EPTRI
European Paediatric Translational Research Infrastructure

EPTRI General Assembly and Scientific Meeting 2024

TEMATIC RESEARCH PLATFORM PAEDIATRIC MEDICINES FORMULATIONS

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UNIVERSITÀ DEGLI STUDI DI BARI ALDO MORO

100 UniBa 1925 2025
ai prossimi cent'anni

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

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PHARMACEUTICAL TECHNOLOGIES & COSMETICS

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

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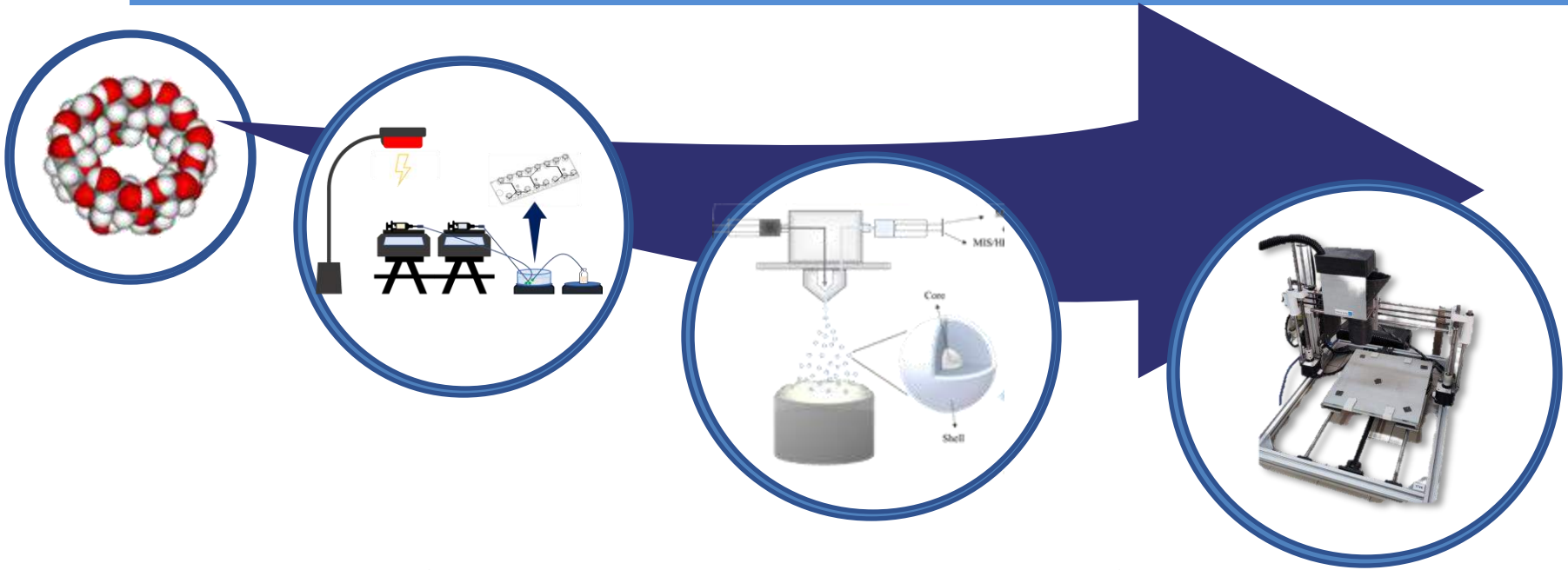


Lab-made and scalable platforms to produce tailored products with features that meet the specific requirements of children:

- 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 both 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

Università degli Studi di Bari Aldo Moro

Integrated services are provided by the five Thematic Research Platforms:

Paediatric Medicines Discovery

Paediatric Biomarkers & Biosamples

Developmental Pharmacology

Paediatric Medicines Formulations

Paediatric Medical Devices

Thematic Research Platform: Paediatric Medicines Formulations

Coordinators

Catherine Tuleu
University College London

Nunzio Denora
University of Bari 'Aldo Moro'

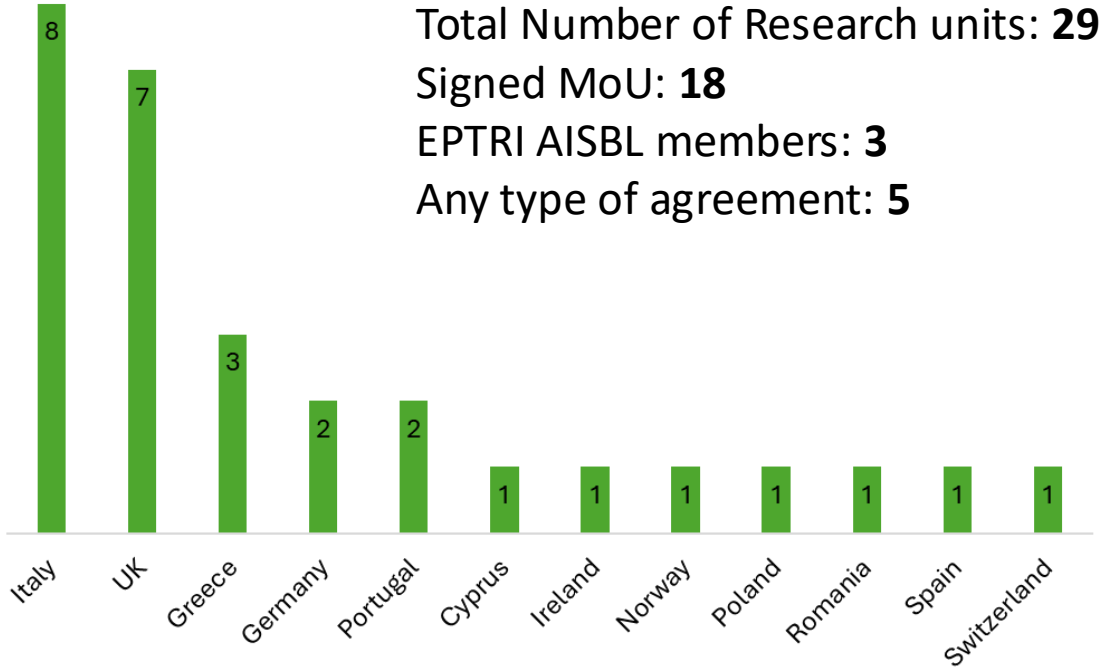
Paediatric Medicines Formulations

This 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.

Paediatric Medicines Formulations

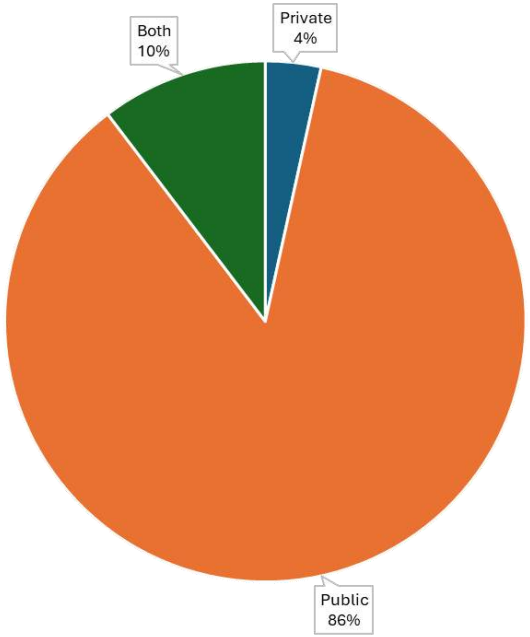
- Pre-formulation advice and Pre-formulation studies
- Formulation of drug for paediatric use for non-enteral routes of administration
- Paediatric in vitro palatability assessment
- Formulation of drug for paediatric use for enteral routes of administration
- Assessment and design of drug delivery systems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

Geographical distribution of Research Units

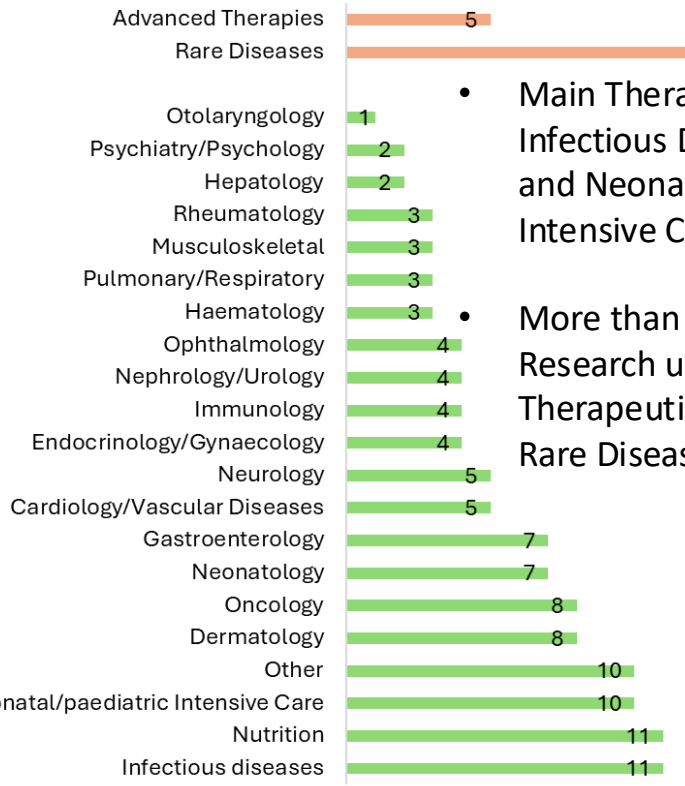


Total Number of Research units: **29**
Signed MoU: **18**
EPTRI AISBL members: **3**
Any type of agreement: **5**

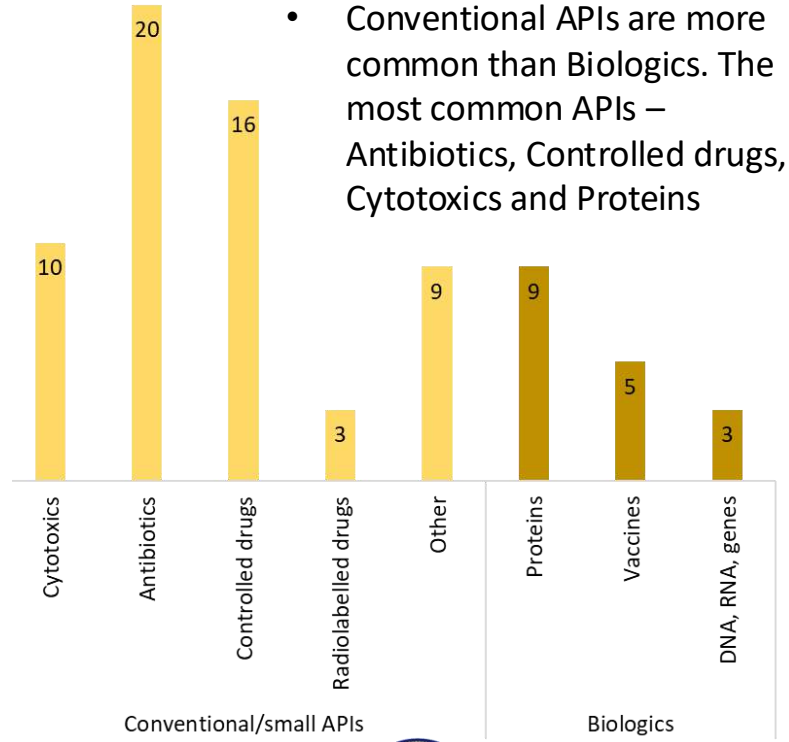
Funding Sources



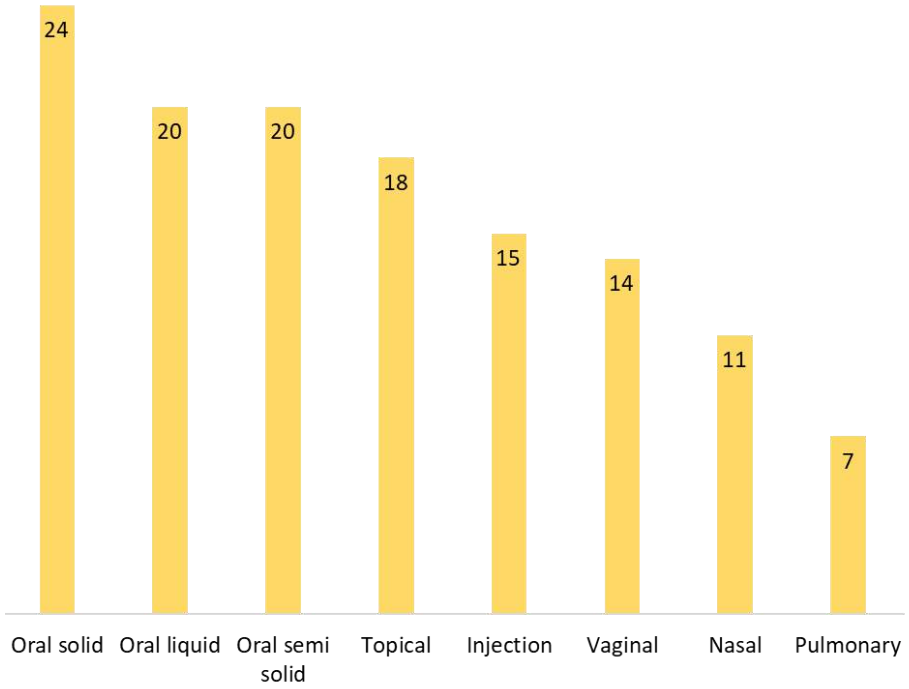
EPTRI - TRP - PAEDIATRIC MEDICINES FORMULATIONS



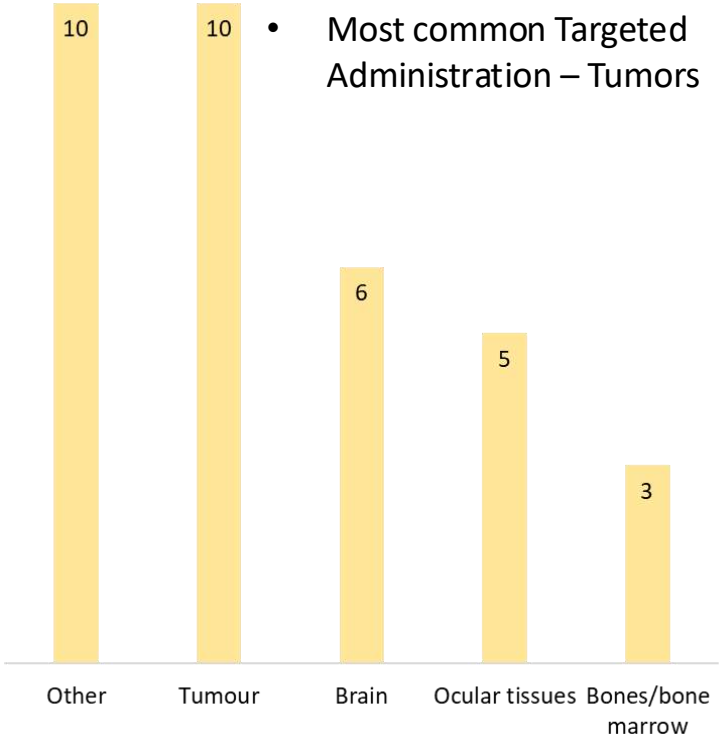
- Main Therapeutic areas – Infectious Diseases, Nutrition and Neonatal/Paediatric Intensive Care
- More than 50% of the Research units work in Therapeutic areas that involve Rare Diseases



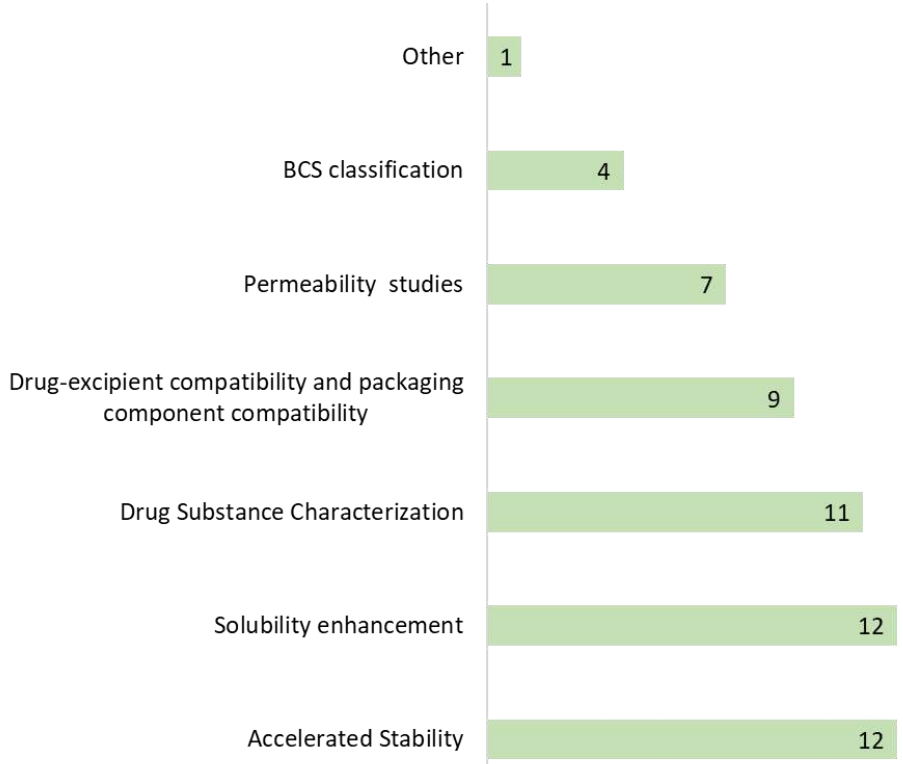
- Conventional APIs are more common than Biologics. The most common APIs – Antibiotics, Controlled drugs, Cytotoxics and Proteins



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

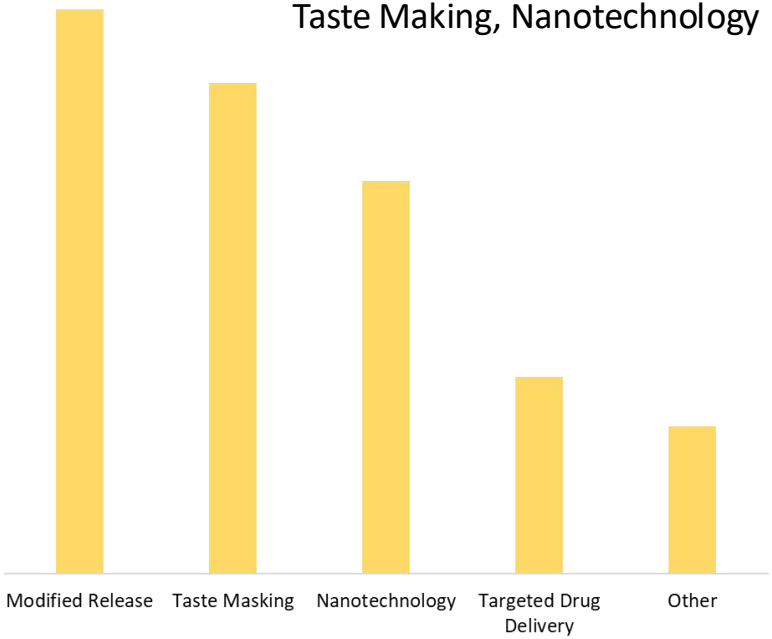


- Most common Targeted Administration – Tumors

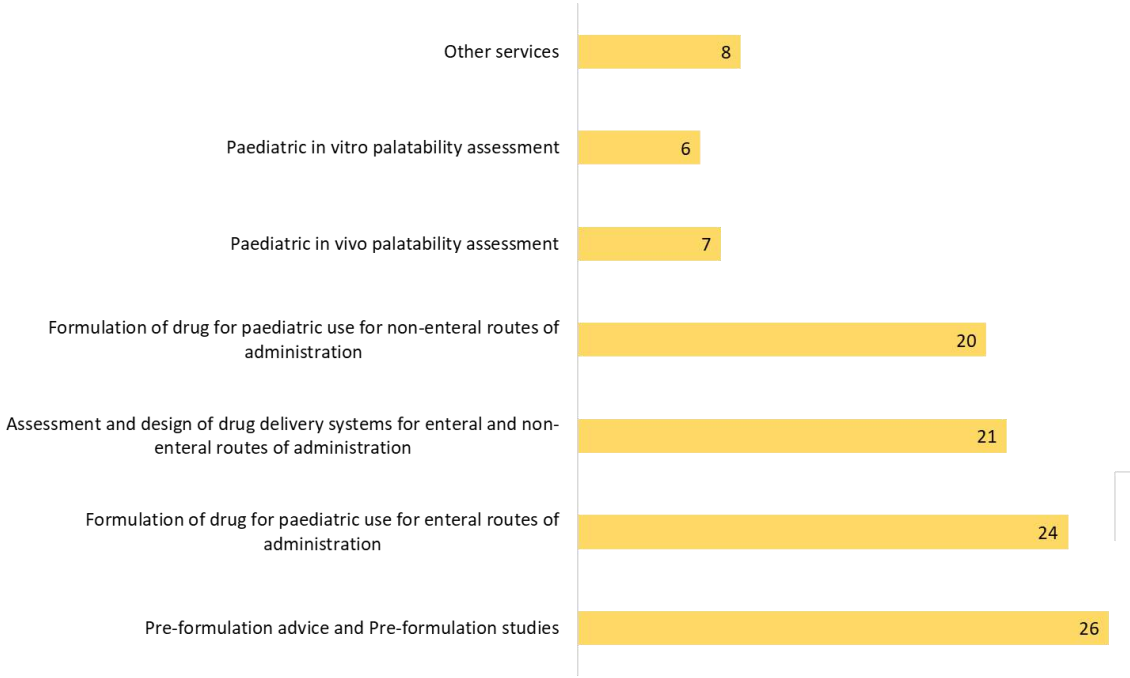


- Most pre-formulation capabilities – Accelerated stability, Solubility enhancement, Drug substance Characterization

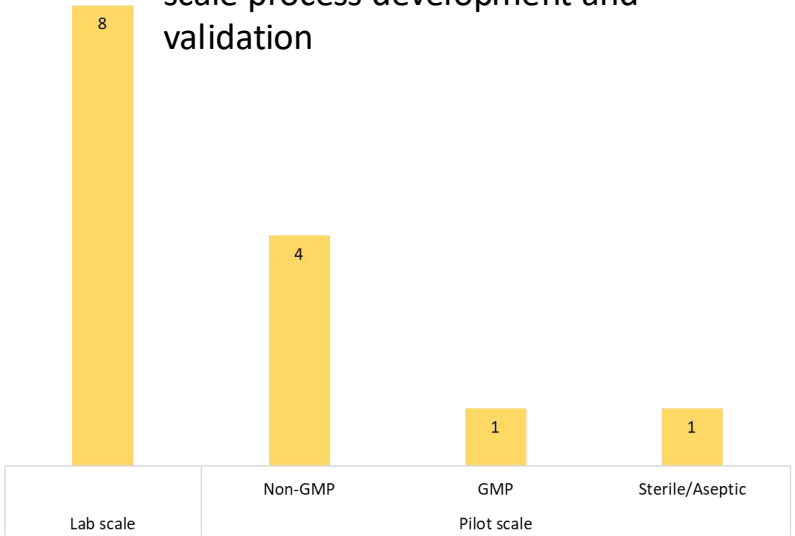
- Most common Formulation Specialization – Modified Release, Taste Making, Nanotechnology



Common services that the Research Units can readily provide



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



CASE STUDIES

- **Budesonide case studies: cyclodextrin derivativities, prilling technology and direct powder extrusion 3D printing for the production of paediatric formulation;**

- **Microfluidic platform for the production of Lipid based Nanoparticles:**

a) **Solid Lipid Nanoparticles for the brain delivery of the brain-derived neurotrophic factor (BDNF);**

b) **Lipid Nanoparticles loaded with nucleic acids for the potential treatment of rare paediatric disorders.**

BUDESONIDE CASE STUDIES

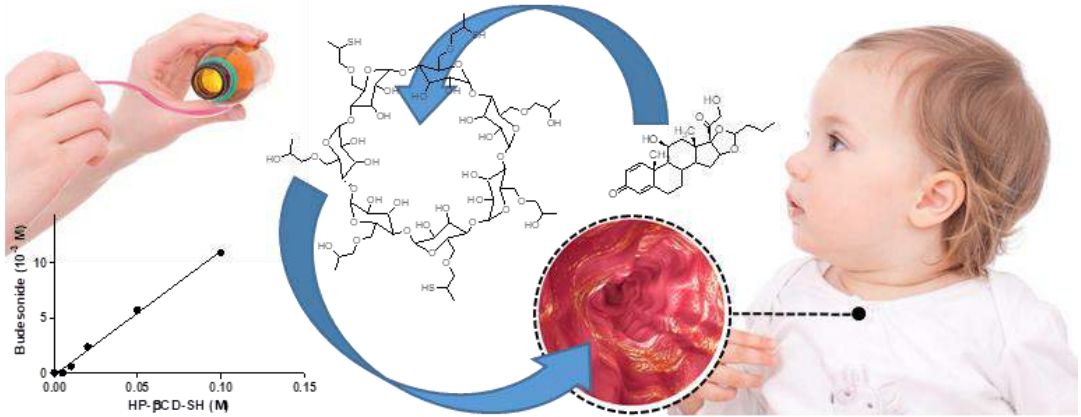
- ✓ Budesonide (BD), a potent second-generation glucocorticoid with local anti-inflammatory action and reduced systemic side effects;
- ✓ BD is BCS Class II drug;
- ✓ BD is used for the local treatment of rare paediatric diseases such as the Eosinophilic Esophagitis (EoE) and the Eosinophilic Colitis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

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.

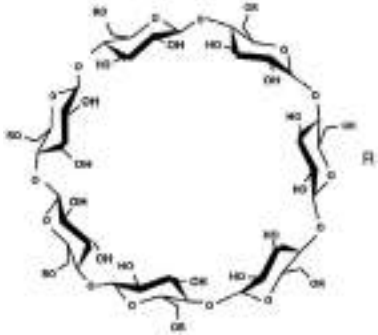
Thiolated hydroxypropyl-β-cyclodextrin as mucoadhesive excipient for oral delivery of budesonide in liquid paediatric formulation

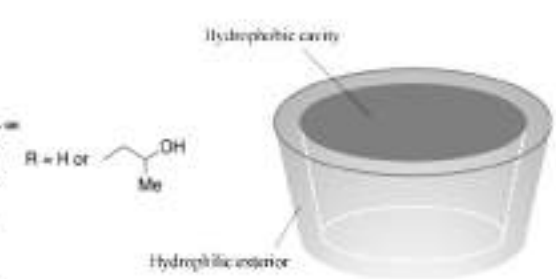


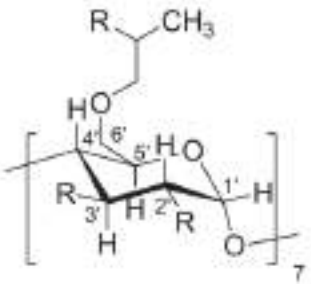
Aim: To improve the current therapeutic practice for the local treatment of EoE in paediatric patients, a new mucoadhesive BUD-based solution was realized using thiolated hydroxypropyl-β-cyclodextrin as solubilizing and mucoadhesive excipient.

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

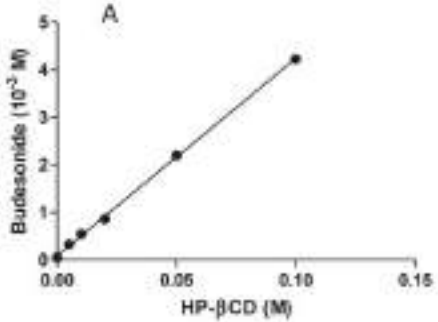


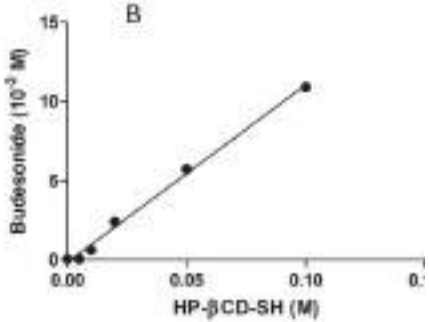




HP-βCD-SH

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]	2513.28	0.112 ± 0.004	0.9982
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.

BUDESONIDE CASE STUDIES

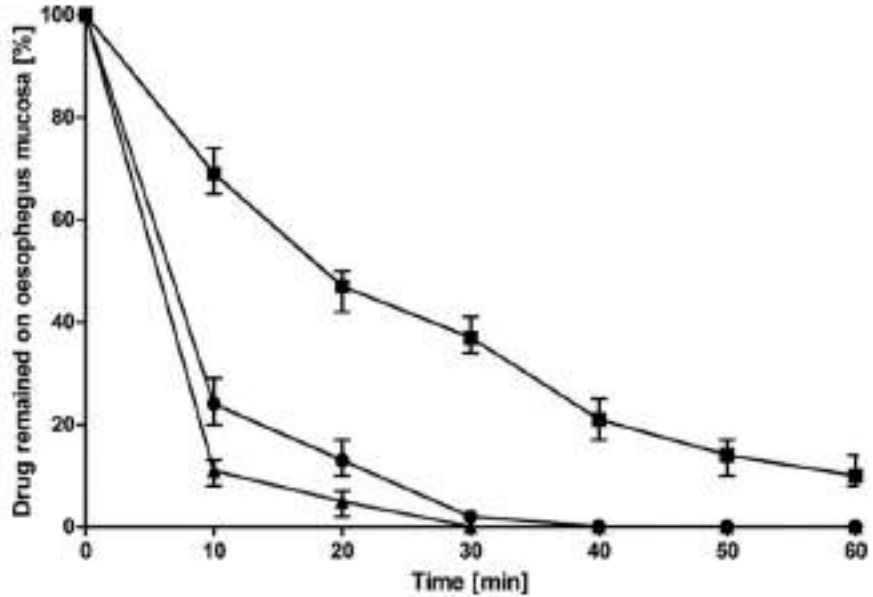
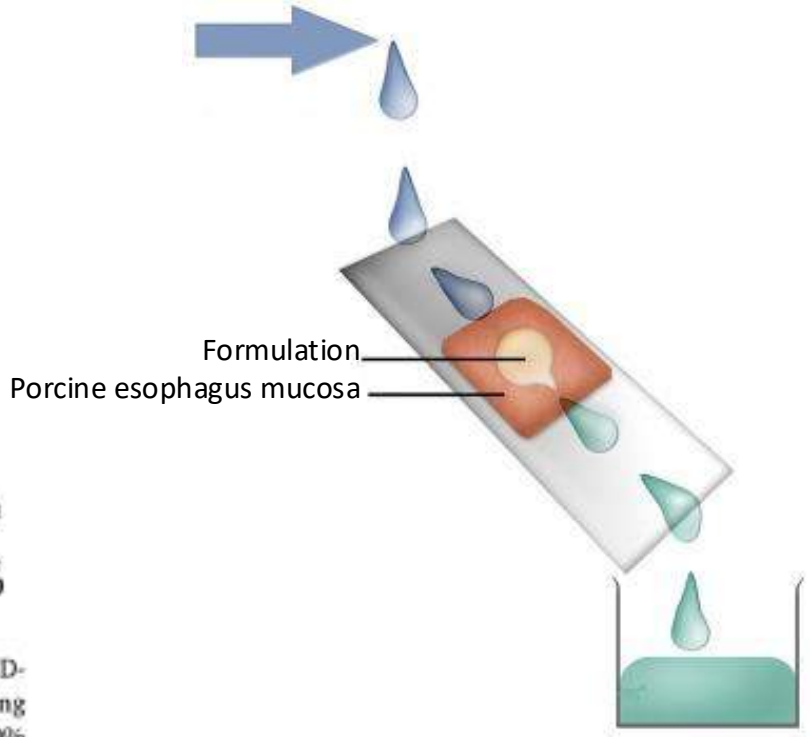


Fig. 11. Residence time of BUD in BUD/HP-β-CD complex (●), BUD/HP-β-CD-SH complex (■), and BUD as control (▲) on porcine esophagus mucosa being continuously rinsed with 100 mM phosphate buffer pH 6.8 at 37 °C and 100% relative humidity.



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.

The need

Pre-formulative and formulative studies

Technology transfer

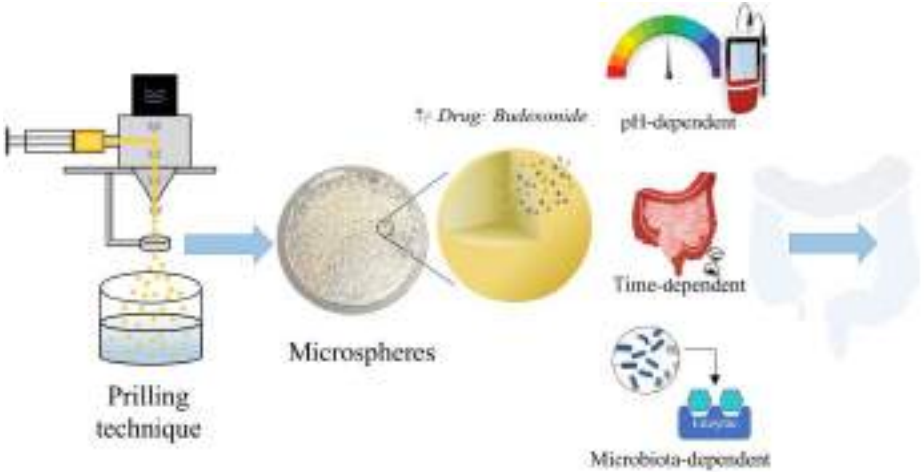
Inflammatory bowel diseases (IBD)

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

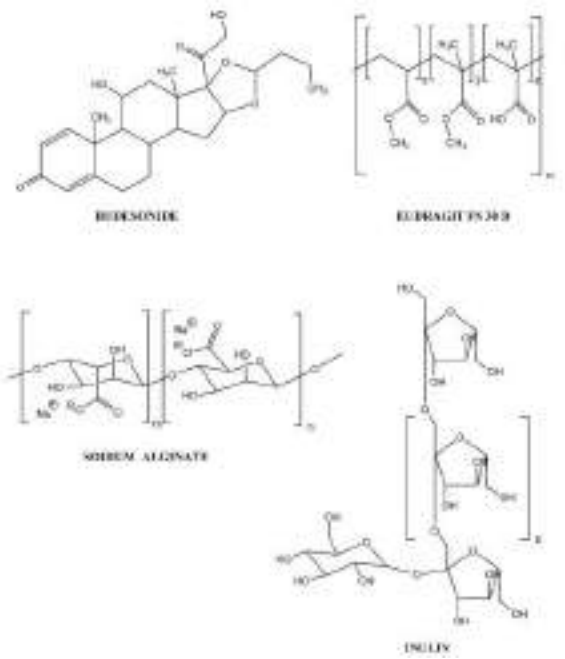
Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/ inulin-based microspheres as a paediatric formulation



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

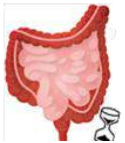
V. D'Amico et al. Colonic budesonide delivery by multistimuli alginate/Eudragit® FS 30D/inulin-based microspheres as a paediatric formulation. Carbohydrate Polymers 302 (2023) 120422.

BUDESONIDE CASE STUDIES

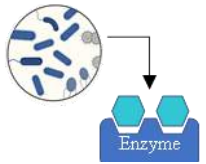


Eudragit FS 30D is a pH-sensitive polymetaacrylate that dissolves at pH values above 7.0;

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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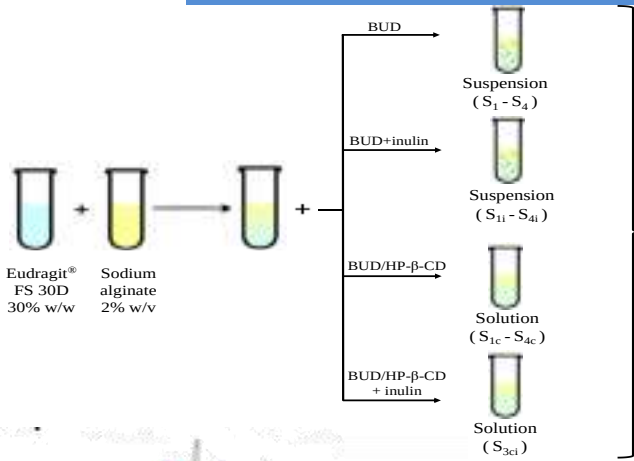
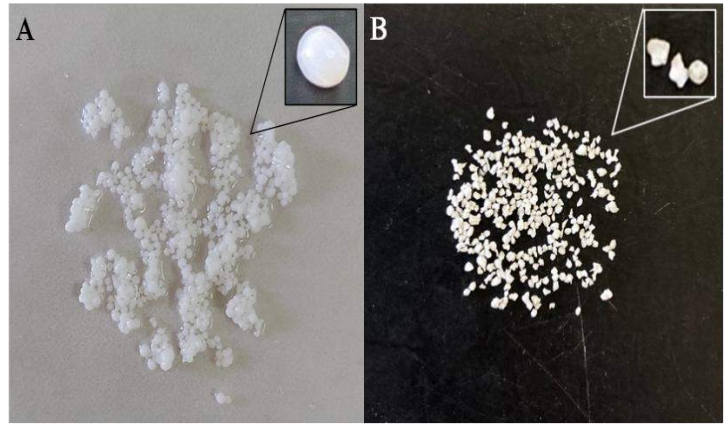
BUDESONIDE CASE STUDIES





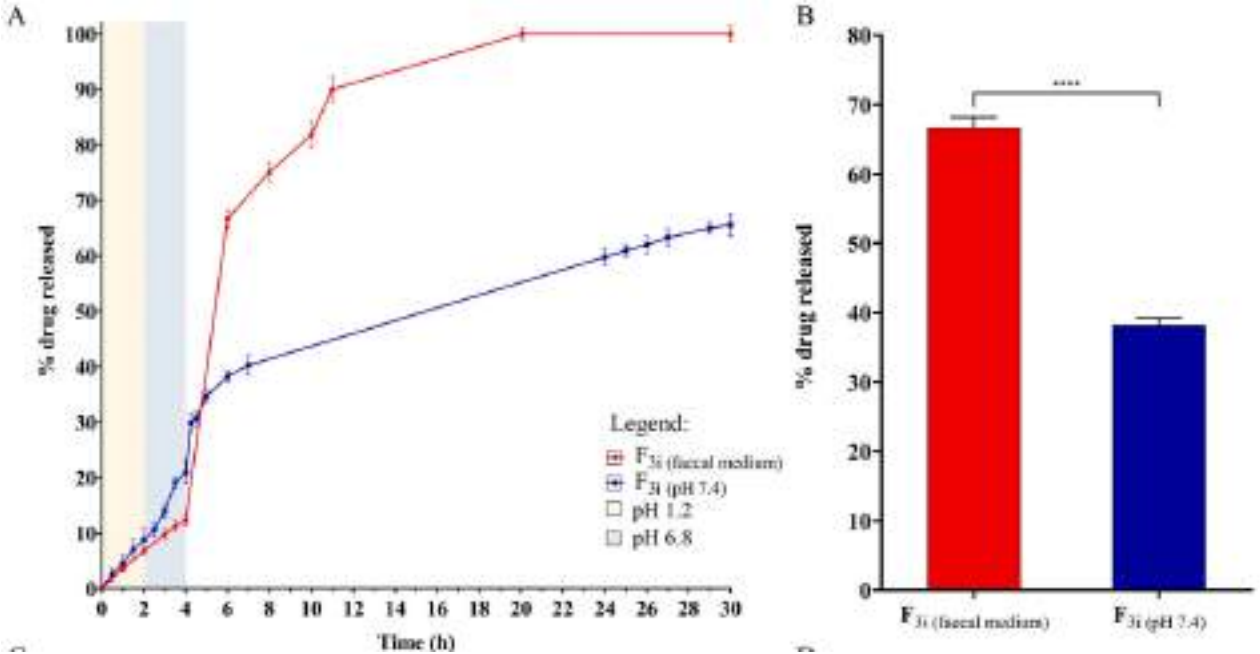
Polymeric feed (100 mL) was processed by the prilling/vibration technique.

Feeds code	Eudragit® FS 30D (g)	Alginate 2 % w/v (g)	Ratio	BUD (mg)	Inulin (g)	BUD/HP-β-CD* (g)
S_{4c}	–	2.00	0:1	75.0	–	–
S_1	0.97	1.93	0.5:1	75.0	–	–
S_2	3.53	1.77	2:1	75.0	–	–
S_3	6.32	1.58	4:1	75.0	–	–
S_4	10.00	1.33	7.5:1	75.0	–	–
S_{4c}	–	2.00	0:1	–	–	6.42
S_{1c}	0.97	1.93	0.5:1	–	–	6.42
S_{2c}	3.53	1.77	2:1	–	–	6.42
S_{3c}	6.32	1.58	4:1	–	–	6.42
S_{4c}	10.00	1.33	7.5:1	–	–	6.42
S_{4i}	–	2.00	0:1	75.0	0.80	–
S_{1i}	0.97	1.93	0.5:1	75.0	1.36	–
S_{2i}	3.53	1.77	2:1	75.0	1.32	–
S_{3i}	6.32	1.58	4:1	75.0	1.36	–
S_{4i}	10.00	1.33	7.5:1	75.0	4.53	–
S_{3ci}	6.32	1.58	4:1	–	1.36	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.

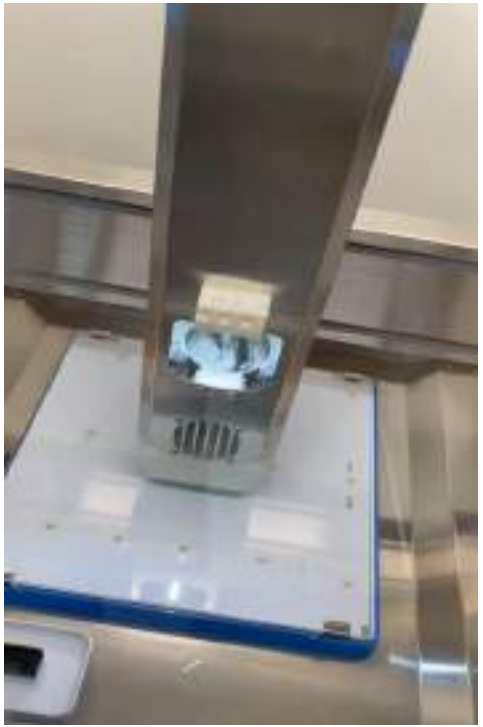
In vitro release studies under different pH conditions and faecal medium simulating the colonic environment.



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

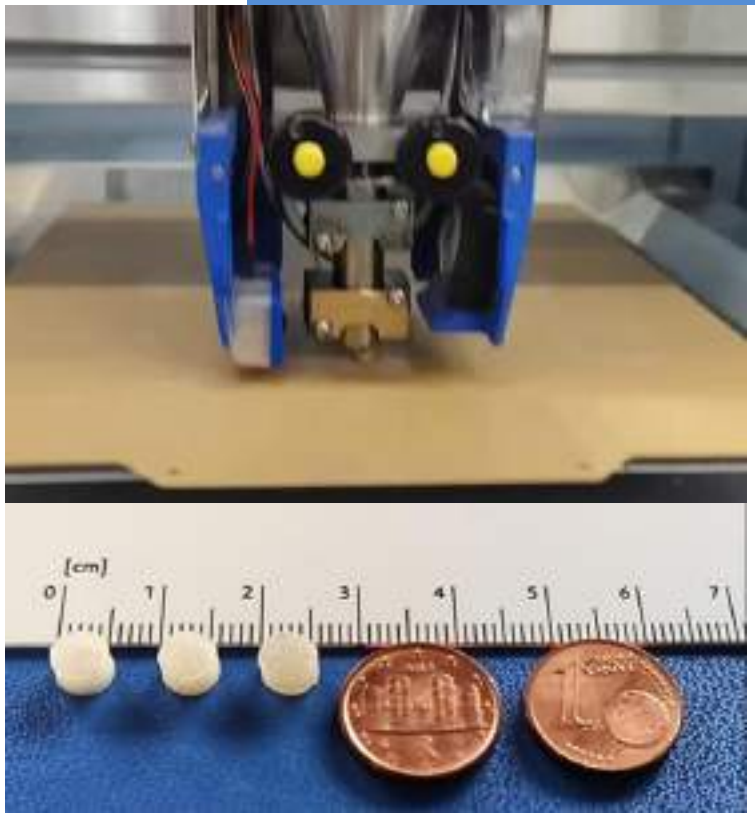


Combining the **hot melt extrusion (HME)** process with the **3D printing** technique to generate from pharmaceutical grade powders or pellets customizable solid dosage forms.

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	130.08 ± 20.17	0.71 ± 0.09	0.022	> 484.90	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	3.70 ± 0.21

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

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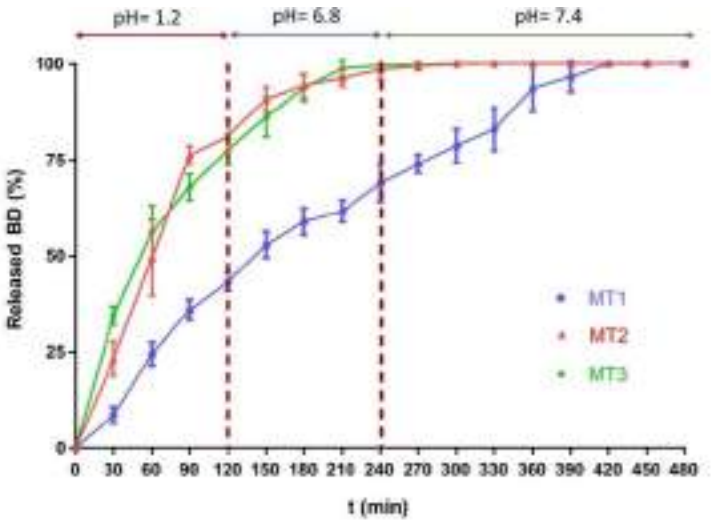
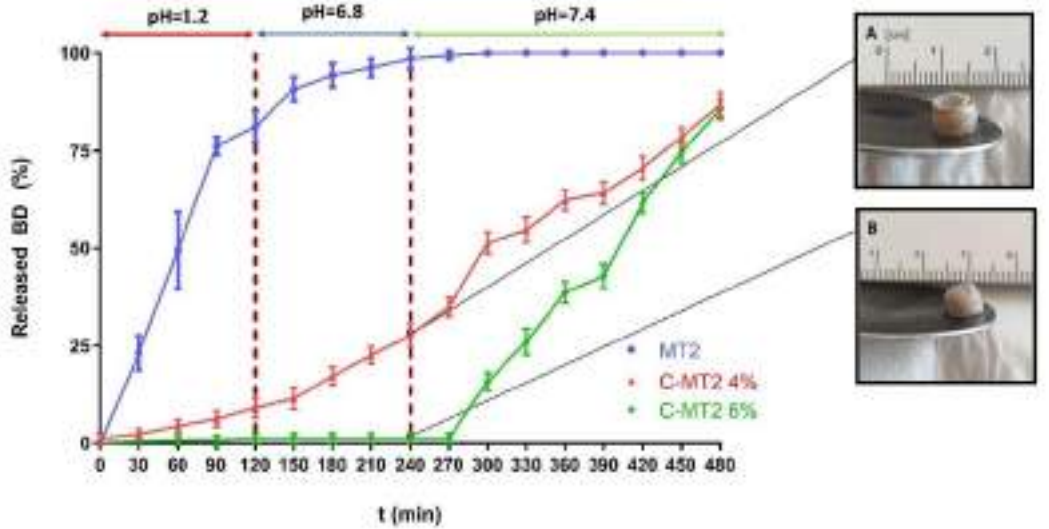
BUDESONIDE CASE STUDIES



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

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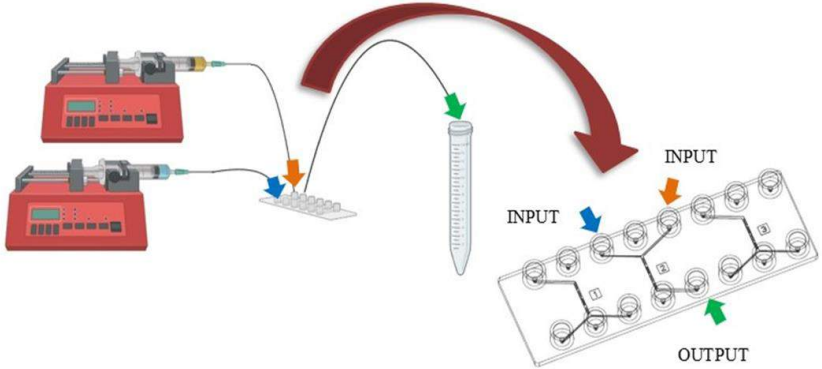
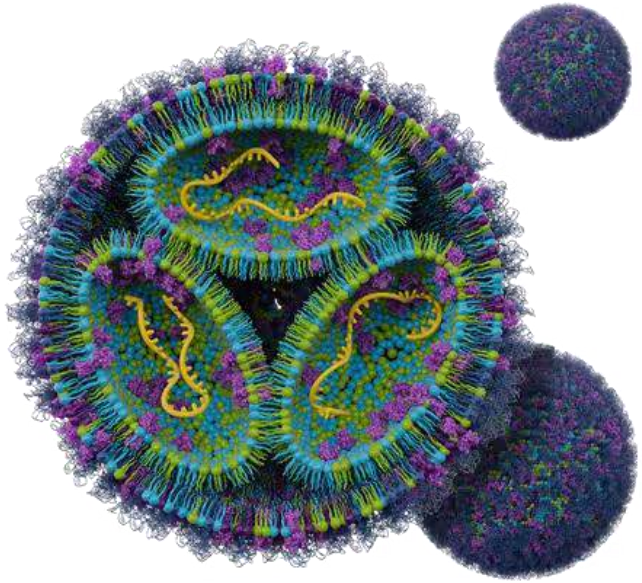
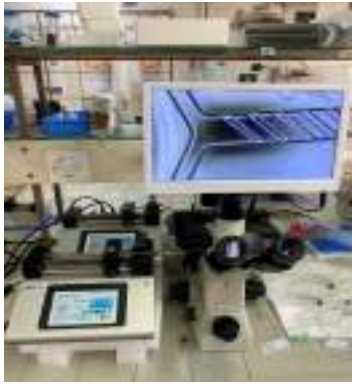
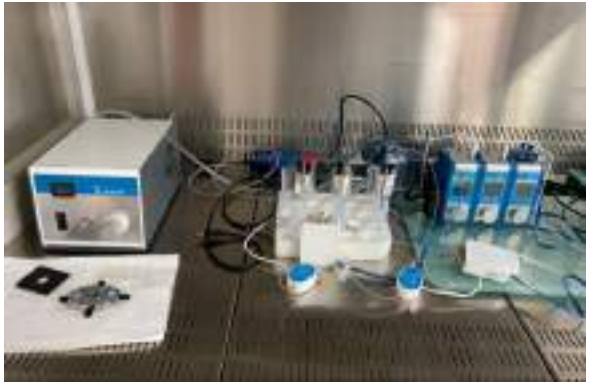
Microfluidic platform for the production of Lipid-based Nanoparticles









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.

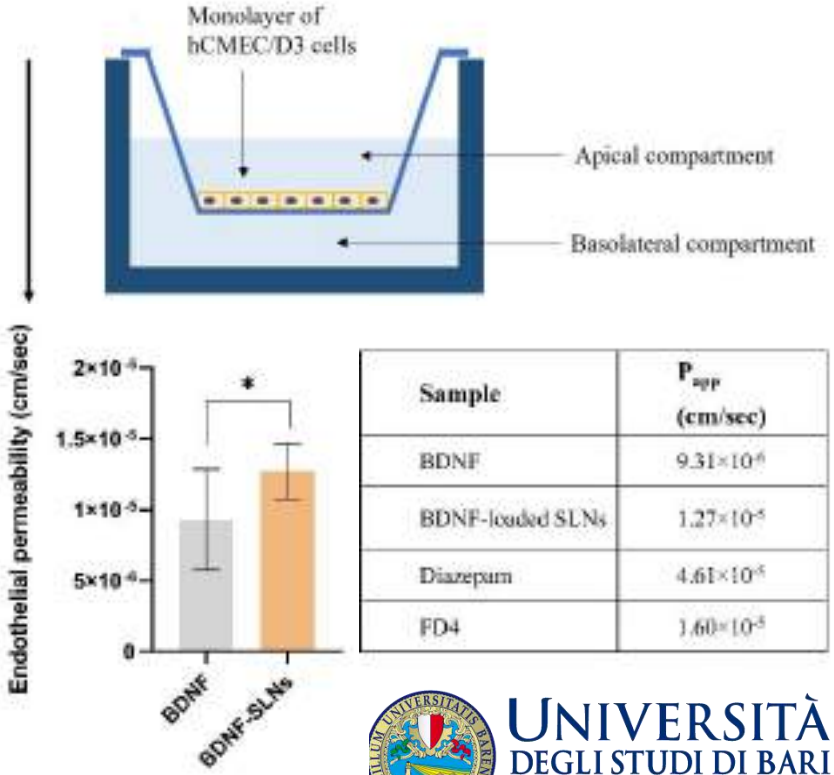
Need for innovative non invasive formulations!

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

MF-ASSISTED PRODUCTION OF BDNF-SLNs

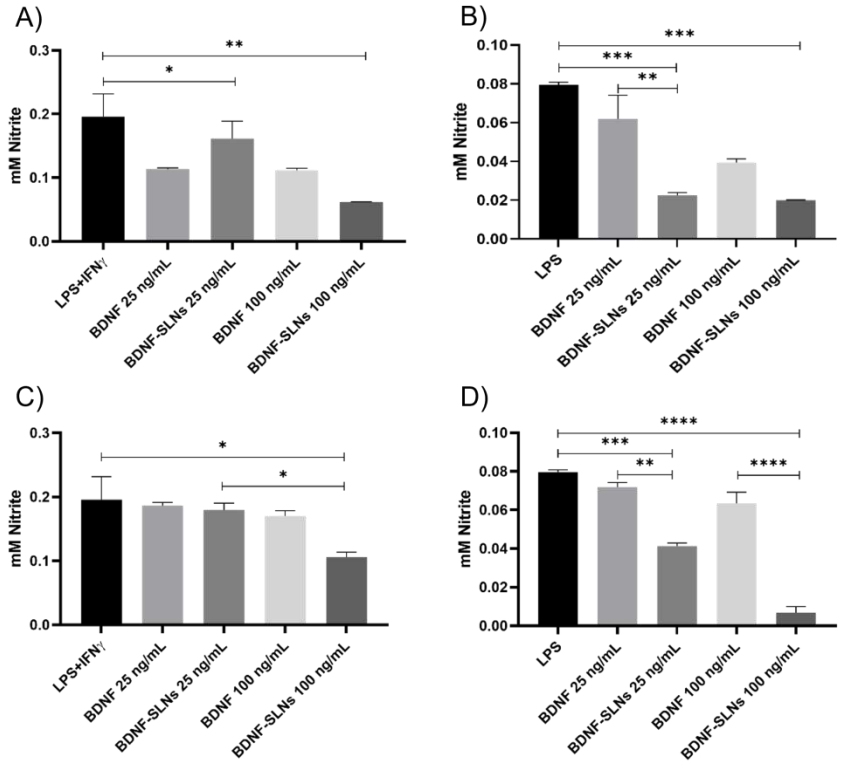
The *in vitro* permeability study was conducted by assessing the permeability of plain BDNF and BDNF-SLNs across the BBB model of hCMEC/D3 cell line.

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}

MF-ASSISTED PRODUCTION OF BDNF-SLNs

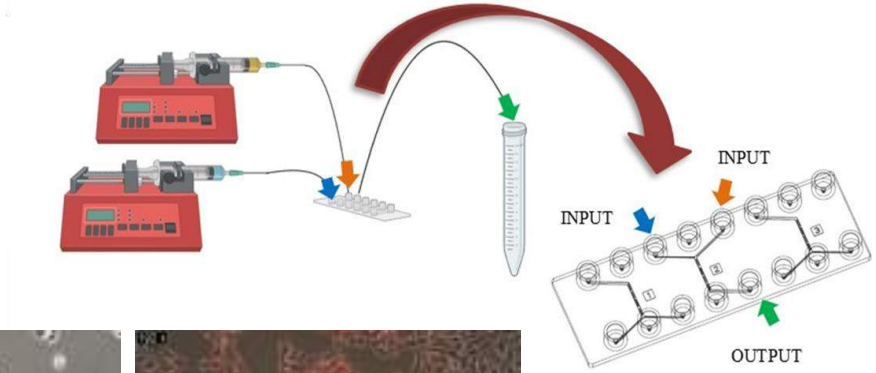


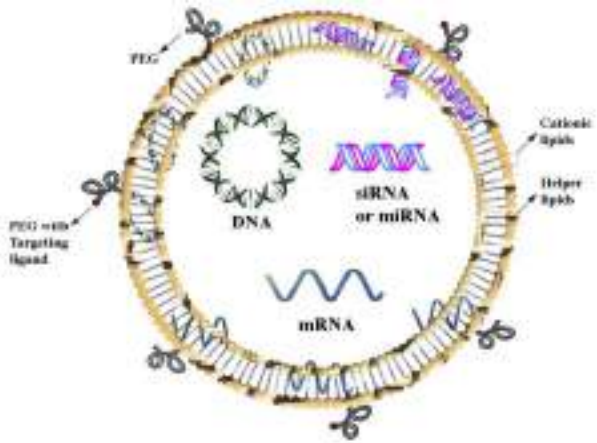
Comparison about free BDNF (25 ng/mL and 100 ng/mL) and BDNF-SLNs (25 ng/mL and 100 ng/mL) in a simulated TBI-related neuroinflammatory condition.

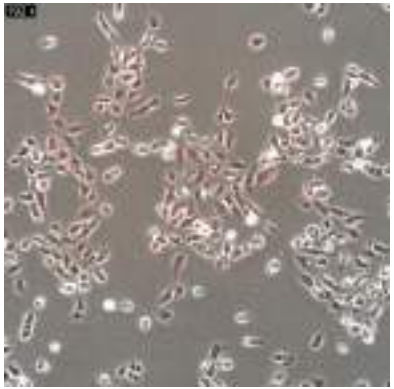
A, B) Data about pre-incubation of N9 cell line with free BDNF and BDNF-SLNs for 4 hours, then it was performed the treatment with (A) LPS+IFN-γ and (B) LPS alone up to 24 hours. (C, D) Data about pre-treatment of the N9 cell line with (C) LPS+IFN-γ and (D) LPS alone for 1 hour, then free BDNF and BDNF-SLNs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

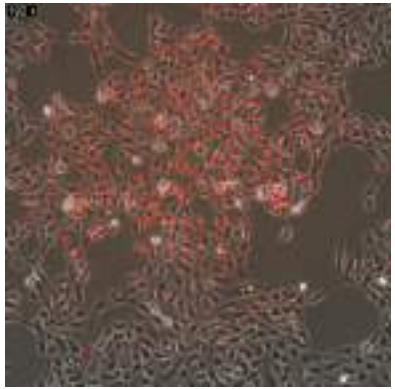
The formulation of BDNF-SLNs (100 ng/mL) was capable to reduce the iNOS activation resulting in less nitrite production in each tested condition compared to free BDNF at the same concentration.

Microfluidic-Assisted Production of Lipid Nanoparticles as Nucleic Acid Delivery Systems









CONCLUSION

We learned to be a team, sharing our knowledge in the development and production of pediatric formulations.

ACKNOWLEDGMENTS

International Children's Advisory Network

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19 July 9:00 – 13:00 - EPTRI Scientific Meeting 2024

EPTRI Scientific Meeting 2024		
11:15-11:30 15 min	Regulatory aspects of pediatric medicinal products optimization	Paola Minghetti
11:30-11:45 15 min	Innovative Drug delivery Systems	Dimitrios G. Fatouros
11:45-12:00 15 min	KIDS experience in the paediatric formulations' lab	