Thematic Research Platform Paediatric Medicines Formulations

University of Bari Aldo Moro

EPTRI General Assembly and Scientific Meeting – Bologna – 14/03/2025

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

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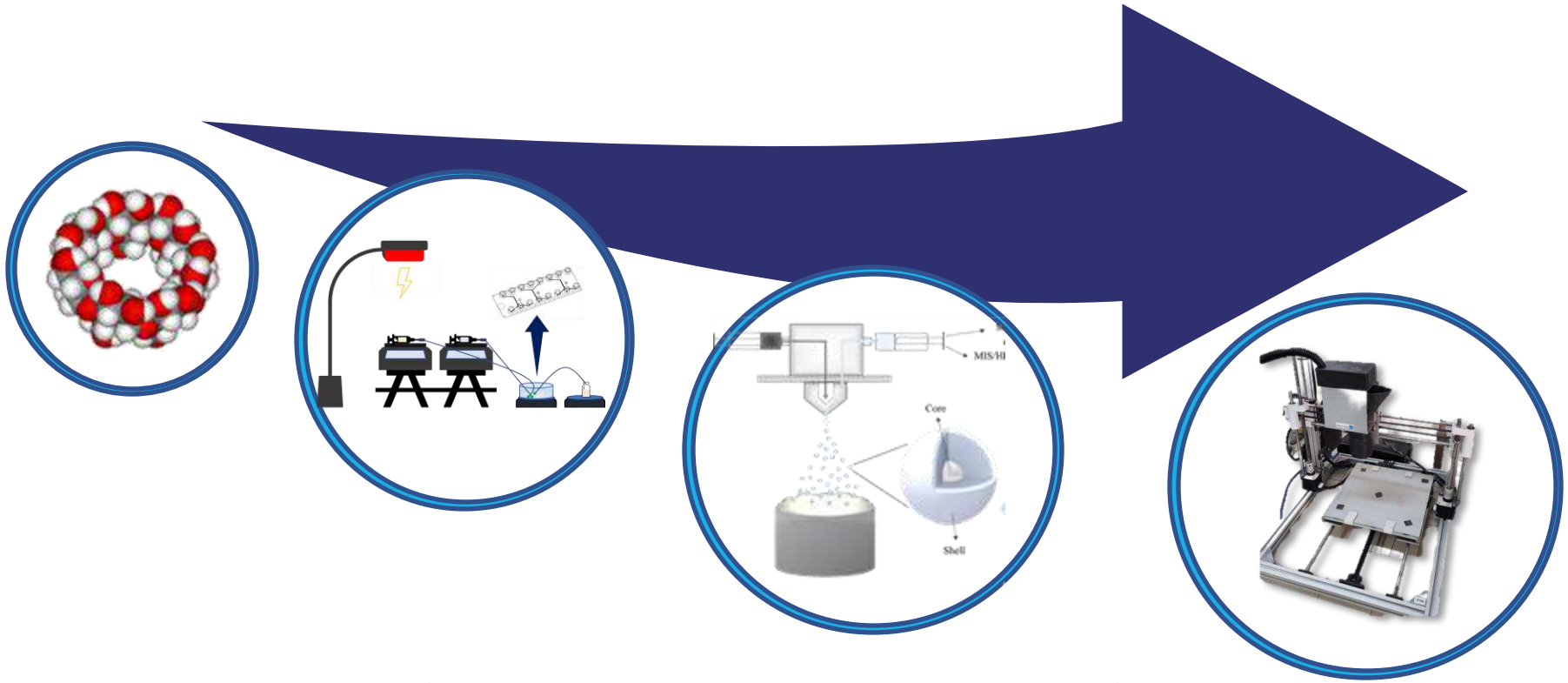
PHARTECO LAB
the Unit of Pharmaceutical Technology and Regulations,
Department of Pharmacy – Pharmaceutical Sciences,
University of Bari Aldo Moro



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

- microfluidics, prilling technology
- direct powder extrusion 3D printing

The European Paediatric Translational Research Infrastructure (EPTRI), started as an EU-supported initiative (EU-EPTRI-ID n. 777554), is a distributed Research Infrastructure (RI) composed of several research units grouped within Thematic Research Platforms – TRPs.

EPTRI is a non-profit research organisation incorporated in the form of an Association Internationale Sans But Lucrative (AISBL) governed by Belgian law, based in Leuven.

https://eptri.eu/

EPTRI
European Paediatric Translational Research Infrastructure

EPTRI
European Paediatric Translational Research Infrastructure

Università degli Studi di Bari Aldo Moro

EPTRI - THEMATIC RESEARCH PLATFORMS (TRP)

Integrated services are provided by the five Thematic Research Platforms:

Paediatric Medicines Discovery

Paediatric Biomarkers & Biosamples

Developmental Pharmacology

Paediatric Medicines Formulations

Paediatric Medical Devices

EPTRI - THEMATIC RESEARCH PLATFORMS (TRP)

Thematic Research Platform: Paediatric Medicines Formulations

Coordinators

Catherine Tuleu
University College London

Nunzio Denora
University of Bari 'Aldo Moro'

Paediatric Medicines Formulations

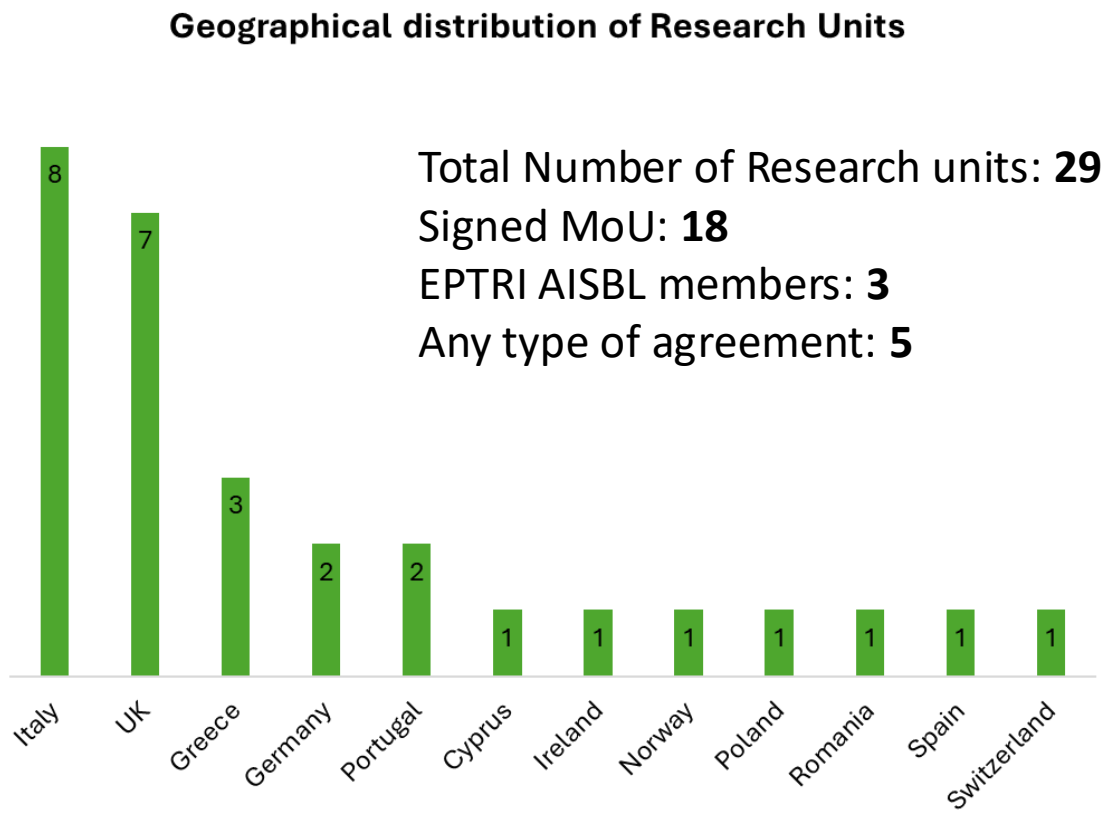
EPTRI – TRP – PAEDIATRIC MEDICINES FORMULATIONS

Paediatric Medicines Formulations TRP **covers the gap in medicines formulations** tailored for children use in all paediatric ages, **facilitating the development of appropriate age-specific formulations providing innovative technologies** for better and safer dosage forms for preterm neonates, infants, toddlers, children, and adolescents.

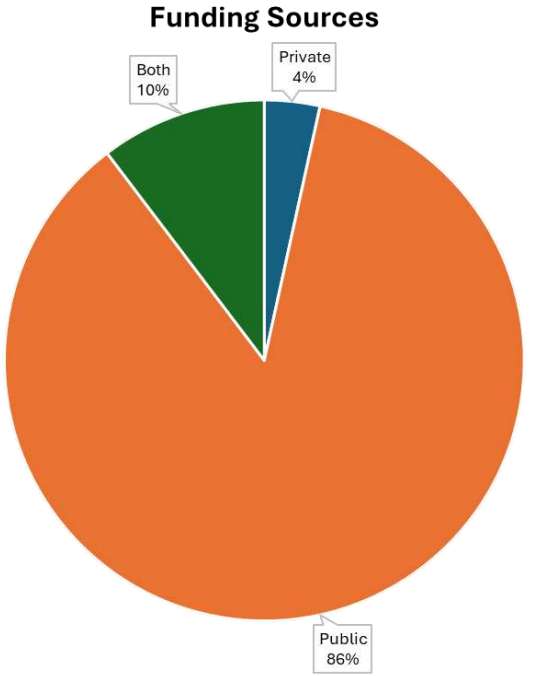
- Pre-formulation advice and Pre-formulation studies
- Formulation of drug for paediatric use for non-enteral routes of administration
- Paediatric in vitro palatability assessment
- Formulation of drug for paediatric use for enteral routes of administration
- Assessment and design of drug delivery systems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

Paediatric Medicines Formulations

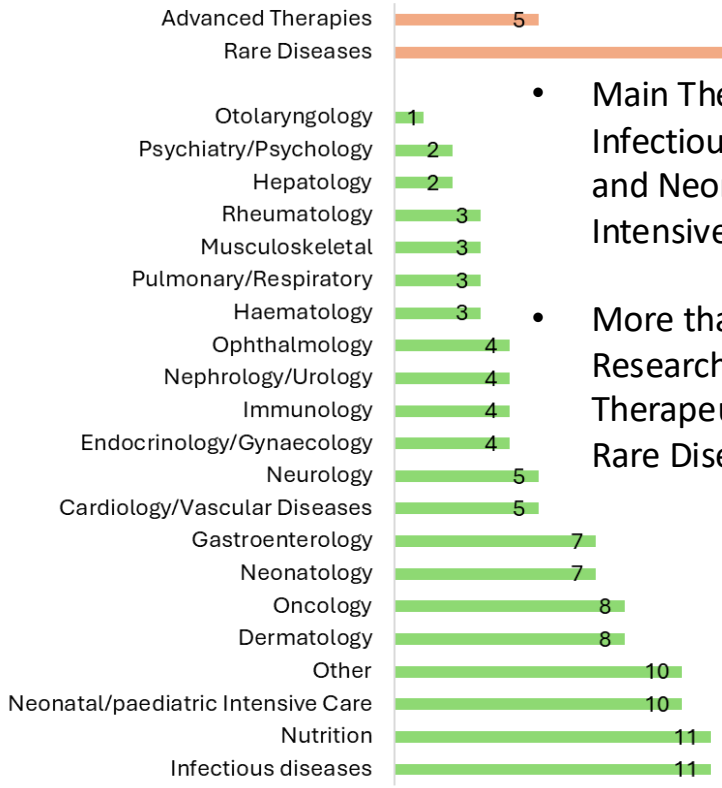
EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS



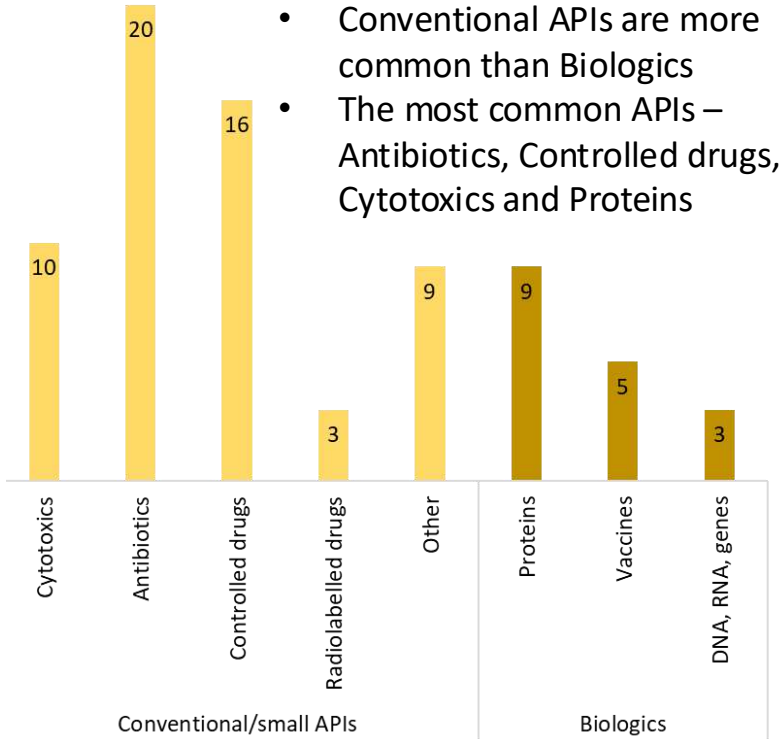
Total Number of Research units: **29**
Signed MoU: **18**
EPTRI AISBL members: **3**
Any type of agreement: **5**



EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS

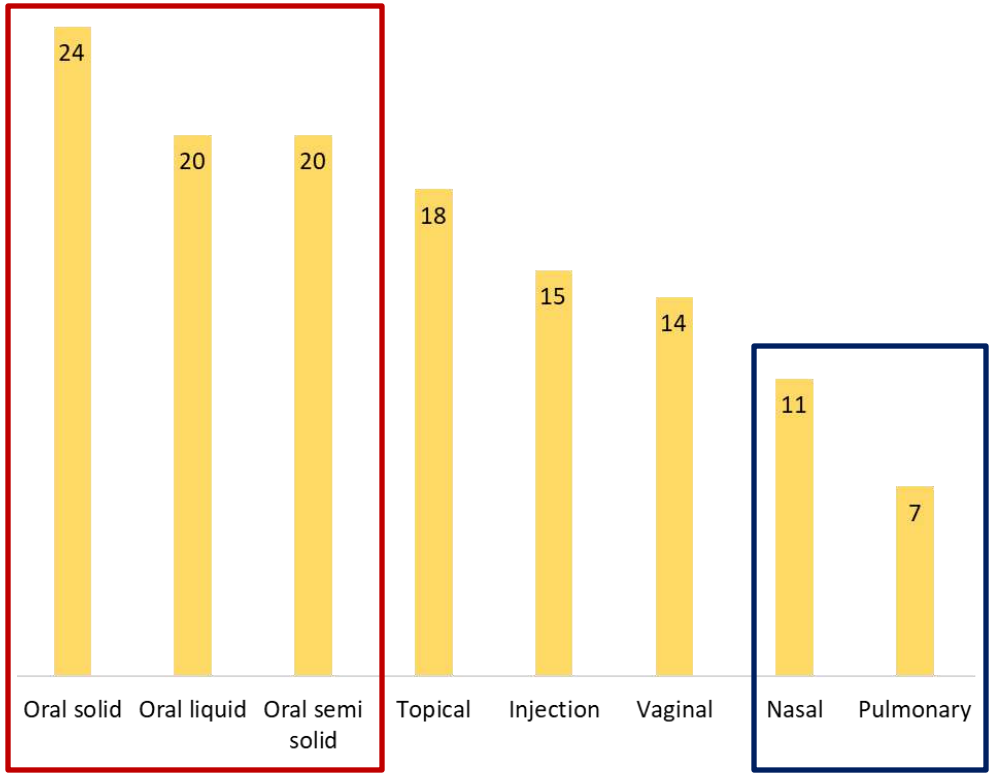


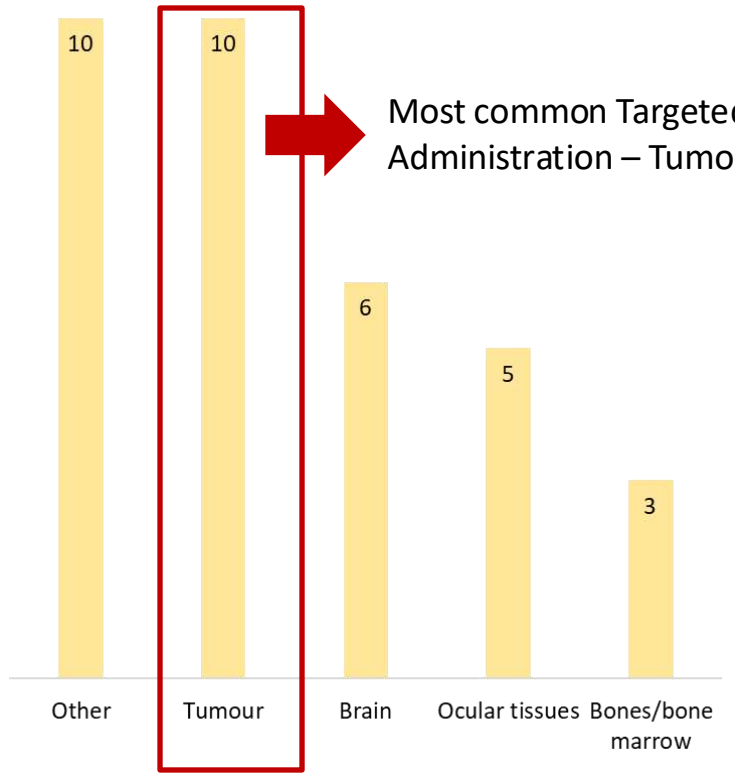
- Main Therapeutic areas – Infectious Diseases, Nutrition and Neonatal/Paediatric Intensive Care
- More than 50% of the Research units work in Therapeutic areas that involve Rare Diseases



- Conventional APIs are more common than Biologics
- The most common APIs – Antibiotics, Controlled drugs, Cytotoxics and Proteins

EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS

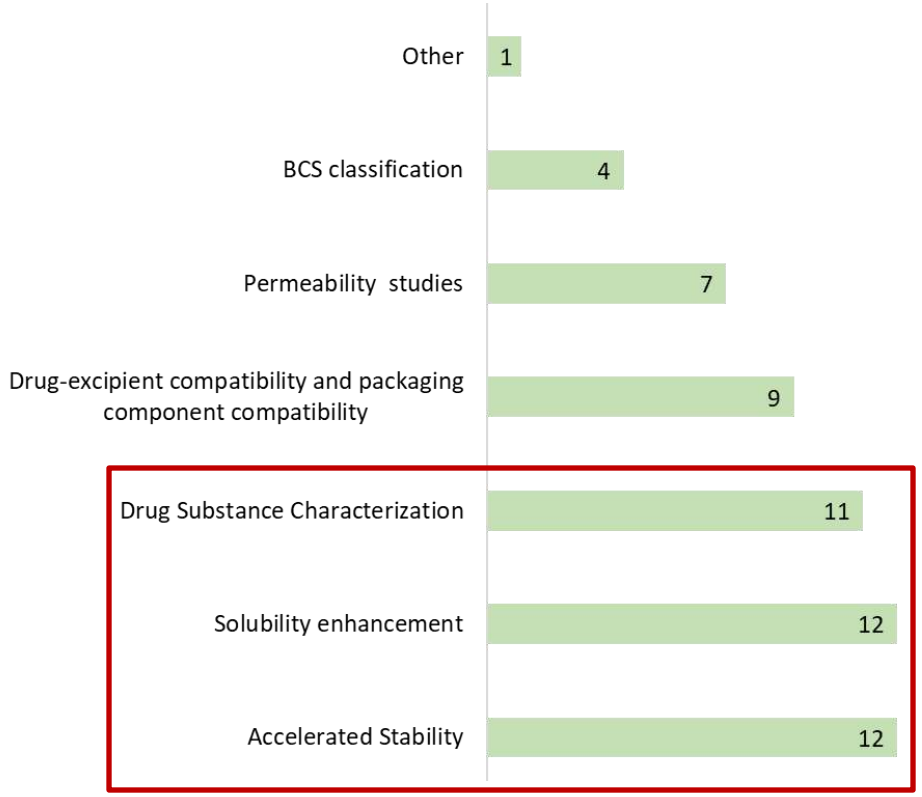


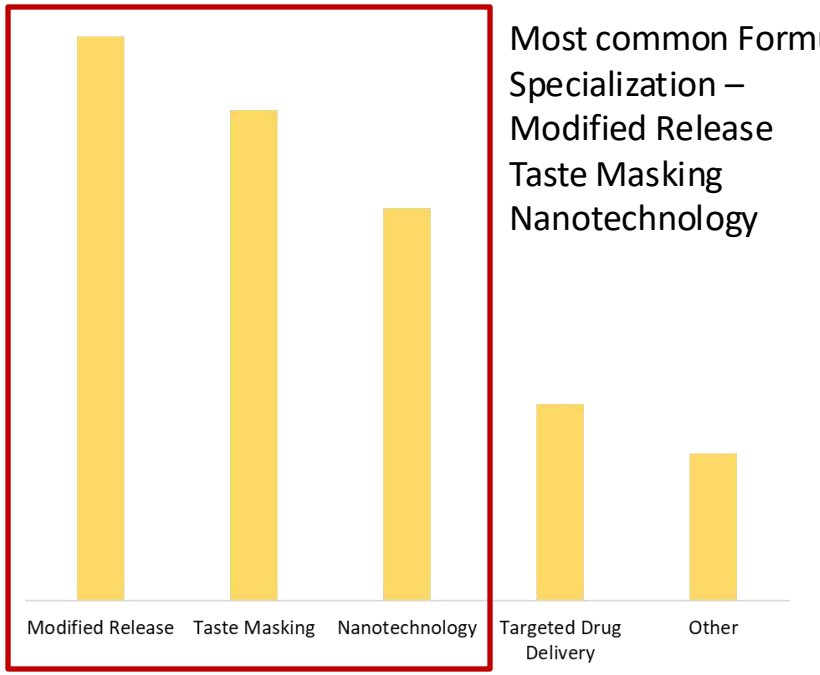


Most common Targeted Administration – Tumors

- Most common Routes of Administration - Oral and Topical routes
- Least common Routes of Administration – Pulmonary and Nasal

EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS

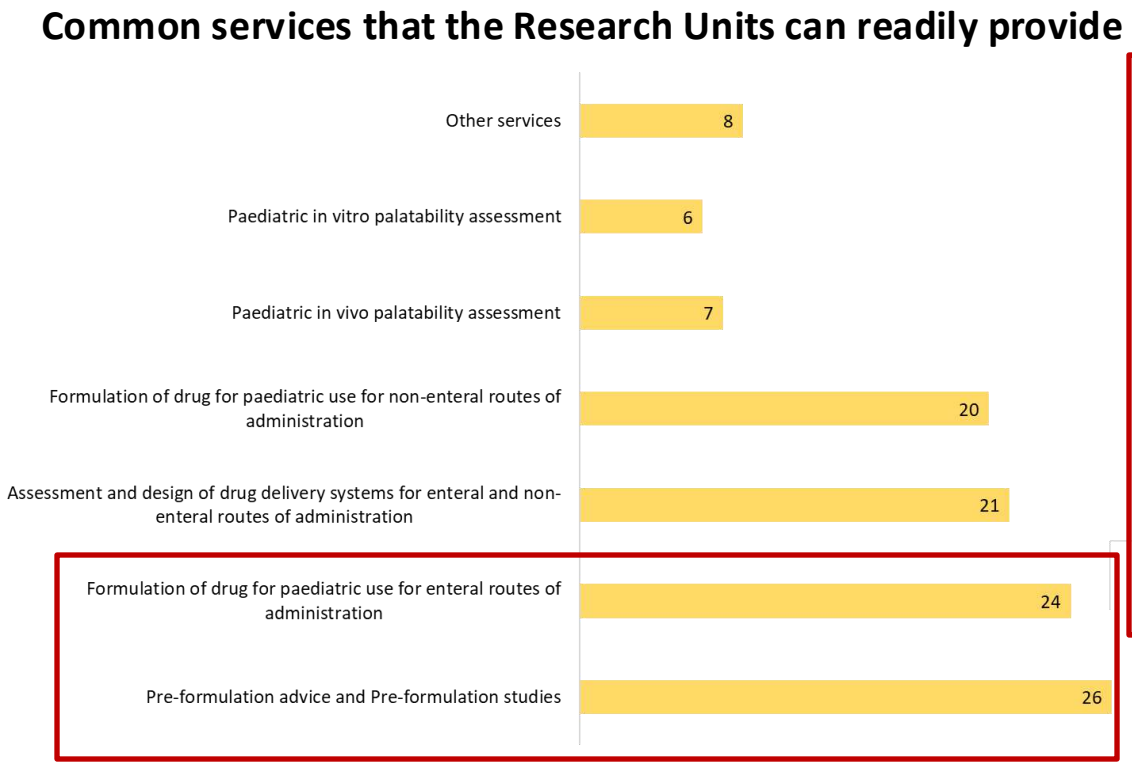


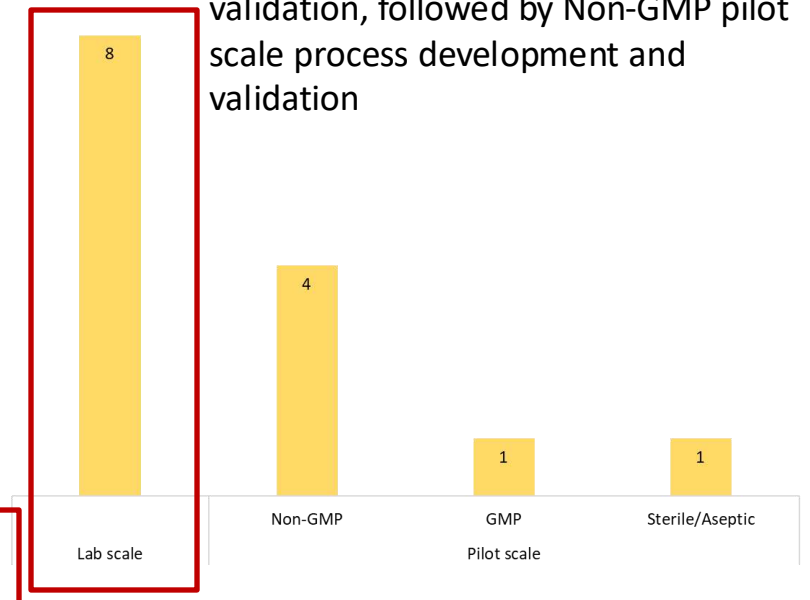


Most common Formulation Specialization –
Modified Release
Taste Masking
Nanotechnology

- Most pre-formulation capabilities – Accelerated stability, Solubility enhancement, Drug substance Characterization

EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS





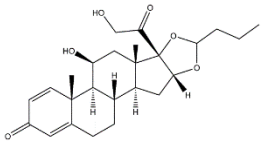
- Laboratory scale is the most common type of process development and validation, followed by Non-GMP pilot scale process development and validation

CASE STUDIES

- Cyclodextrin
- Prilling technology
- Direct powder extrusion 3D printing
- Microfluidic platform for the production of Lipid based Nanoparticles

BUDESONIDE CASE STUDIES

- ✓ Budesonide (BD), a potent second-generation glucocorticoid with local anti-inflammatory action and reduced systemic side effects
- ✓ BD is BCS Class II drug



- ✓ BD is used for the local treatment of rare paediatric diseases such as the **Eosinophilic Esophagitis (EoE)** and the **Eosinophilic Colitis (EC)**

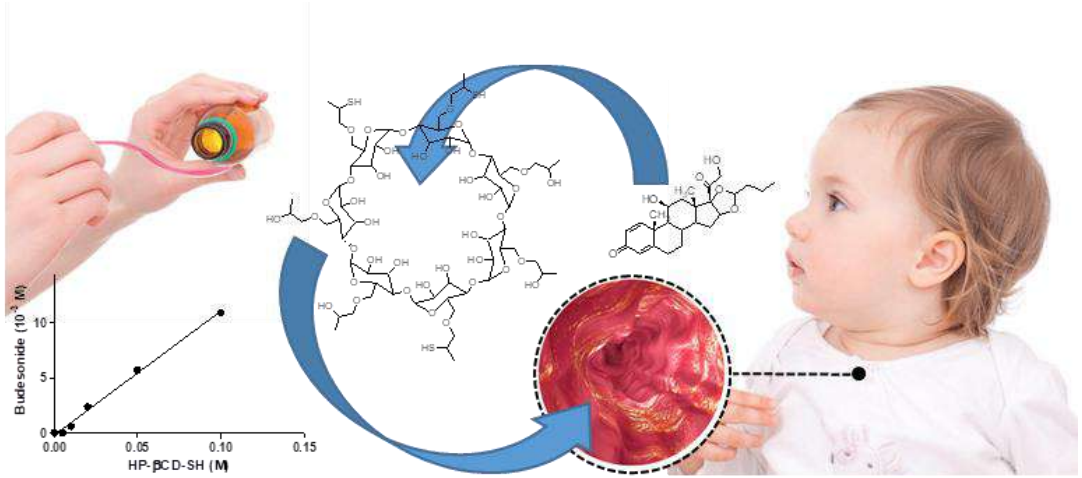
BUDESONIDE CASE STUDIES

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

There are no commercial medicines indicated for EoE paediatric treatment

BD could be extemporaneously formulated as viscous oral suspensions

BUDESONIDE CASE STUDIES

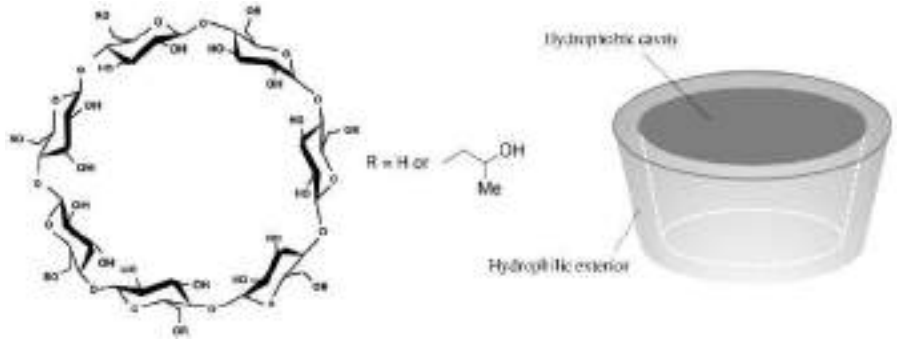


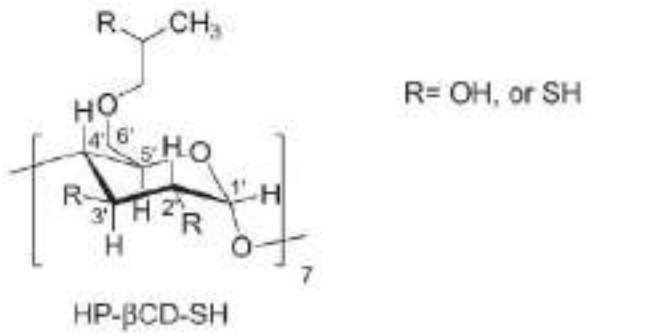
Hydroxypropyl-β-cyclodextrin as solubilizing excipient for oral delivery of budesonide in liquid paediatric formulation

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 hydroxypropyl-β-cyclodextrin as solubilizing excipient and sodium carboxymethylcellulose as mucoadhesive excipient

Spennacchio, A.; Lopalco, A.; Racaniello, G.F.; et al. Mucoadhesive Budesonide Solution for the Treatment of Pediatric Eosinophilic Esophagitis. *Pharmaceuticals* **2024**, *17*, 550. https://doi.org/10.3390/ph17050550

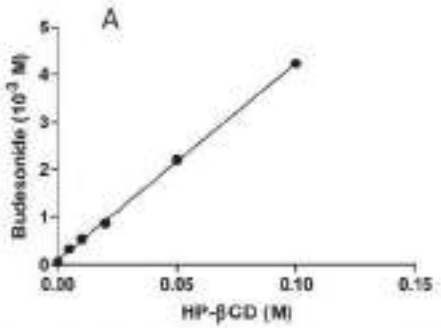
BUDESONIDE CASE STUDIES

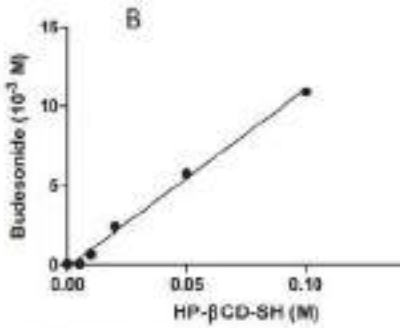




R= OH, or SH

HP-βCD-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.

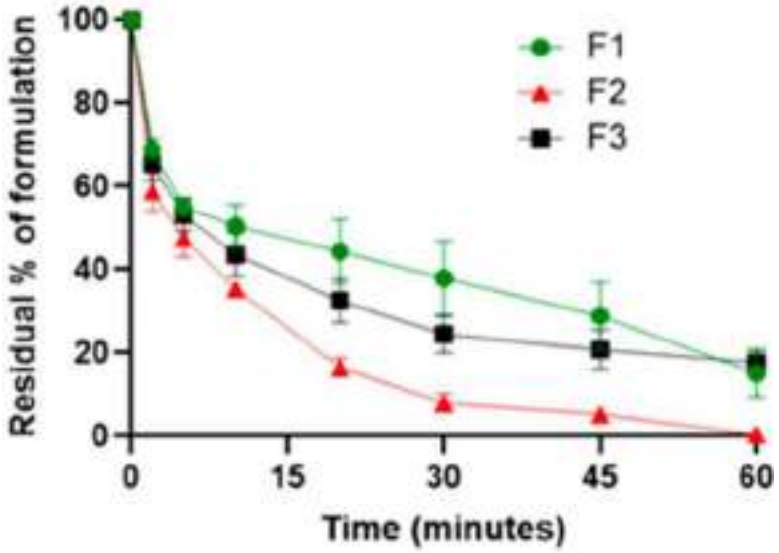
Sample	S (10^{-3} M)	$K_{1:1}$ (M^{-1})	Slope (p)	R^2
HP-β-CD	4.3*	861.11	0.041 ± 0.005	0.9993
HP-β-CD-SH	10.9*	2513.52	0.112 ± 0.004	0.9962
BUD	0.05028	–	–	–

* 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.

BUDESONIDE CASE STUDIES



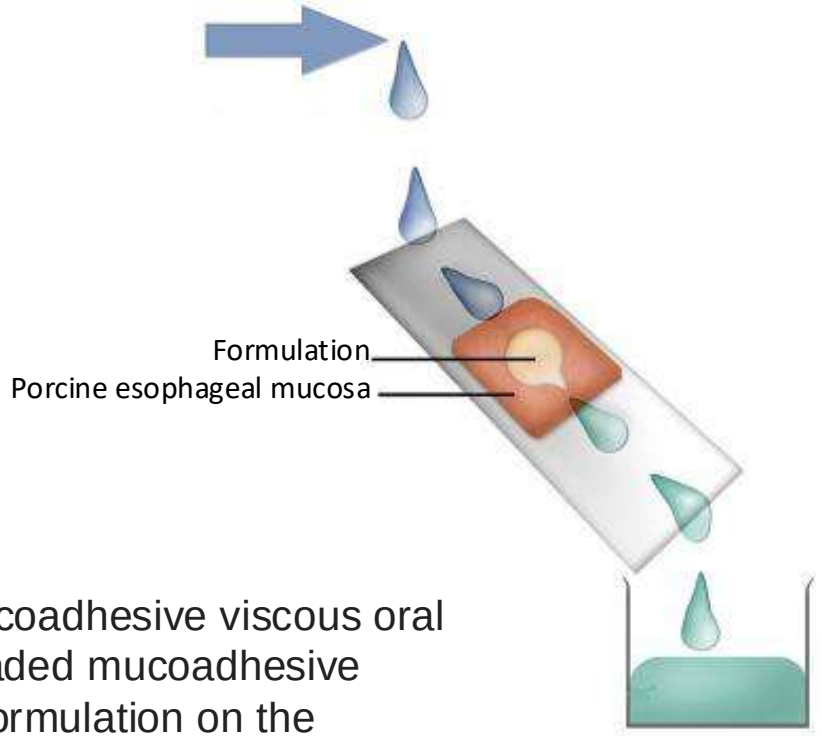


Fig. 1. Mucoadhesive properties of F1 (BU-loaded mucoadhesive viscous oral solution), F2 (BU-loaded oral solution), and F3 (BU-loaded mucoadhesive viscous oral suspension) expressed as residual % of formulation on the esophageal mucosa as a function of time (minutes) at 37 °C

Spennacchio, A.; Lopalco, A.; Racaniello, G.F.; et al. Mucoadhesive Budesonide Solution for the Treatment of Pediatric Eosinophilic Esophagitis. *Pharmaceuticals* **2024**, *17*, 550. https://doi.org/10.3390/ph17050550

FROM BENCH TO BEDSIDE

ePTRI
European Paediatric Translational Research Infrastructure

CVBF®
Clinical Validation from Biopharmaceutical Findings

FONDAZIONE PER LA RICERCA FARMACOLOGICA GIANNI BENZI ONLUS

The need

Pre-formulative and formulative studies

Technology transfer

BUDESONIDE CASE STUDIES

Inflammatory bowel diseases (IBD)

IBD treatment usually involves drug therapy, lifestyle and in extreme cases surgery
The therapeutic approach is based on the use of anti-inflammatory drugs to reduce localised inflammation

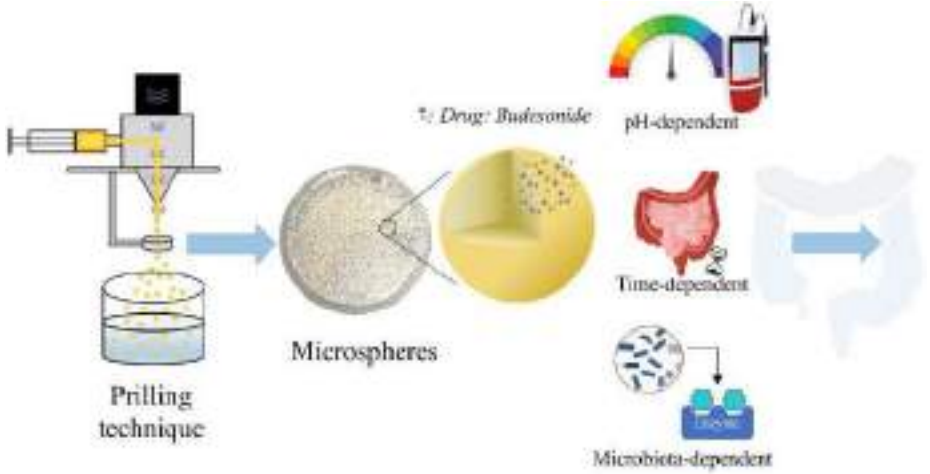
BD is the drug of choice for the treatment of paediatric IBD

Limits of the commercial formulations:

- Dose is more appropriate for adults;
- A single trigger, such as pH, could be not enough for a selective BD colon delivery

BUDESONIDE CASE STUDIES

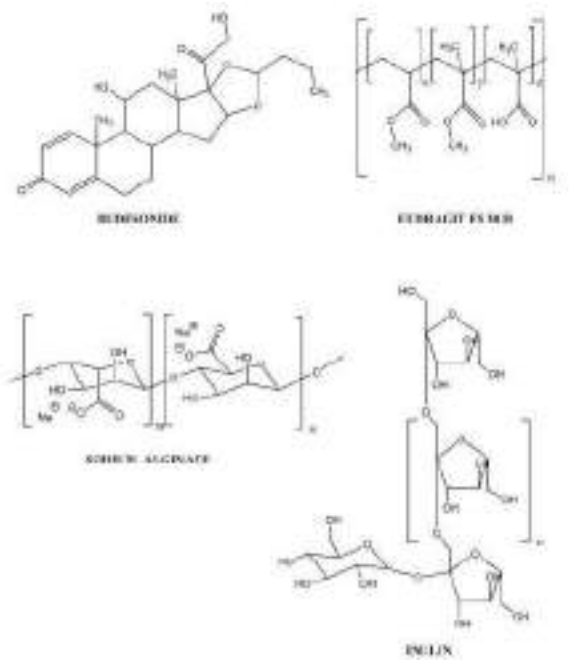
Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/ inulin-based microspheres as a paediatric formulation



Aim: To develop a colon-targeted budesonide-loaded multiparticulate that can respond to parallel triggers resident in the colon and eligible as paediatric formulation.

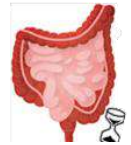
V. D'Amico et al. Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/inulin-based microspheres as a paediatric formulation. Carbohydrate Polymers 302 (**2023**) 120422.

BUDESONIDE CASE STUDIES

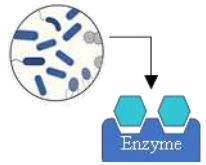


Eudragit FS 30D is a pH-sensitive polymetaacrylate that dissolves at pH values above 7.0;

Alginate is a polysaccharide that allows a time dependent drug release for its ability to swell in intestinal fluid;



Inulin is a bacteria sensitive oligo-saccharide resistant in the stomach and small intestine and degraded by enzymes produced by resident colonic bacteria. In addition, inulin exerts favorable properties in decreasing the risk of IBD.



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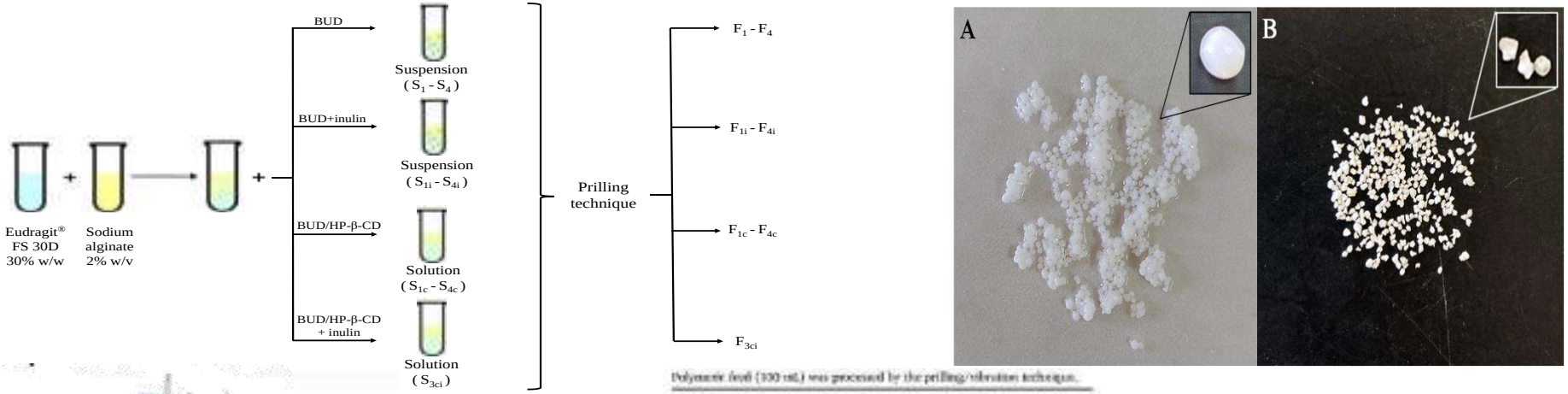
BUDESONIDE CASE STUDIES



Polymeric feed (100 mL) was processed by the prilling/vibration technique.

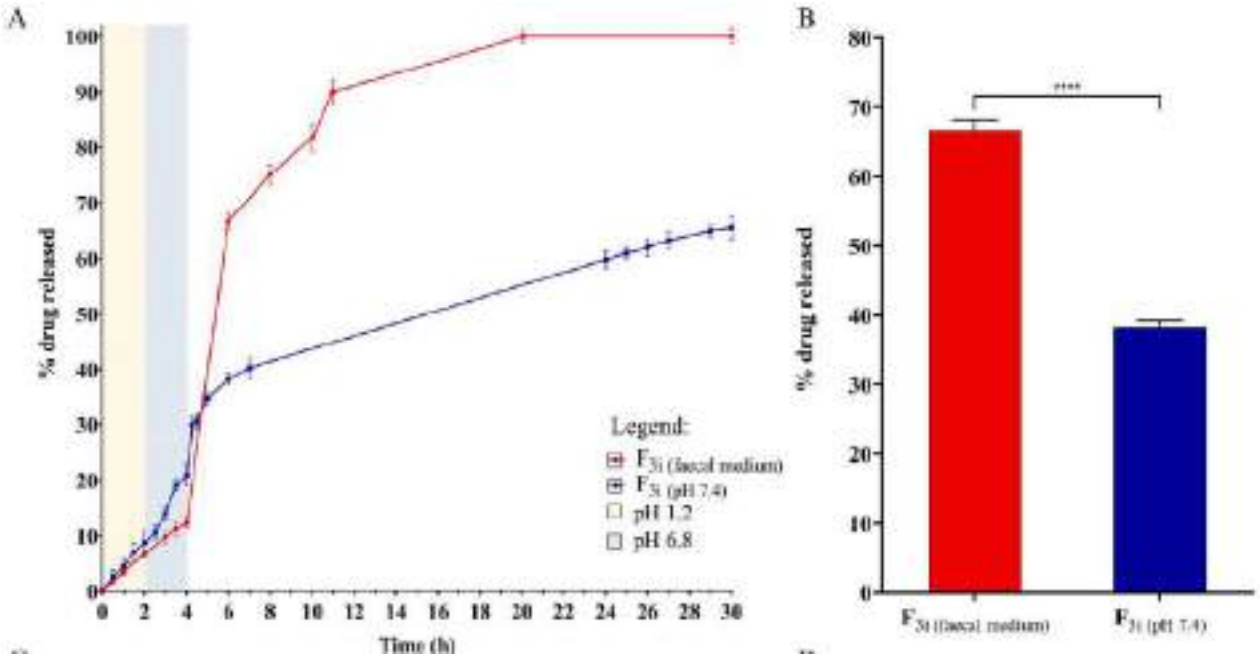
Feeds code	Eudragit® FS 30D (g)	Alginate 2 % w/v (g)	Ratio	BUD (mg)	Inulin (g)	BUD HP β-CD* (g)
S_1	–	1.00	0:1	75.0	–	–
S_2	0.97	1.93	0.5:1	75.0	–	–
S_3	0.53	1.77	2:1	75.0	–	–
S_4	0.32	1.58	4:1	75.0	–	–
S_5	10.00	1.33	7.5:1	75.0	–	–
S_{1c}	–	1.00	0:1	–	–	6.42*
S_{2c}	0.97	1.93	0.5:1	–	–	6.42*
S_{3c}	0.53	1.77	2:1	–	–	6.42*
S_{4c}	0.32	1.58	4:1	–	–	6.42*
S_{5c}	10.00	1.33	7.5:1	–	–	6.42*
S_{1i}	–	1.00	0:1	75.0	0.91	–
S_{2i}	0.97	1.93	0.5:1	75.0	1.16	–
S_{3i}	0.53	1.77	2:1	75.0	2.13	–
S_{4i}	0.32	1.58	4:1	75.0	3.16	–
S_{5i}	10.00	1.33	7.5:1	75.0	4.53	–
S_{3ci}	0.53	1.84	4:1	–	3.16	6.42*

* Corresponding to 75 mg of BUD.

V. D'Amico et al. Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/inulin-based microspheres as a paediatric formulation. Carbohydrate Polymers 302 (2023) 120422.

BUDESONIDE CASE STUDIES

In vitro release studies under different pH conditions and faecal medium simulating the colonic environment



After 2 hours in faecal medium (totally 6 h), the cumulative release of BD is 65%

After 12 hours a cumulative release of 90% is realized in faecal medium

V. D'Amico et al. Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/inulin-based microspheres as a paediatric formulation. Carbohydrate Polymers 302 (2023) 120422.

BUDESONIDE CASE STUDIES

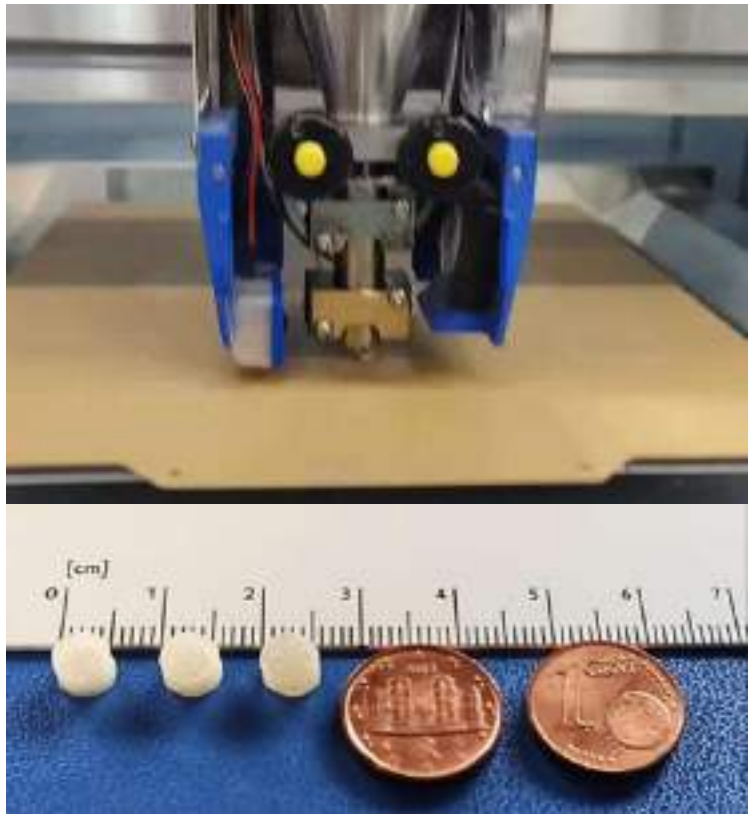
Budesonide loaded mini-tablets for the treatment of eosinophilic colitis in paediatric patients

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.

BUDESONIDE CASE STUDIES



M. Pistone et al. International Journal of Pharmaceutics
https://doi.org/10.1016/j.ijpharm.**2023.**122592

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 %

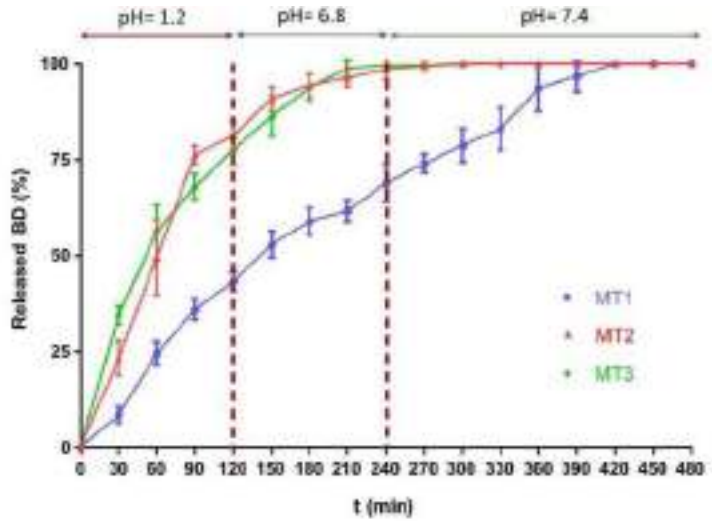
Tablets mass 130 mg, therapeutic dose 1 mg of BD;
All formulations comply with pharmacopoeia-required tests.

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

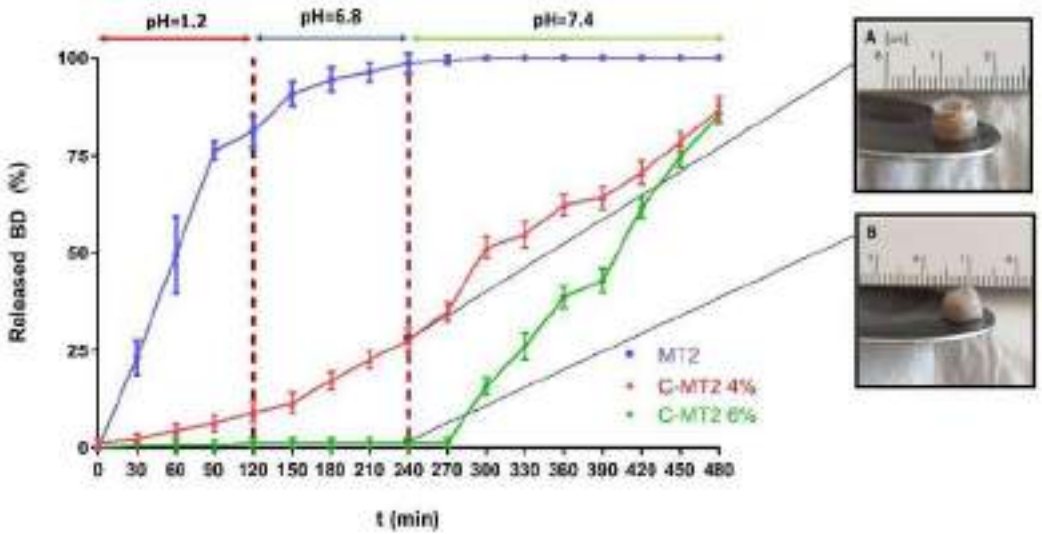
MT	Weight Uniformity* (mg)	Drug content* (mg)	Friability* (%)	Breaking Force (N)*	Dimensions (mm)*	
					Diameter	Height
1	128.68 ± 20.17	0.71 ± 0.09	0.022	~484.66	3.17 ± 0.23	4.24 ± 0.33
2	127.68 ± 10.68	0.68 ± 0.09	0.064	298.67 ± 62.14	5.52 ± 0.21	3.78 ± 0.13
3	130.40 ± 18.39	0.69 ± 0.05	0.034	320.08 ± 97.70	3.46 ± 0.18	3.78 ± 0.21

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

BUDESONIDE CASE STUDIES



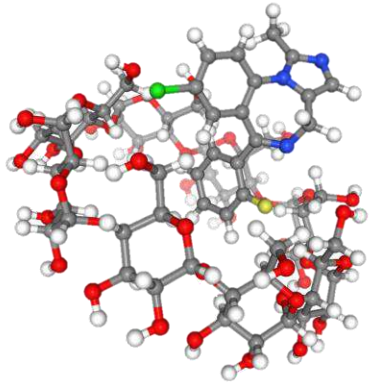
Dissolution profiles of the three different formulations (MT1, MT2, MT3) studied in an acid medium (HCl 0.1 N) for two hours, followed by a further two hours in a buffer solution at pH = 6.8 and finally in a buffer solution at pH = 7.4 for the remaining time



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

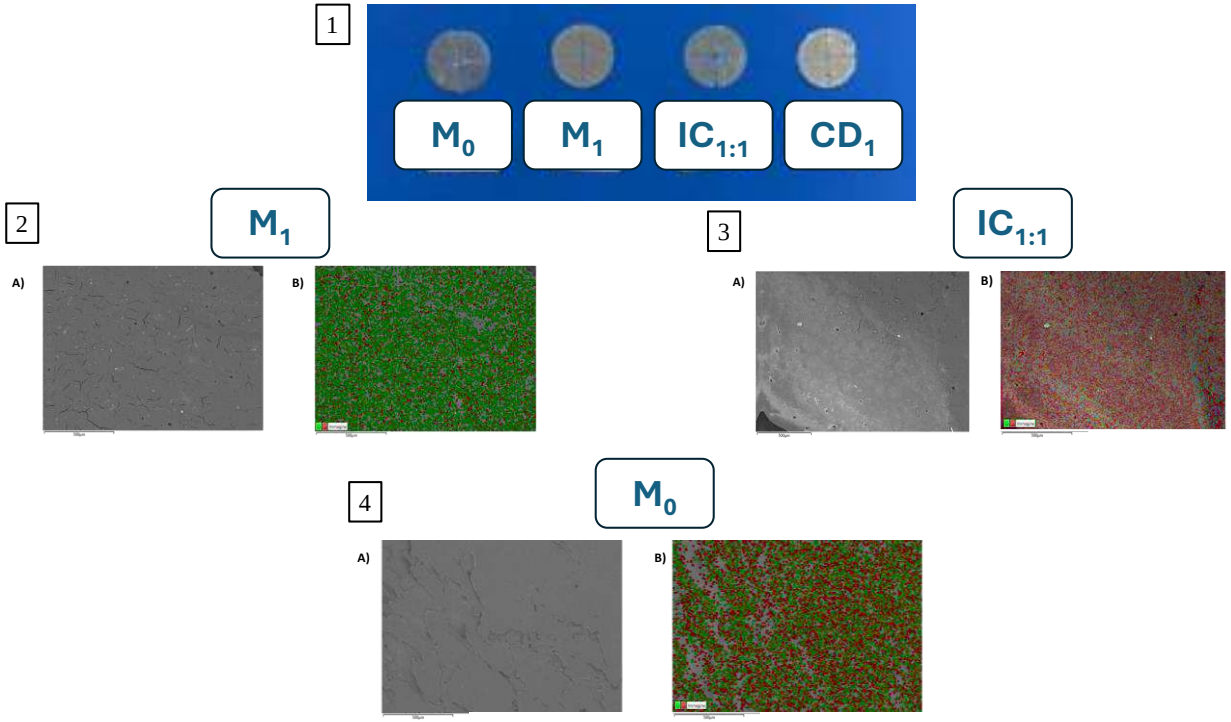
M. Pistone et al. International Journal of Pharmaceutics
https://doi.org/10.1016/j.ijpharm.2023.122592

MIDAZOLAM CASE STUDY



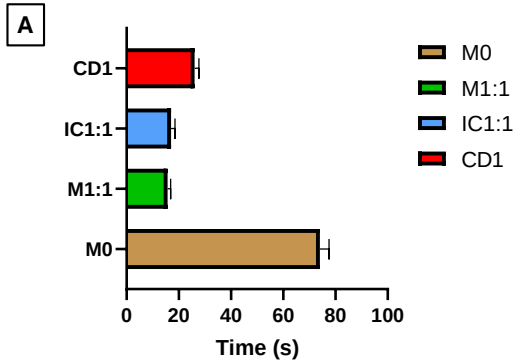
Molecular representation of MDZ/γ-CD inclusion complex **IC1:1**

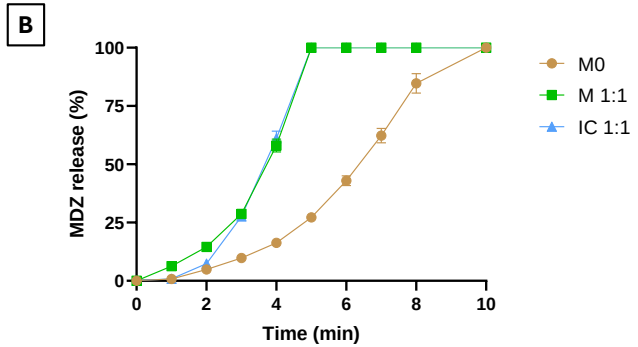
Manuscript under review



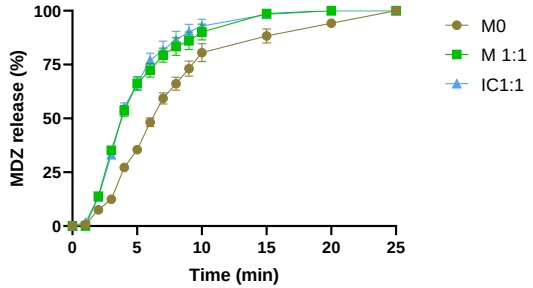
MIDAZOLAM CASE STUDY

Printed films	Weight* (g)	Diameter (mm)	Thickness (mm)
M0	0.050 ± 0.004	14.96 ± 0.16	0,67 ± 0.05
M1:1	0.049 ± 0.005	15.12 ± 0.22	0,71 ± 0.06
IC1:1	0.050 ± 0.004	15.26 ± 0.24	0,69 ± 0.04
CD1	0.052 ± 0.007	14.88 ± 0.14	0.72 ± 0.06





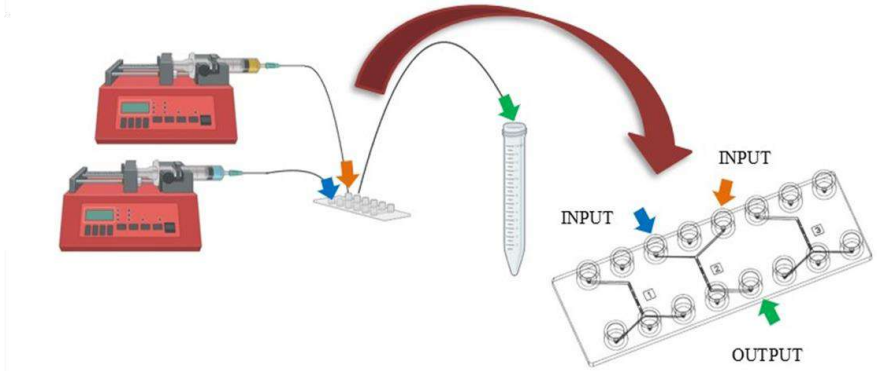
In-vitro mucoadhesion and dissolution test

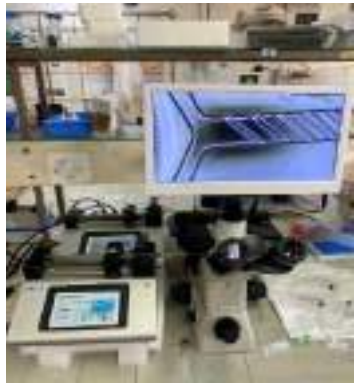


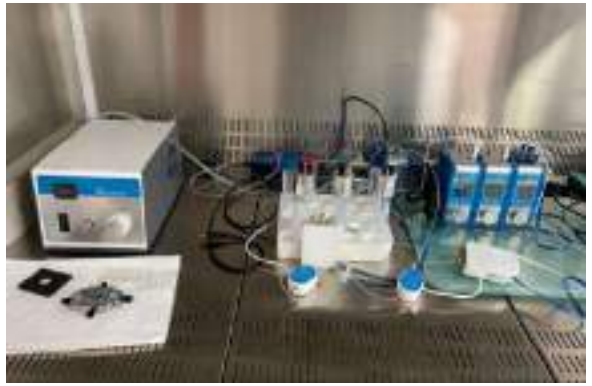
Ex-vivo mucoadhesion and dissolution test

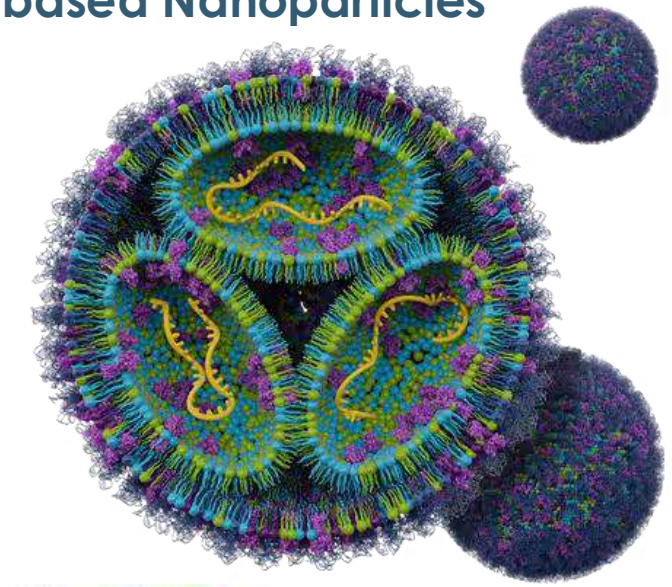
MICROFLUIDIC PLATFORM

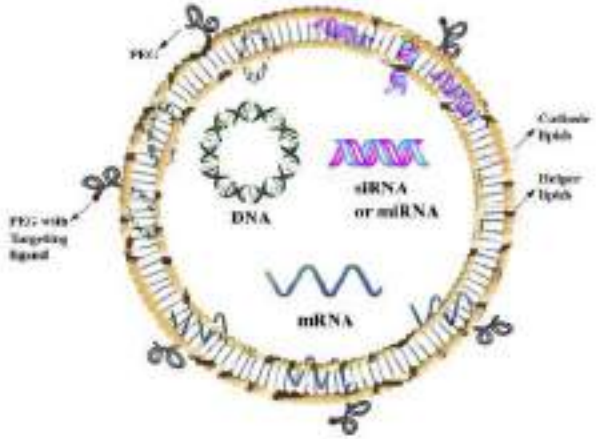
Microfluidic platform for the production of Lipid-based Nanoparticles









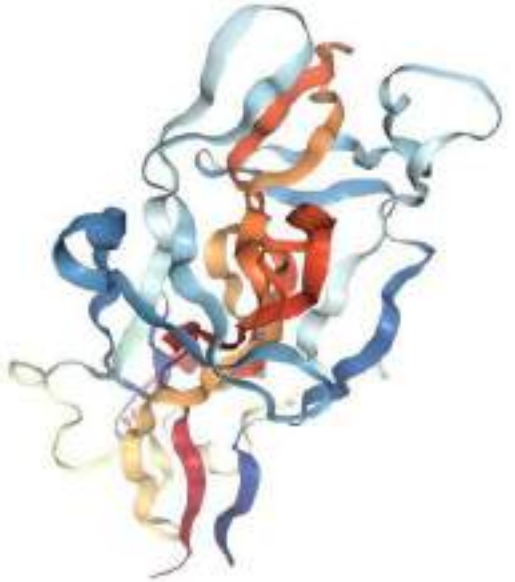


MICROFLUIDIC PLATFORM

MF-ASSISTED PRODUCTION OF BDNF-SLNs FOR BRAIN DELIVERY: AN *IN VITRO EVALUATION*

Traumatic Brain Injury (TBI) is a traumatic brain condition with high incidence in children, representing one of the main causes of disability/death worldwide.

The brain-derived neurotrophic factor (BDNF) has been highlighted as potential growth factor implicated in restorative and regeneration processes in neural tissue by interacting with its TrK receptor.



Need for innovative non invasive formulations!

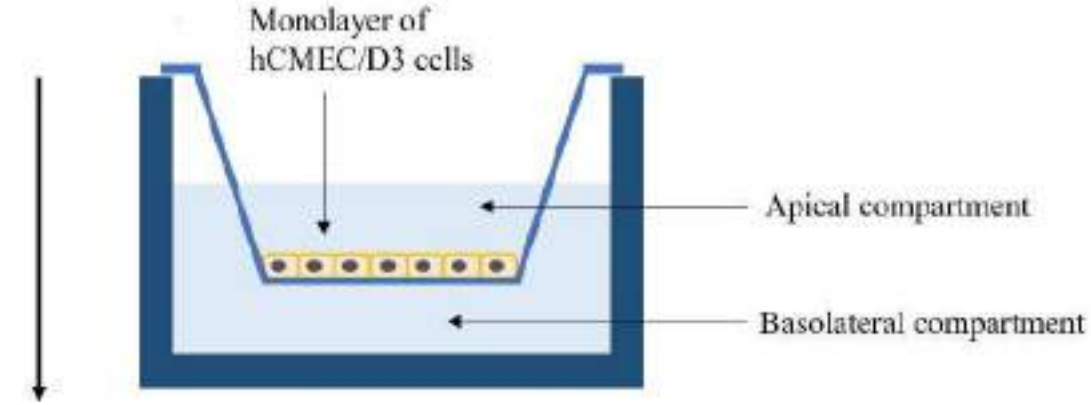
- pH sensitive protein
- short half-life
- low permeability accross BBB

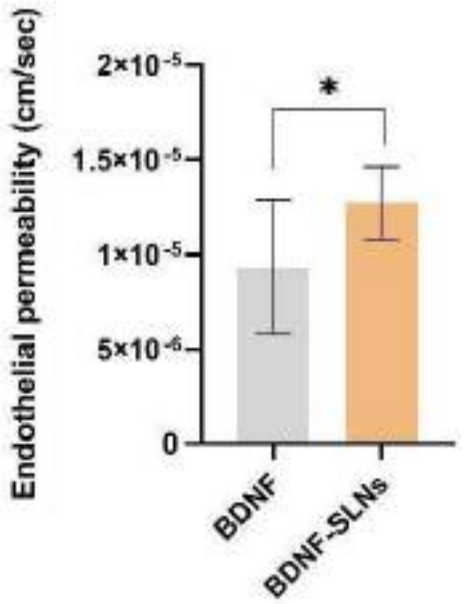
MICROFLUIDIC PLATFORM

MF-ASSISTED PRODUCTION OF BDNF-SLNs

The *in vitro* permeability study was conducted by assessing the permeability of plain BDNF and BDNF-SLNs across the BBB model of hCMEC/D3 cell line.

The permeation of the BBB model was evaluated after 3h of incubation by measuring the amount of BDNF collected in the basolateral compartment.

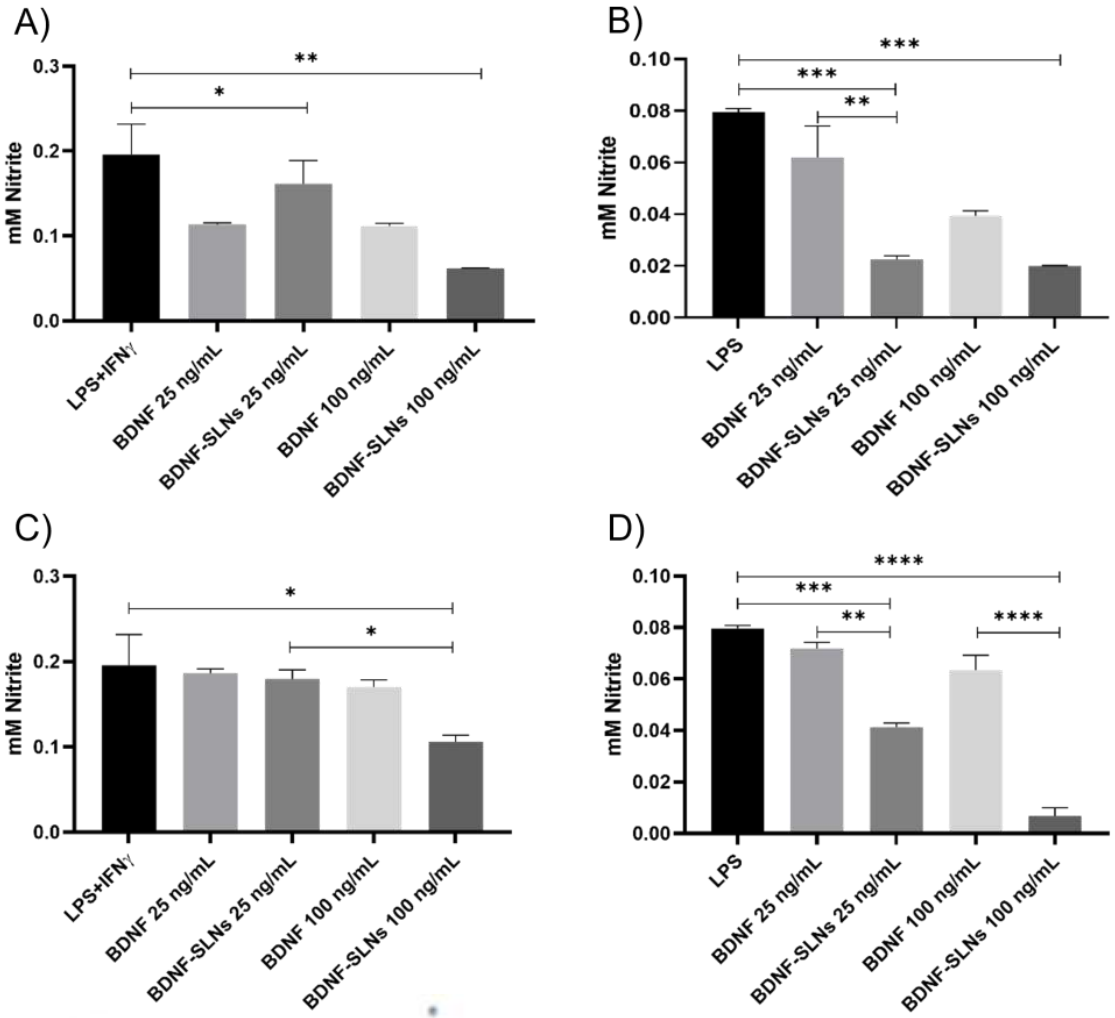




Sample	P_{app} (cm/sec)
BDNF	9.31×10^{-6}
BDNF-loaded SLNs	1.27×10^{-5}
Diazepam	4.61×10^{-5}
FD4	1.60×10^{-5}

MICROFLUIDIC PLATFORM

MF-ASSISTED PRODUCTION OF BDNF-SLNs



Comparison about free BDNF (25 ng/mL and 100 ng/mL) and BDNF-SLNs (25 ng/mL and 100 ng/mL) in a simulated TBI-related neuroinflammatory condition.

A, B) Data about pre-incubation of N9 cell line with free BDNF and BDNF-SLNs for 4 hours, then it was performed the treatment with (A) LPS+IFN-γ and (B) LPS alone up to 24 hours. (C, D) Data about pre-treatment of the N9 cell line with (C) LPS+IFN-γ and (D) LPS alone for 1 hour, then free BDNF and BDNF-SLNs were added up to 24 hours.

The formulation of BDNF-SLNs (100 ng/mL) was capable to reduce the iNOS activation resulting in less nitrite production in each tested condition compared to free BDNF at the same concentration.

MICROFLUIDIC PLATFORM

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Microfluidic formulation of diazoxide-loaded solid lipid nanoparticles as a Novel approach for Friedreich's ataxia treatment

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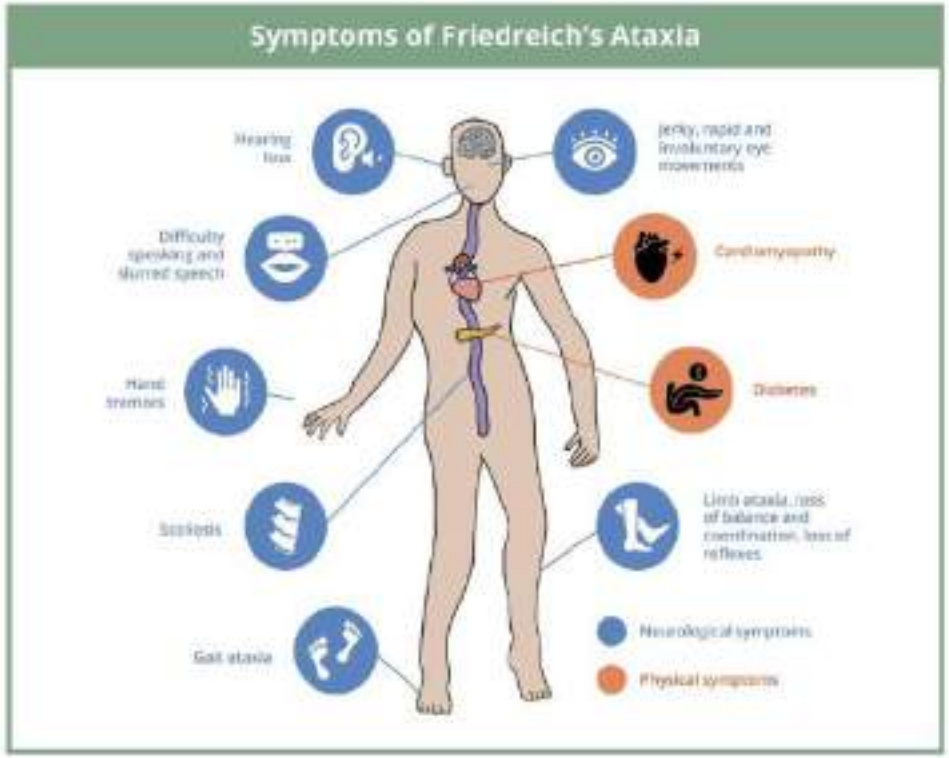

Friedreich's ataxia (FRDA) is a rare neurodegenerative disorder that typically presents in childhood or adolescence, primarily affecting the spinal cord, cerebellum, and brainstem causing a range of neurological and physical symptoms.

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