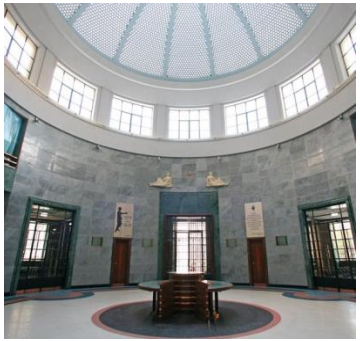


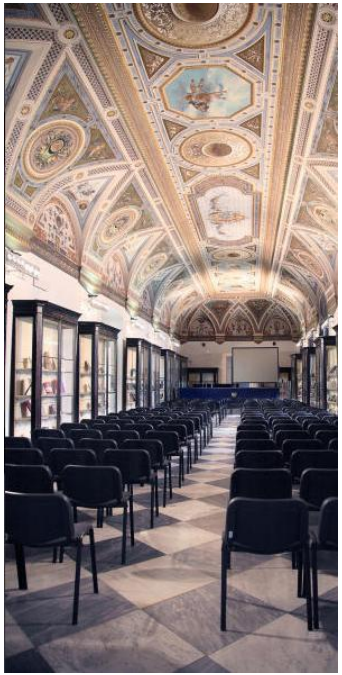
GREEN PHARMA R.D.I.: Building a Research and Innovation Ecosystem for Rare Disease Drug Development

Nunzio Denora
University of Bari Aldo Moro
Department of Pharmacy – Pharmaceutical Sciences
nunzio.denora@uniba.it

The University of Bari “Aldo Moro” - UniBa





1925 – The Adriatic University was founded.
2008 – The University of Bari was named to prof. Aldo Moro.

The Department of Pharmacy – Pharmaceutical Sciences



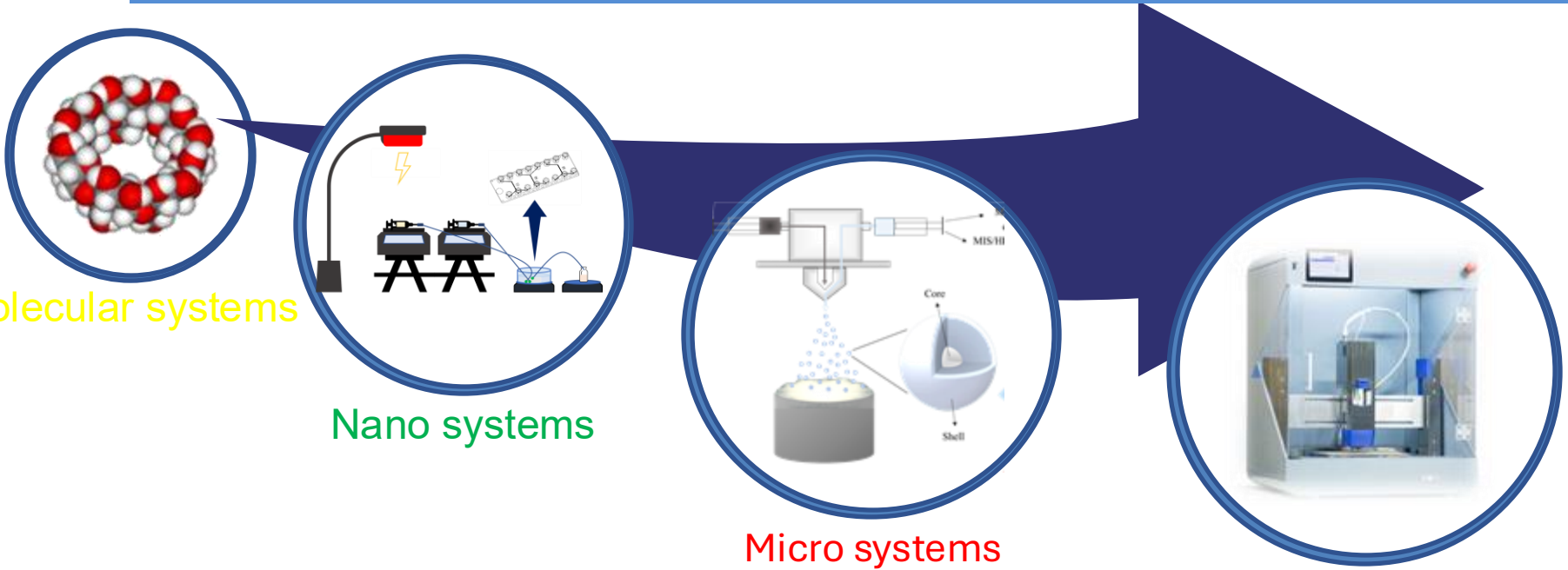
1985 – The Department of Pharmaceutical Chemistry was established.

2012 – Retitled as Department of Pharmacy – Pharmaceutical Sciences.

@Phartecolab
@Phartecolab

PharTeCo Lab – Pharmaceutical Technologies & Cosmetics
The Unit of Pharmaceutical Technology and Legislation, Department of Pharmacy – Pharmaceutical Sciences, University of Bari "Aldo Moro"

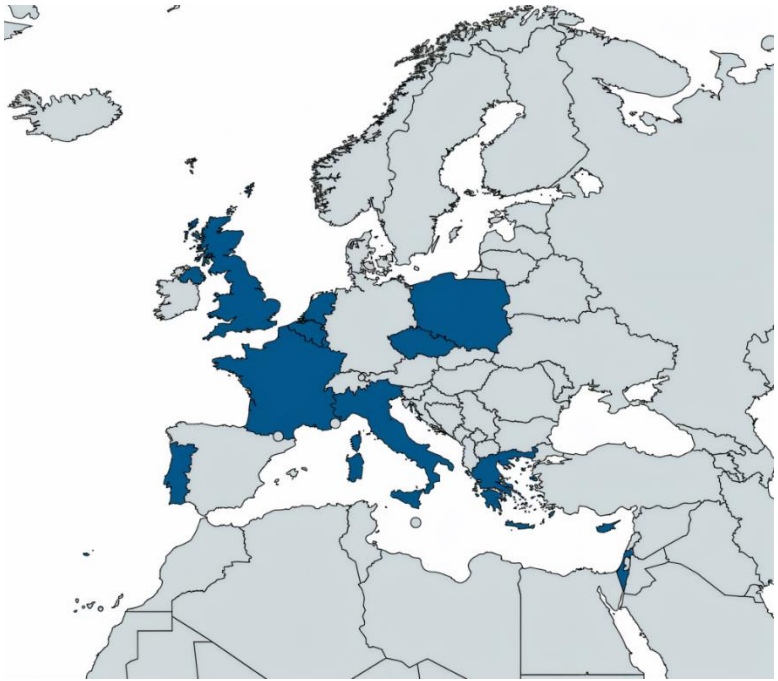
PharTeCoLab – Pharmaceutical Technology Platforms



Lab-made and scalable platforms to produce tailored formulations with features that meet the specific requirements of children

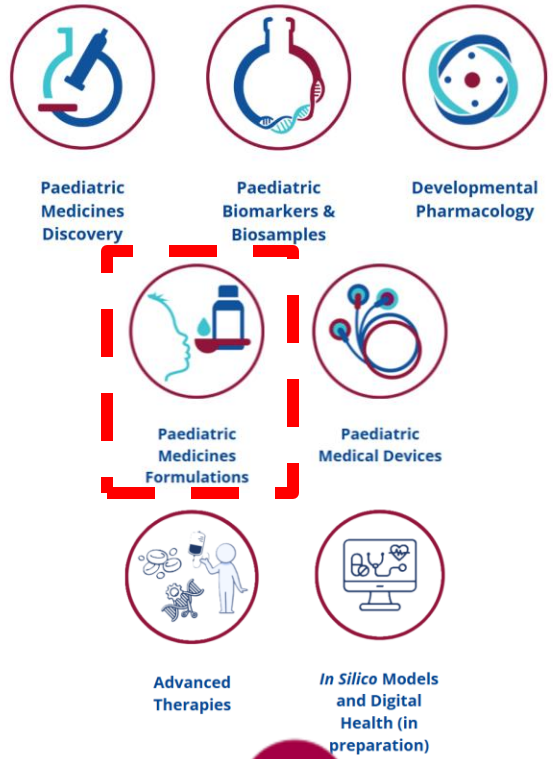
EPTRI – European Paediatric Translational Research Infrastructure

EPTRI
European Paediatric Transnational Research Infrastructure



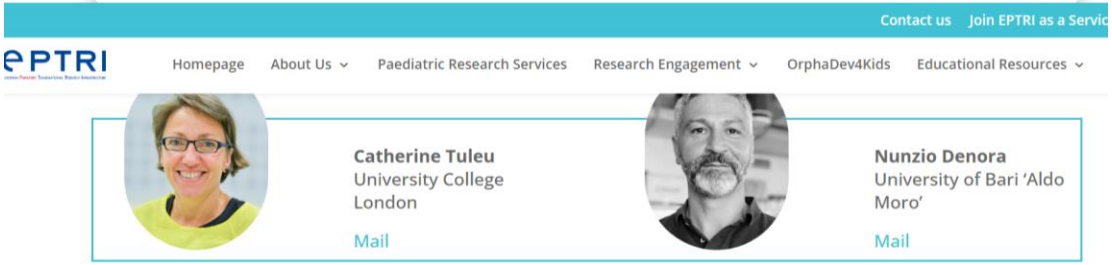
KU LEUVEN
UNIVERSITEIT GENT
UZA
THE CYPRUS INSTITUTE OF NEUROLOGY & GENETICS
INSTITUTE OF PHYSIOLOGY CAS
ATHENA Research & Innovation Information Technologies
Milo Health
CVBF
UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO
gb FONDAZIONE PER LA RICERCA TRASLAZIONALE GIANNI BENZI ONLUS
LA NOSTRA FAMIGLIA
UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA
Penta Child Health Research
TEDDY NETWORK
ALYN HOSPITAL
Contact us Join EPTRI as a Service
OrphaDev4Kids Educational Resources
ANDO ASSOCIAÇÃO NACIONAL DISPLASIAS ÓSSEAS
UCL
DUCHENNE DATA FOUNDATION

Thematic Research Platforms – TRPs



Paediatric Medicines Formulations TRP

- Pre-formulation advice and Pre-formulation studies
- Formulation of drug for paediatric use for non-enteral routes of administration
- Paediatric in vitro palatability assessment
- Formulation of drug for paediatric use for enteral routes of administration
- Assessment and design of drug delivery systems for enteral and non-enteral routes of administration
- Paediatric in vivo palatability assessment





Paediatric Medicines Formulations

GREEN PHARMA R.D.I.

PROJECT IDEA TITLE:
GREEN PHARMA. R.D.I. – **GREEN** compounding and **PHARMA**ceutical **R**epurposing for rare **D**iseases **I**nnovation ecosystem

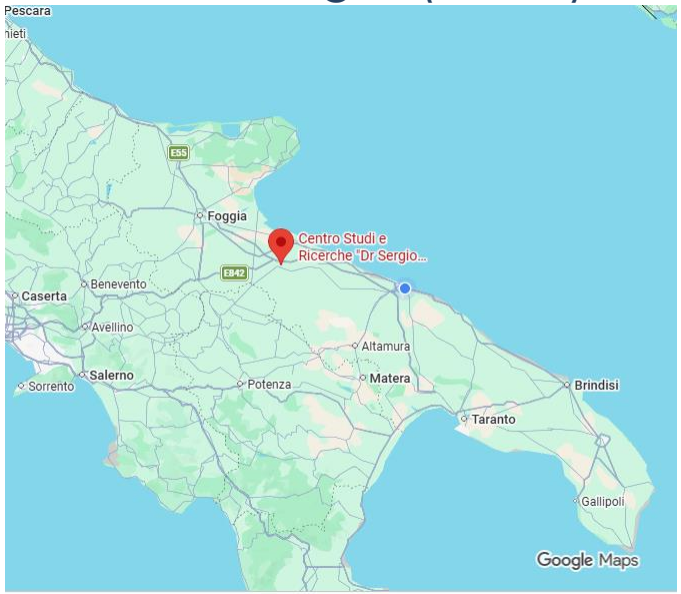
DURATION:
60 months (5 years), from 1 January 2024 to 31 December 2028

LEAD APPLICANT:
Polytechnic University of Bari

PARTNERS:
Farmalabor Srl; Diotima Society; Consortium for Biological and Pharmacological Evaluations (CVBF); University of Bari Aldo Moro; University of Foggia; Gianni Benzi Pharmacological Research Foundation (Non-Profit Organisation).

TOTAL INVESTMENT:
EUR 20,000,000.00 – twenty million euros

LOCATION:
Canosa di Puglia (76012), Via di Piano San Giovanni 47–53



EXPECTED IMPACT:

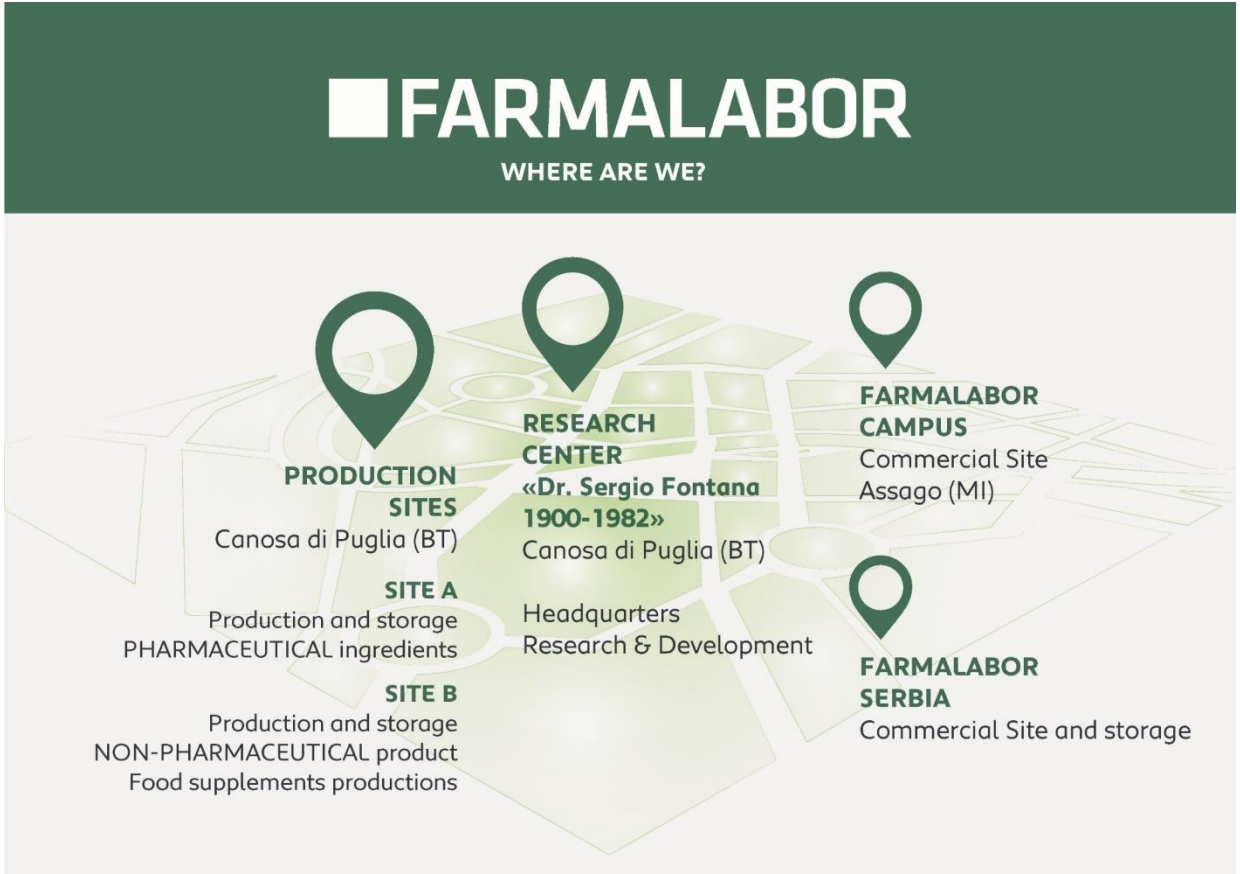
The development of new and effective therapies for all diseases, including rare and paediatric diseases (see the expected impact of Horizon Europe Cluster 1, Destination 3), will enable the exploitation of the therapeutic potential of highly innovative approaches (see the expected impact of Horizon Europe Cluster 1, Destination 5) that are also environmentally safe (see the expected impact of Horizon Europe Cluster 1, Destination 2).

The project has been authorized by the Ministry of Southern Italy and Territorial Cohesion and by the Agency for the Territorial Cohesion



GREEN PHARMA R.D.I.




FARMALABOR
WHERE ARE WE?
PRODUCTION SITES
Canosa di Puglia (BT)
SITE A
Production and storage
PHARMACEUTICAL ingredients
SITE B
Production and storage
NON-PHARMACEUTICAL product
Food supplements productions
RESEARCH CENTER
«Dr. Sergio Fontana 1900-1982»
Canosa di Puglia (BT)
Headquarters
Research & Development
FARMALABOR CAMPUS
Commercial Site
Assago (MI)
FARMALABOR SERBIA
Commercial Site and storage

GREEN PHARMA R.D.I.



Current location of the “Dr. Sergio Fontana (1900–1982) Study and Research Centre” at Via di Piano San Giovanni 47–53 (structures shown in black), and the redevelopment and functionalisation works to transform the site into an Innovation Ecosystem, already approved by the Municipality of Canosa di Puglia (structures shown in red).

Overall view of the GREEN PHARMA Innovation Ecosystem – R.D.I.



GREEN PHARMA R.D.I.

- **Computational laboratory for prioritizing active pharmaceutical ingredients for repurposing in the treatment of paediatric and rare diseases.**
- **Systems Biology Laboratory**
- **Formulation Development Laboratory**
- **Pilot-Scale Manufacturing Laboratory for Repurposed Medicines**
- **Analytical Pharmacotoxicology and Pharmacogenomics Laboratory**
- **Ethical, Regulatory, Authorization, Legal and Social Laboratory (REALS)**

INNOVATION ECOSYSTEM

Eosinophilic Esophagitis (EoE)

Eosinophilic Esophagitis (EoE) is antigen-mediated oesophageal inflammatory disease treated with a therapeutic approach ranging from elimination of harmful foods from the diet to a pharmacological therapy based on:



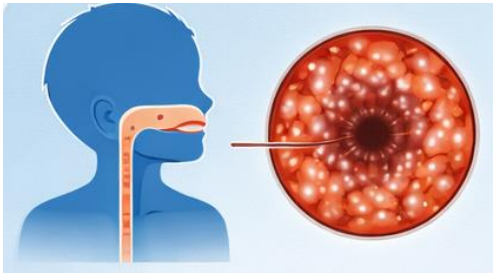
- **Proton pump inhibitors;**
- **Topical corticosteroids;**
- **Monoclonal antibodies**.

No longer classified as a rare disease in EU. While it was once considered rare, its prevalence has significantly increased (between 50 and 100 cases per 100,000 people)

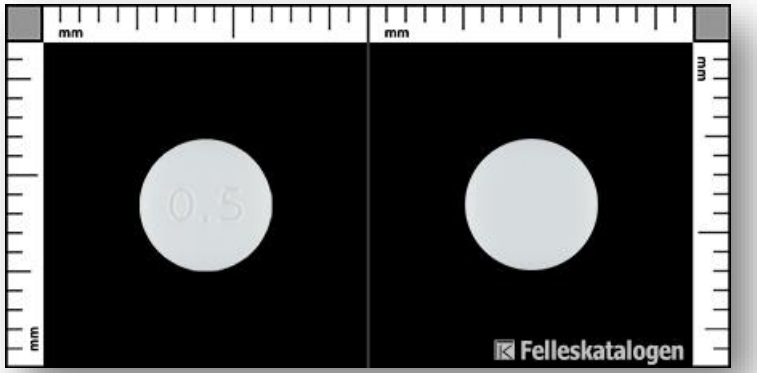
Eosinophilic Esophagitis (EoE)



- ✓ Budesonide (BD), a potent second-generation glucocorticoid with local anti-inflammatory action and reduced systemic side effects;
- ✓ BD is used for the local treatment of paediatric diseases such as the **Eosinophilic Esophagitis** (EoE) and the **Eosinophilic Colitis** (EC);
- ✓ BD is BCS Class II drug.



Eosinophilic Esophagitis (EoE)



There are no commercial budesonide-based medicines indicated for EoE paediatric treatment.

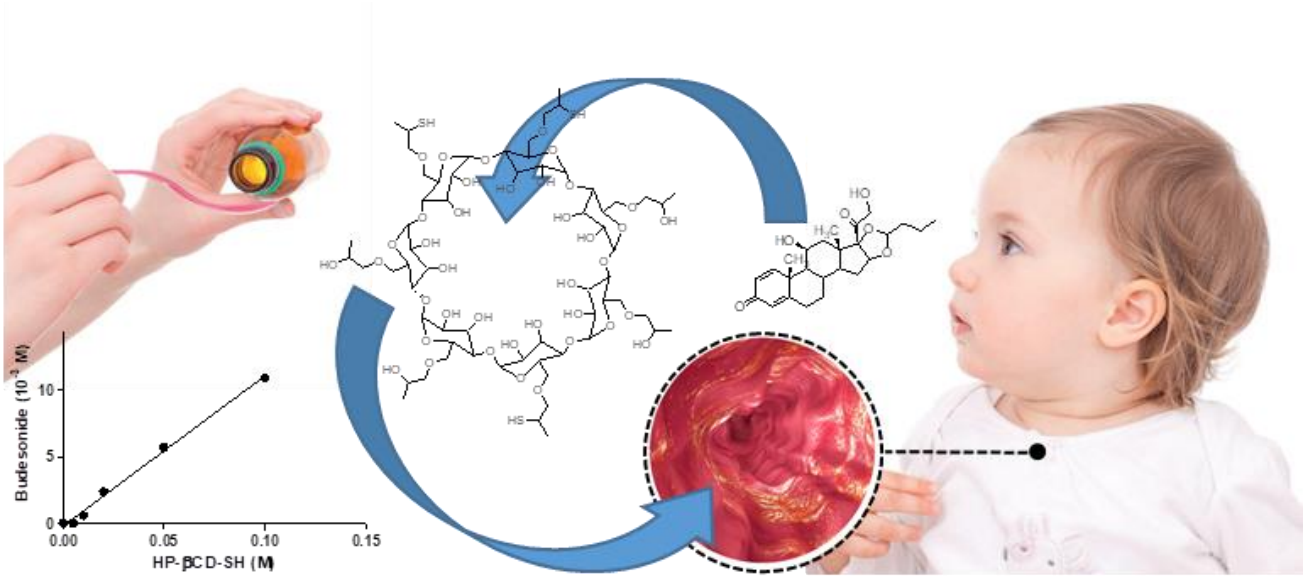
BD could be extemporaneously formulated as viscous oral suspensions.



Limits:

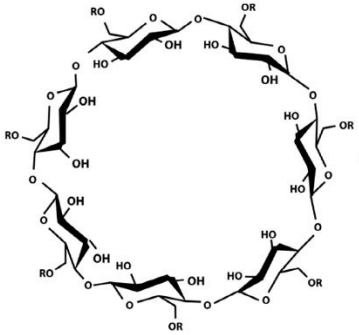
- Solid dosage form authorised for adults;
- The suspension is characterised by low bioavailability.

Eosinophilic Esophagitis (EoE)



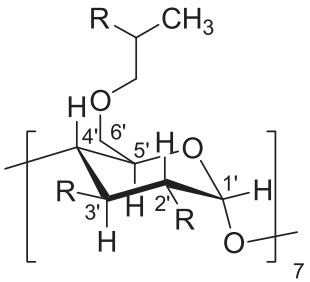
Aim: To improve the current therapeutic practice for the local treatment of EoE in paediatric patients, a new mucoadhesive BUD-based solution was realized using both pristine and thiolated hydroxypropyl-β-cyclodextrins as solubilizing agents.

Eosinophilic Esophagitis (EoE)



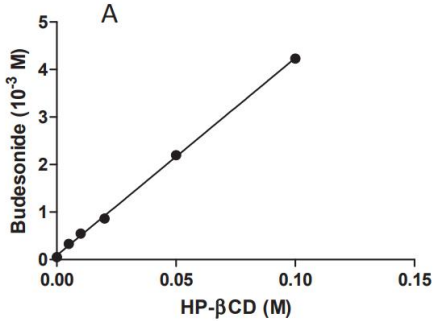
R = H or

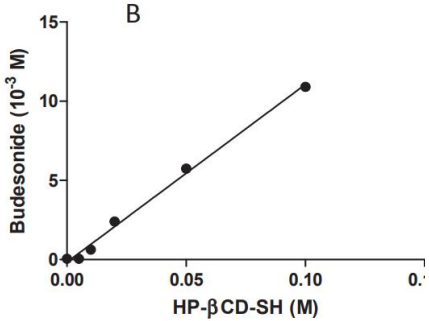




HP-βCD-SH

R= OH, or SH





Solubility (S) and Phase solubility studies at 25 °C in water of BUD/HP-β-CD and BUD/HP-β-CD-SH complexes. Results are expressed as mean ± S.D of three experiments.

Sample	S (10^{-3} M)	$K_{1:1}$ (M^{-1})	Slope (p)	R^2
HP-β-CD	4.3[a]	861.11	0.041 ± 0.005	0.9993
HP-β-CD-SH	10.9[a]	2513.52	0.112 ± 0.004	0.9962
BUD	0.05028	–	–	–

[a] Water solubility of BUD with 100 mM of oligomer.

Fig. 4. Phase solubility studies of inclusion complexes of BUD with HP-β-CD (A) and HP-β-CD-SH (B). Each value is the average of three different experiments ± standard deviation.

V. Laquintana et al. Thiolated hydroxypropyl-β-cyclodextrin as mucoadhesive excipient for oral delivery of budesonide in liquid paediatric formulation. International Journal of Pharmaceutics 572 (2019) 118820.

Eosinophilic Esophagitis (EoE)

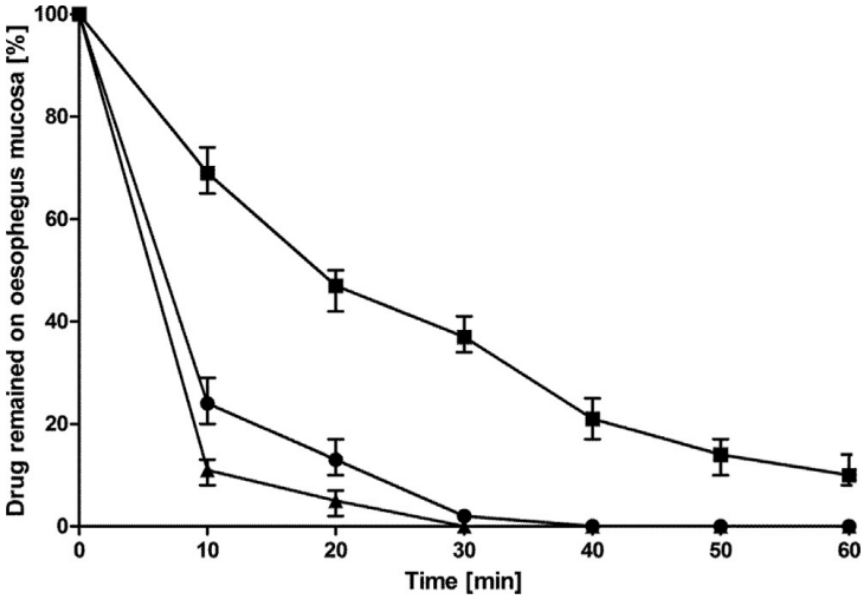
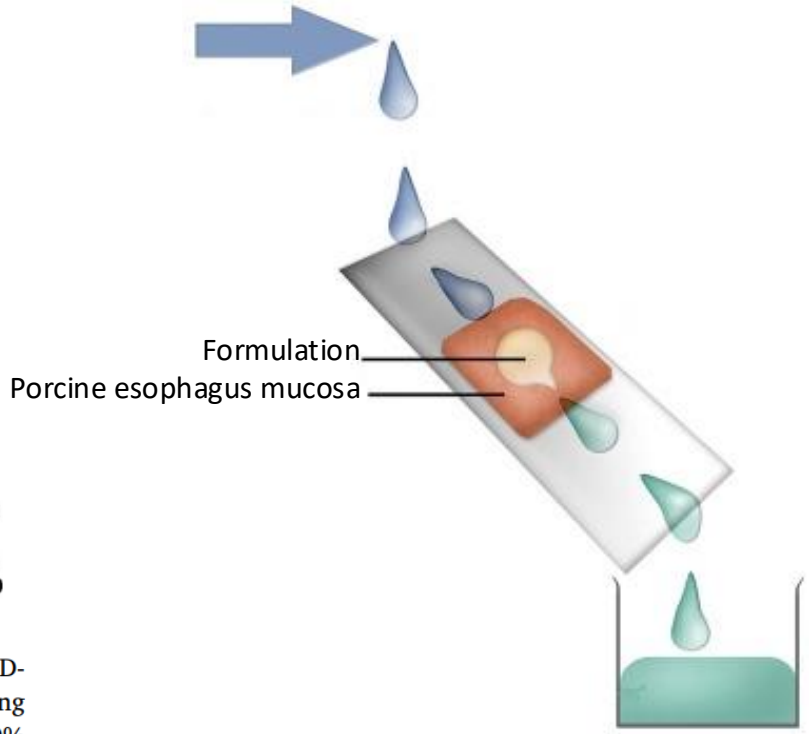


Fig. 11. Residence time of BUD in BUD/HP-β-CD complex (●), BUD/HP-β-CD-SH complex (■), and BUD as control (▲) on porcine esophagus mucosa being continuously rinsed with 100 mM phosphate buffer pH 6.8 at 37 °C and 100% relative humidity.

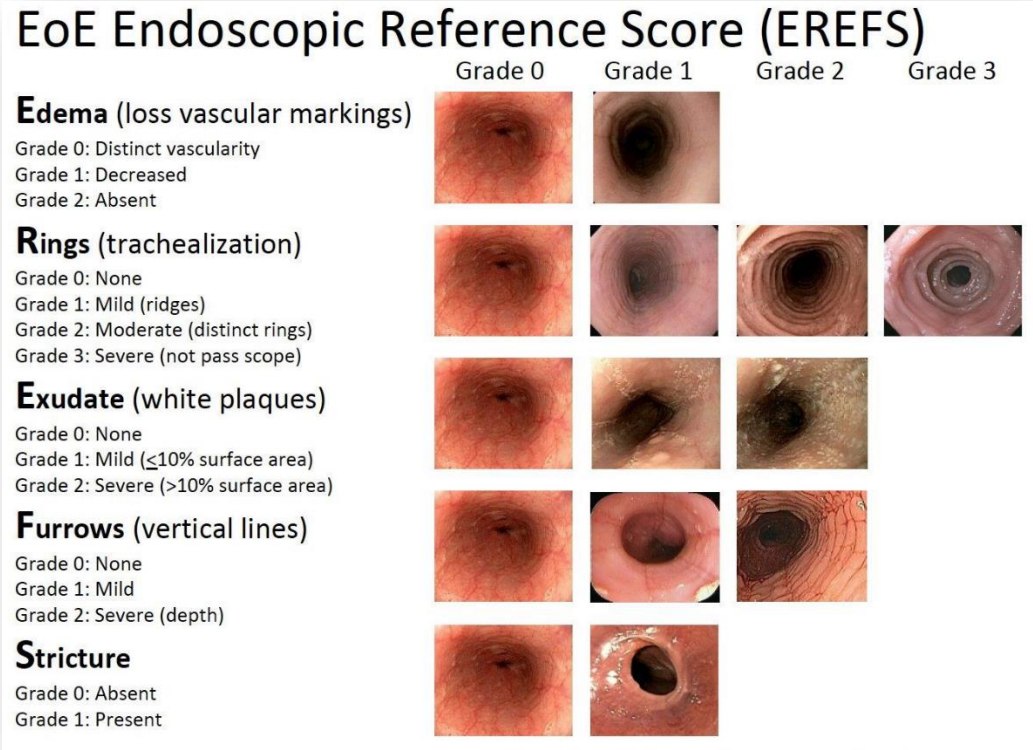


V. Laquintana et al. Thiolated hydroxypropyl-β-cyclodextrin as mucoadhesive excipient for oral delivery of budesonide in liquid paediatric formulation. International Journal of Pharmaceutics 572 (2019) 118820.

Eosinophilic Esophagitis (EoE)

Endoscopy Results

10 patients (8 males; mean age 14.3 years, range 12–16)
All completed the 12 weeks treatment (good compliance)
Histological remission in 8 out of 10 patients (<15 eosinophils/HPF)
Two non-responders showed clinical remission.



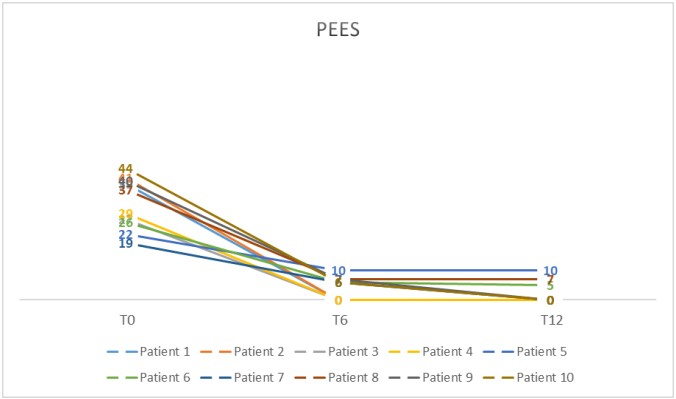
REGIONE PUGLIA

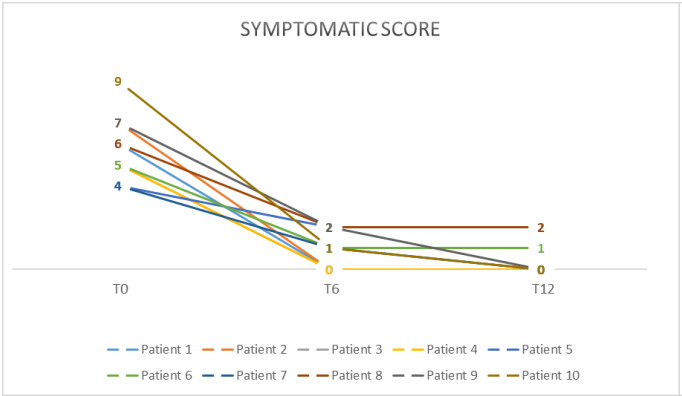
UniBa

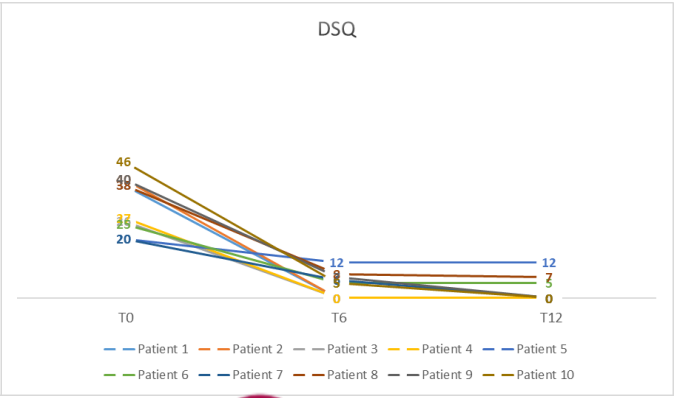
Eosinophilic Esophagitis (EoE)

Results – Symptoms

Reduction in symptom score already after the first 6 weeks of therapy.
75% of patients were asymptomatic at the end of the study.

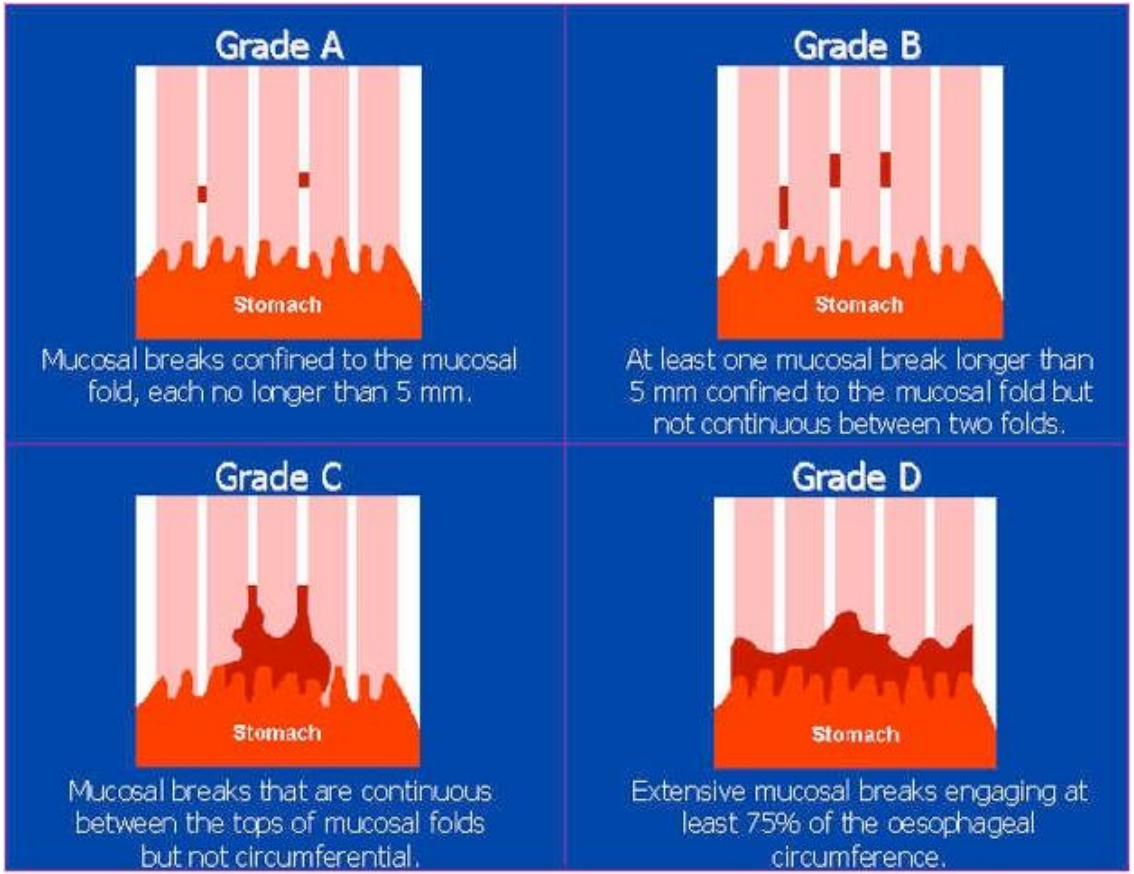






REGIONE PUGLIA

Eosinophilic Esophagitis (EoE)



Results – Safety

No adverse events, no fungal infections;
Three cases of Grade A erosive esophagitis, resolved after PPI therapy;

Eosinophilic Colitis (EC)

Budesonide loaded mini-tablets for the treatment of eosinophilic colitis in paediatric patients



Combining the **hot melt extrusion (HME)** process with the **3D printing** technique to generate from pharmaceutical grade powders or pellets customizable solid dosage forms.

Direct Powder Extruder (DPE)

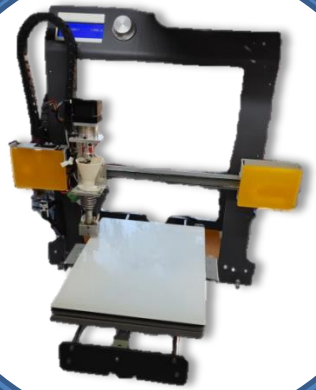
- Extrude material directly from pellets or powders using a single-screw extruder;
- Preparation of the filament by Hot Melt Extrusion (HME) is not necessary;
- Continuous, single step production process.

DEVELOPMENT STAGES OF THE NEW 3DFORME®

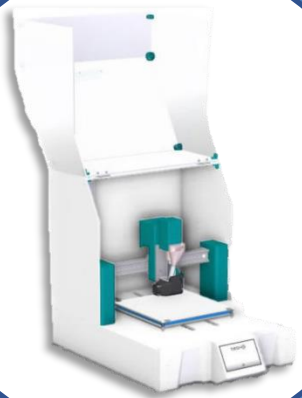
3DFormE®



2019



2021



2022



2023

FARMALABOR

AMable

Coordinated by Fraunhofer ILT

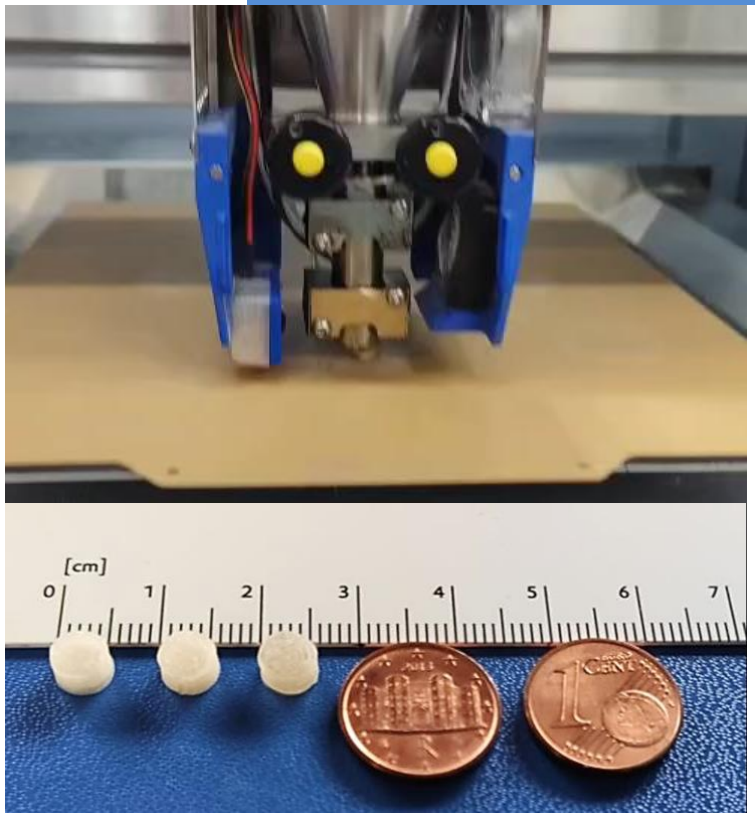
This project has been partially funded from the European Union Horizon 2020 research and innovation programme under grant agreement No 768775

ARESS Agenzia Regionale per la Salute ed il Sociale Puglia

Technology readiness level (TRL) 8

UniBa

Eosinophilic Colitis (EC)



Printing parameters:

- Geometry: Cylindrical (5×4 mm)
- Printing Temperature: 180 °C (T_m 260 °C)
- Build plate temperature: 70 °C
- Print speed: 5 mm/s
- Infill pattern: Concentric
- Infill Density: 70 %

Tablets mass 130 mg, therapeutic dose 1 mg of BD;
All formulations comply with pharmacopoeia-required tests.

For each formulation, the characteristics of each MT obtained by DPE.

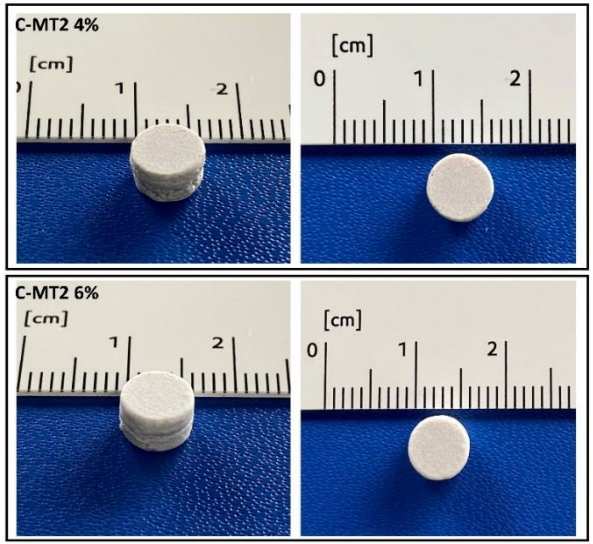
MT	Weight Uniformity* (mg)	Drug content* (mg)	Friability* (%)	Breaking Force (N)*	Dimensions (mm)*	
					Diameter	Height
1	128.08 ± 20.17	0.71 ± 0.09	0.022	> 484.00	5.17 ± 0.29	4.14 ± 0.33
2	127.08 ± 10.68	0.68 ± 0.09	0.064	298.67 ± 62.14	5.52 ± 0.21	3.78 ± 0.13
3	130.40 ± 18.39	0.60 ± 0.05	0.038	320.08 ± 97.70	5.46 ± 0.18	3.76 ± 0.21

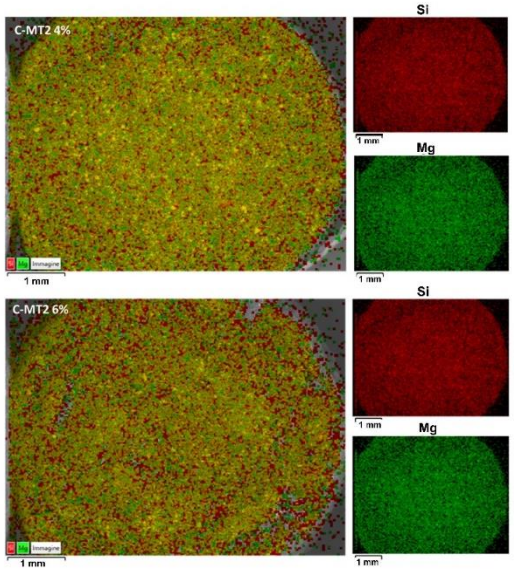
* The value is the average of 10 tablets. ± is the deviation standard.

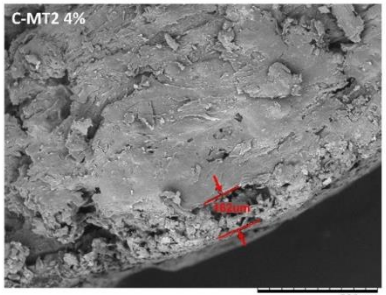
M. Pistone et al. International Journal of Pharmaceutics
https://doi.org/10.1016/j.ijpharm.2023.122592

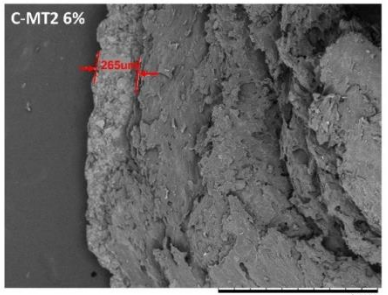
Eosinophilic Colitis (EC)

Coated MT







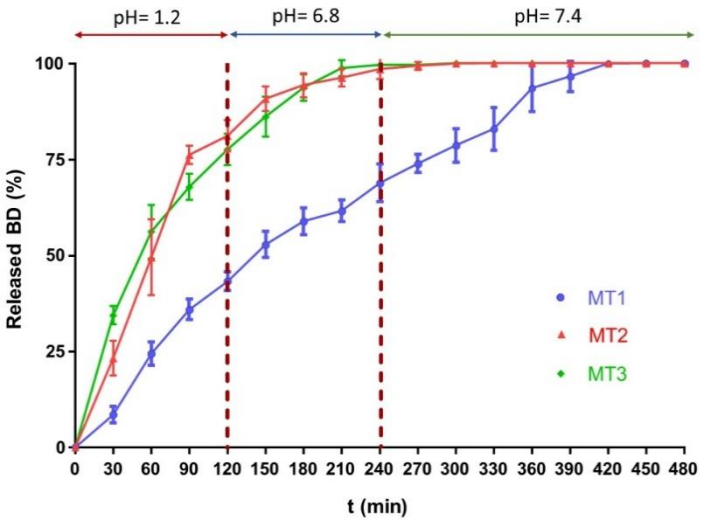


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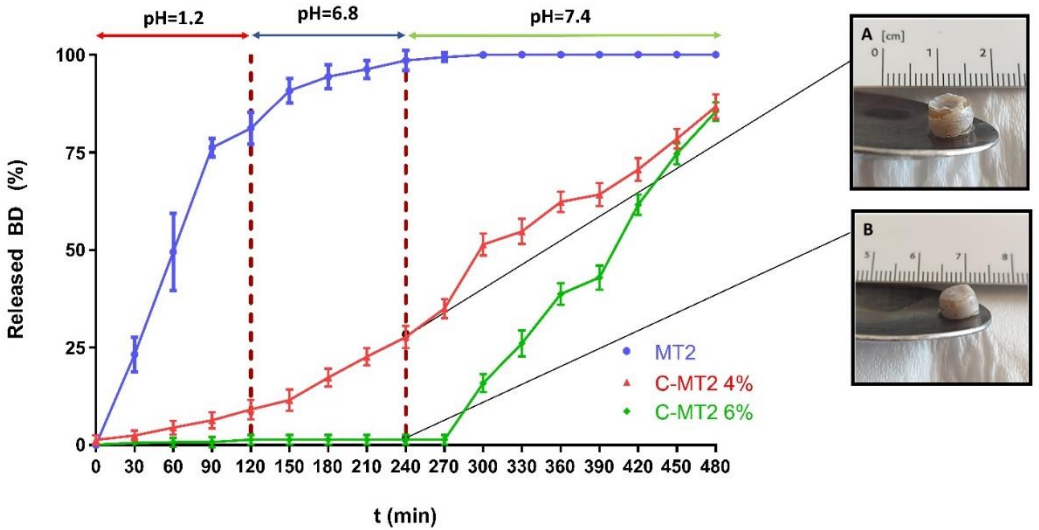
- ✓ SEM images of 3D printed coated mini tablets;
- ✓ homogeneous presence of the elements Mg (green) and Si (red).

M. Pistone et al. International Journal of Pharmaceutics
https://doi.org/10.1016/j.ijpharm.2023.122592

Eosinophilic Colitis (EC)



Dissolution profiles of the three different formulations (MT1, MT2, MT3) studied in an acid medium (HCl 0.1 N) for two hours, followed by a further two hours in a buffer solution at pH = 6.8 and finally in a buffer solution at pH = 7.4 for the remaining time.



Dissolution profiles of the coated formulations (C-MT2 4 % and C-MT2 6 %) compared with the uncoated MT2 formulation.

M. Pistone et al. International Journal of Pharmaceutics
https://doi.org/10.1016/j.ijpharm.2023.122592

CONCLUSIONS



- Paediatric drug exposure is strongly formulation-dependent;
- Rare diseases amplify the challenges of paediatric formulation;
- GREEN PHARMA can turn these challenges into opportunities for paediatric patients, paediatric research, and the territory.

AKNOLEDGMENTS

PharTeCoLab,
Pharmaceutical Technologies & Cosmetics Laboratories
Department of Pharmacy – Pharmaceutical Sciences
University of Bari Aldo Moro





Nunzio Denora

University of Bari Aldo Moro

Department of Pharmacy – Pharmaceutical Sciences

nunzio.denora@uniba.it

#PhartecoLab