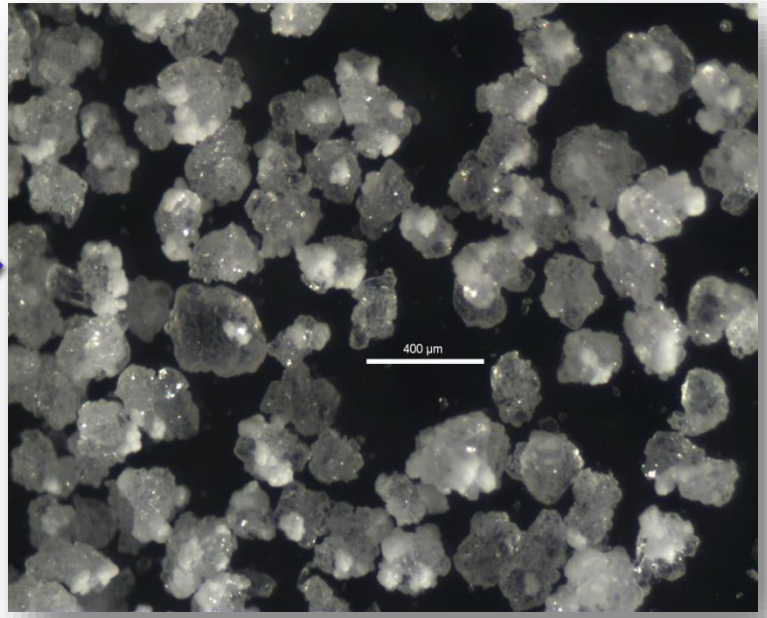
- Granulating microcapsules with a portion of the excipients (ratio 1:7)
- Blending the obtained co-granulate with the remaining portion of inactive ingredients in a granulated form (ratio ≈ 1:1)

Fexofenadine Case Study
Scale Up Production Protocol

Fexofenadine HCl microcapsules



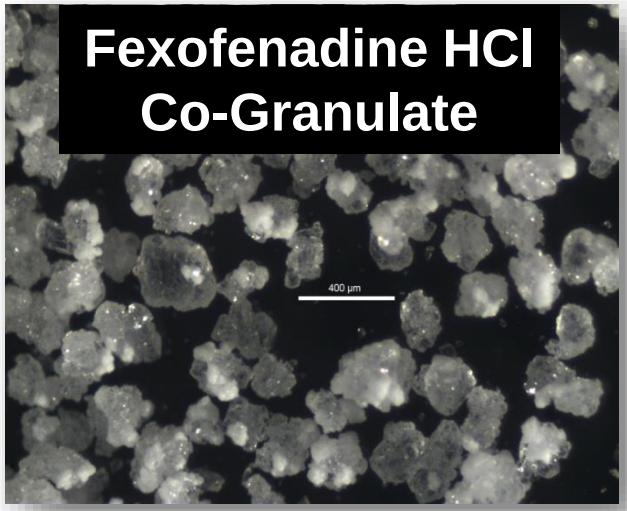
Fexofenadine HCl microcapsules Co-Granulate

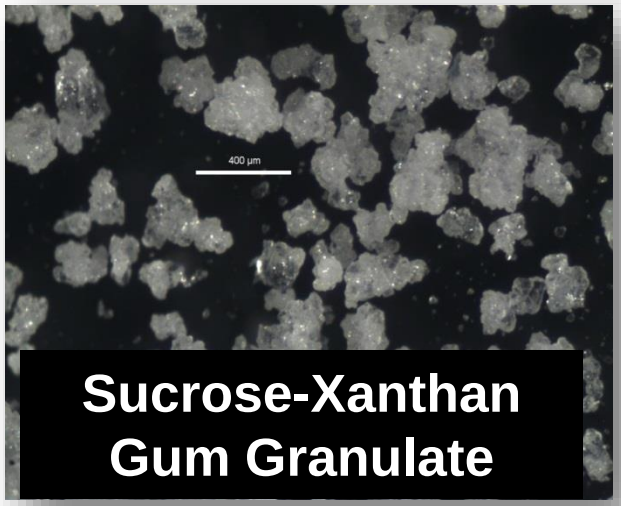


Granulation with sucrose

in top-spray fluid bed

Fexofenadine Case Study
Scale Up Production Protocol





Final Bulk Mix (400 Kg)				
Batch	Assay (mg/g)	RSD	% Recovery	% Released pH 3.0 @15 min (NLT 75%)
D	50.0	1.2	100	99
E	49.6	1.2	99	93
F	50.8	2.8	102	86

Fexofenadine Case Study
Powder Dosage Form in Sachets

Sachet 600 mg → 30 mg strength

Sachet 300 mg → 15 mg strength

Sachet					
Batch	Assay (mg/g)	RSD	% Released pH 3.0 @ 15 min (NLT 75%)	Average filling weight (mg)	AV
G	14.9	2.7	88	299.6±12.4	9.8
H	30.6	1.6	92	599.4±11.2	5.1
I	14.8	2.0	88	297.8±7.3	5.8
L	30.3	2.3	93	604.3±10.8	4.3
M	15.2	2.0	87	306.4±5.7	4.6
N	30.9	1.9	85	605.0±7.6	4.6

VIREAD®* for Pediatric Patients

DRUG	• VIREAD® (tenofovir disoproxil fumarate) once-daily 300 mg tablets were FDA approved in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and adolescents ages 12 and older, and for the treatment of HBV infection in adults and adolescents ages 12 and older.
NEED	• Provide a more convenient dosage formulation that enables ease of administration in the form of a sprinkled powder for pediatric patients while also providing highly effective taste masking of a bitter drug (API)
SOLUTION(S)	• Use Microcaps® taste masking technology to develop an oral powder for pediatric use • Commercial presentation is a multi-dose bottle with a calibrated measuring scoop
PARTNER GILEAD	• VIREAD® oral powder comes in a box that has a bottle of VIREAD® and a dosing scoop (see Figure A).

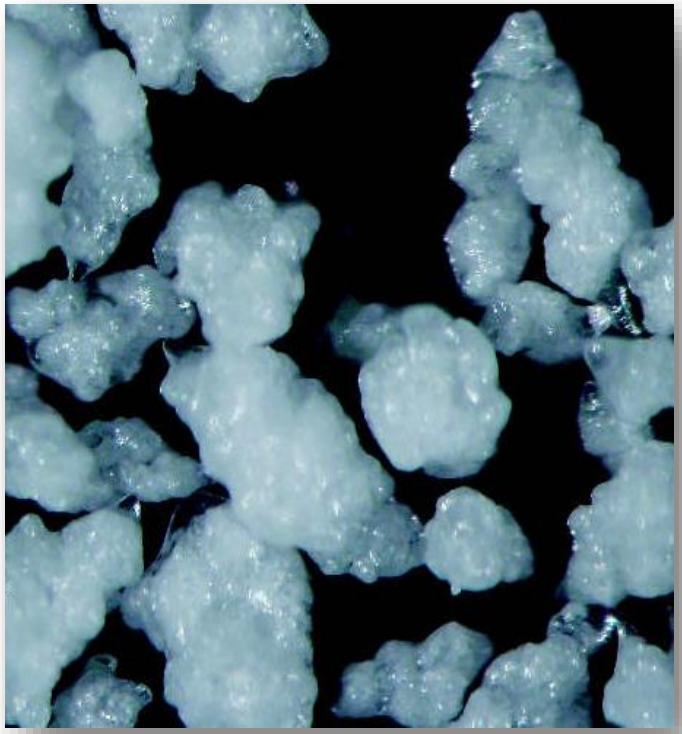
Figure A

*VIREAD is a registered trademark of Gilead Sciences, Inc.

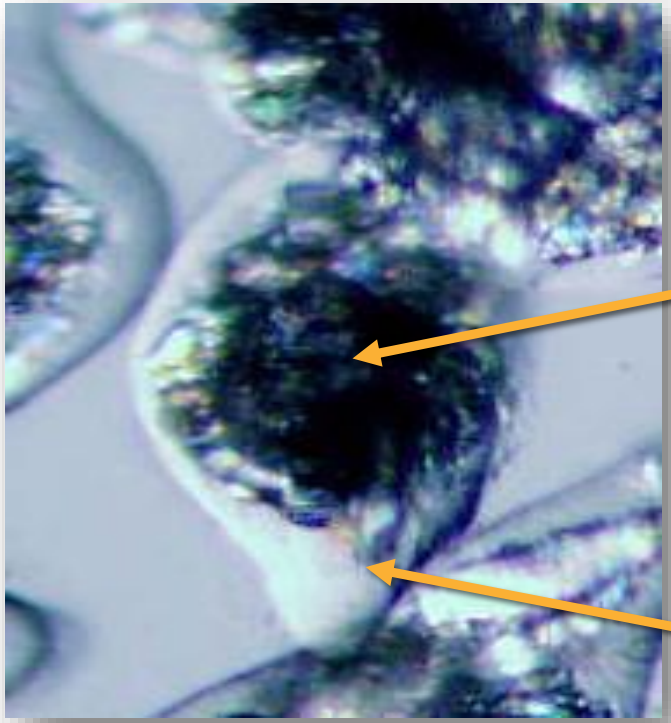
VIREAD® - Microencapsulated Particles

Particle morphology after the application of a polymer coating

Coacervated Granule (50x)



Coacervated Granule (90x)



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Sezione di Tecnologia e Legislazione Farmaceutiche Maria Edvige Sangalli

Associazione Farmaceutici Industria
Società Scientifica

Paediatric-Medicine Development in a Nutshell

Thanks for Your Attention

Questions ?

Paolo Gatti, PhD
Research Fellow and Manager Formulation
pgatti@aptalispharma.com