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DEVELOPMENT OF A NEW ORAL FORMULATION FOR THE TREATMENT OF INFANTILE HEMANGIOMA IN NEWBORNS

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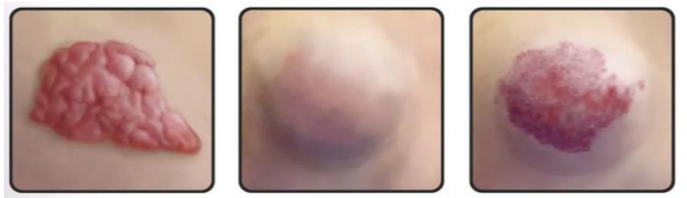
Infantile Hemangioma (IH)

The infantile hemangioma (IH) is the most common benign vascular tumor in the pediatric population.

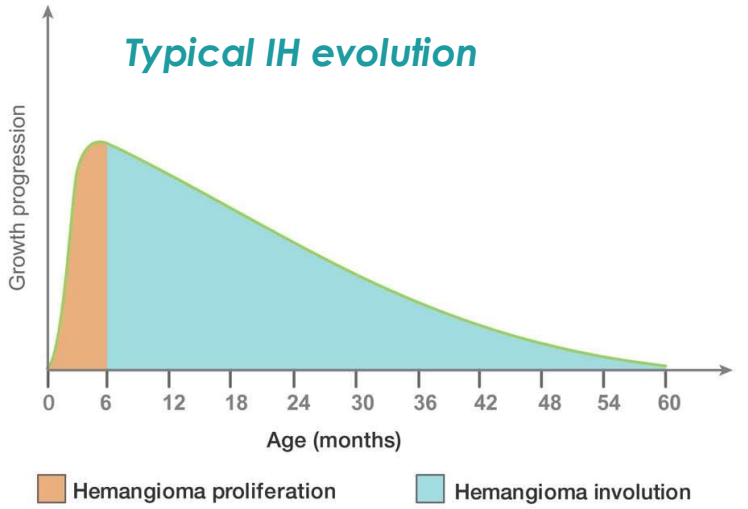
- The incidence varies between 1 and 3% in newborns and 3 and 10% in infants under 12 months of age.
- The prevalence is significantly higher in female, preterm, and low-birth-weight infants
- IH growth is affected by intrinsic influences, (angiogenic and vasculogenic factors) and by external factors (e.g. tissue hypoxia).

What are the risks? Hemangiomas near the eye may compromise vision and near mouth might impair feeding. Very large hemangiomas can ulcerate, cause pain, infections, functional impairment, or permanent disfigurement.



Superficial **Deep** **Mixed**

Typical IH evolution



Pharmacological treatments:

- **Beta-blocker:** Oral propranolol is the first line medication for treating hemangiomas in infants who are 5 weeks of age or older. The medication is usually given twice a day for at least six months. Dose: 1-3 mg/kg/die. A topical form of beta-blocker, timolol, is often given as a liquid drop.
- **Corticosteroids:** most effective in the first 6 months of age, most used are oral prednisone, prednisolone, ect. Dose: 1-4 mg/kg/die

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Infantile Hemangioma (IH)

Propanolol:

- Compounded solutions prepared in the hospital pharmacies ;
- The only commercial formulation for IH is an oral solution of propanolol (Hemangiol®), that can be administered as it is or after dilution in a small quantity of baby-milk or age-adapted apple and/or orange fruit juice.

Eur J Pediatr (2015) 174:1503–1509
DOI 10.1007/s00431-015-2561-1

ORIGINAL ARTICLE

Therapeutic superiority of combined propranolol with short steroids course over propranolol monotherapy in infantile hemangioma

Mohamed M. D. Aly[1] · Alaa F. Hamza[1] · Hesham M. Abdel Kader[1] · Hatem A. Saafan[1] · Mohamed S. Ghazy[2] · Iman A. Ragab[3]

- Recent studies have shown that a combinations of oral propranolol and corticosteroids gives a faster response and significantly reduce the tumor volume in IH patients.

CASE REPORT
BJD
British Journal of Dermatology

Propranolol and prednisolone combination for the treatment of segmental haemangioma in PHACES syndrome

M. Gnarra, L. Solman, J. Harper and S. Batul Syed

Department of Paediatric Dermatology, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, U.K

Original Article

Effect of combined low-dose oral prednisone with beta-adrenergic receptor antagonists for refractory infantile hemangiomas: retrospective cohort study in 76 patients

Chao Liu[1,2#], Ze-Liang Zhao[1#], Hai-Wei Wu[1], Jia-Wei Zheng[1], Yan-An Wang[1], Xue-Jian Liu[3], Xin-Dong Fan[4]

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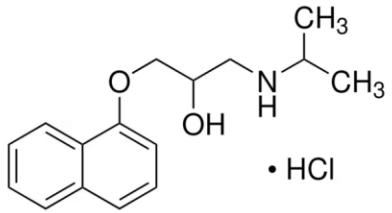
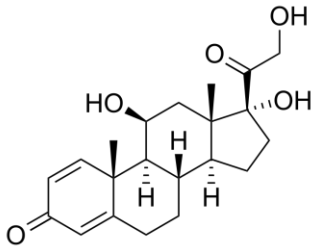
Aim of the study

Microparticles (MPs) containing a combination of:



Propanolol hydrochloride (PROP)

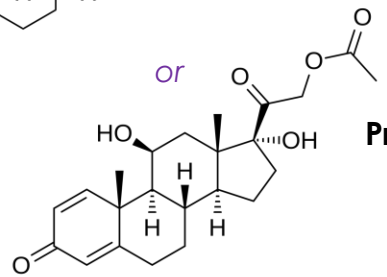
1 mg/kg/die



Prednisolone (PR-OH) Combination I

1 mg/kg/die

or



Prednisone acetate (PR-Ac)

1 mg/kg/die Combination II

Objectives:

1. **Fixed-dose combination of PROP and a corticosteroid**
2. **Controlled drug release**
3. **Age-appropriate formulation for easy administration**

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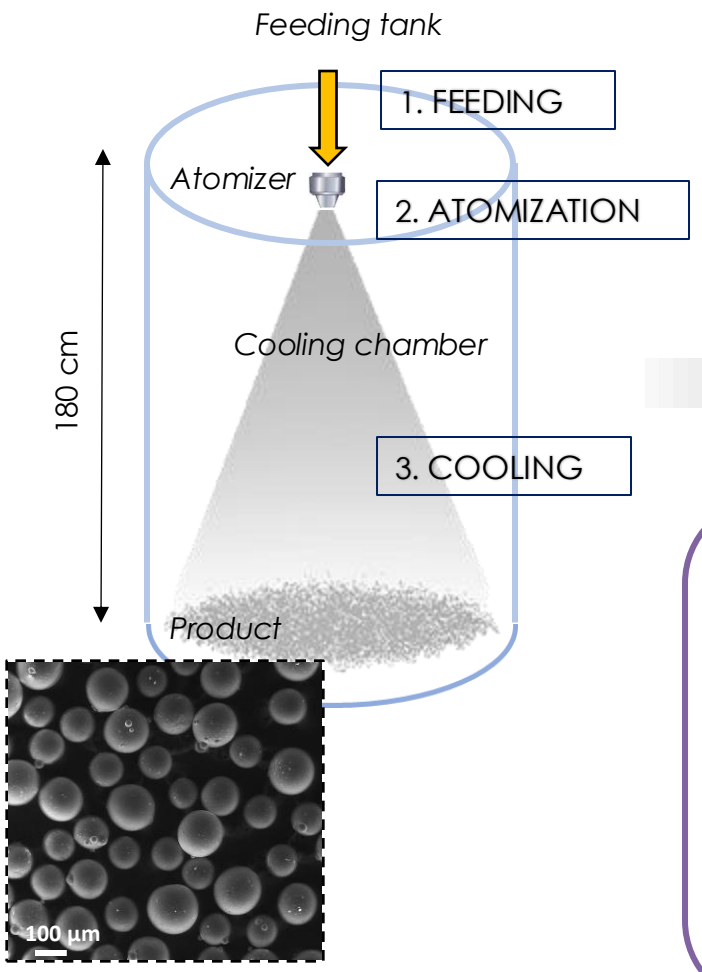
Spray congealing technology



Advantages :

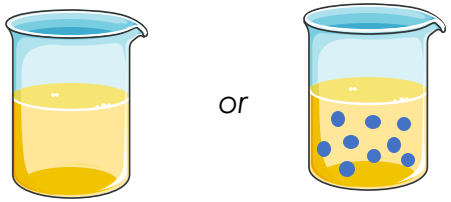
- ✓ Solvent-free
- ✓ Fast, low-cost, *green*
- ✓ High encapsulation efficiency
- ✓ Easily administrable multi-unit dosage form

Disadvantages :

- ✓ Not applicable to thermolabile APIs
- ✓ Limited to low melting excipients

STEP 1

Preparation of the fluid mixture



Molten lipid

60-90°C

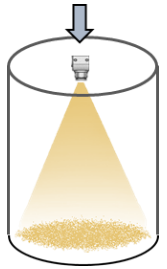
or

Molten lipid + polymer «emulsion»

60-90°C

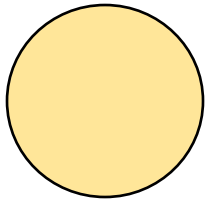
STEP 2

Atomization and solidification



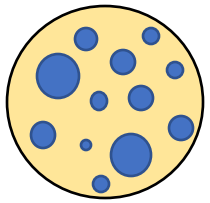
STEP 3

Collection of Microparticles



One-phase lipid as matrix-forming excipient

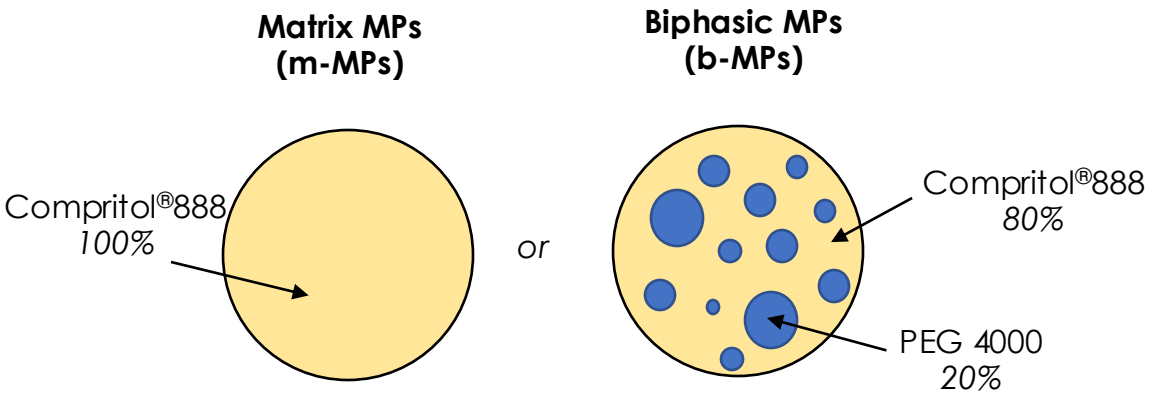
or



Two-phase system: polymeric «cores» in a lipid matrix

Bertoni S. et al. Eur. J. Pharm. Biopharm., 190, 171-183 (2023)
Bertoni S. et al. Pharmaceutics, 14(1):54 (2021)

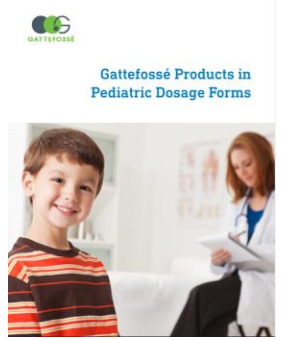
Production and characterization of MPs



+ PROP *1 % w/w* and Pr-OH *1% w/w* (Combination I)
or
PROP *1 % w/w* and Pr-Ac *1% w/w* (Combination II)

Excipients:

- Glyceryl behenate «Compritol®888»
- Polyethylenglycol 4000 (PEG 4000)



Characterization of MPs:

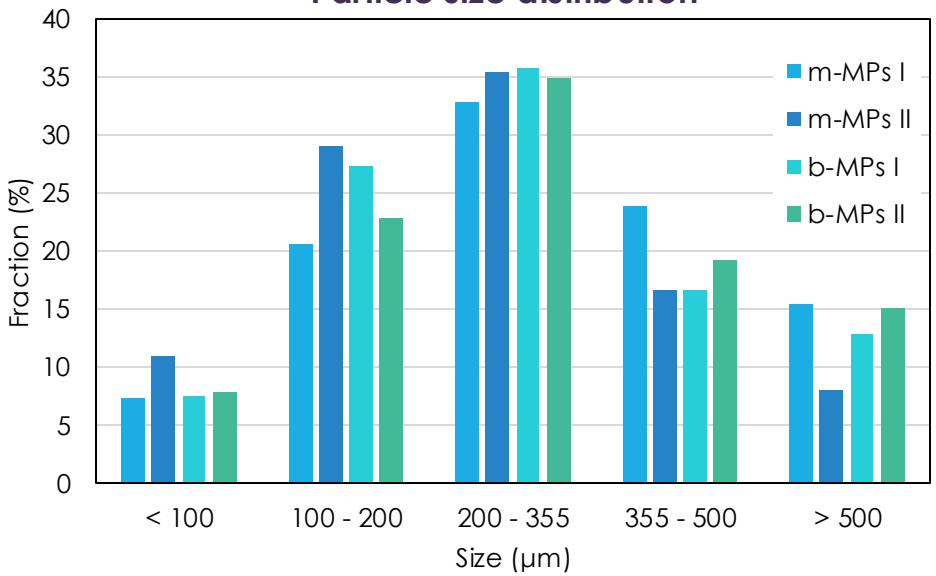
- Particle size (sieving);
- Internal and external morphology (Optical microscopy, Scanning Electron Microscopy (SEM));
- Solid-state properties (Differential scanning calorimetry, Powder X-Ray Diffraction);
- *In vitro* dissolution studies.

Results: Characterization of MPs

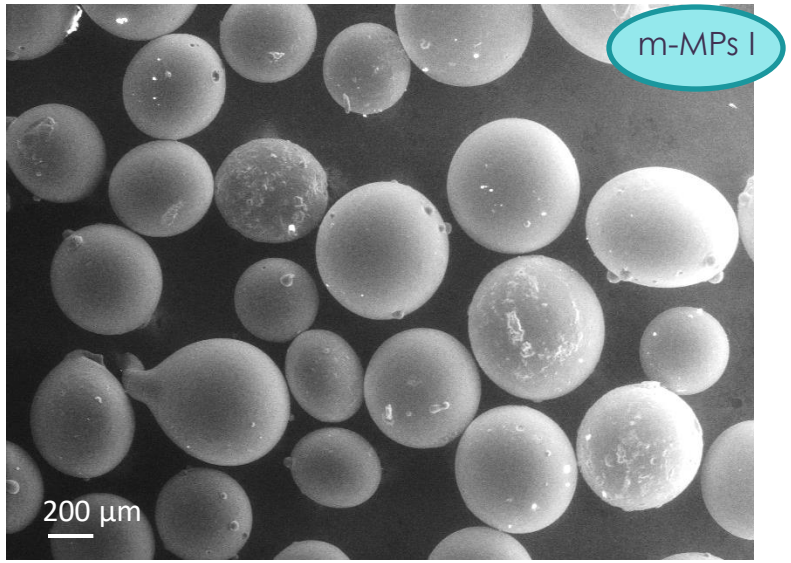
Process Yield

Formulation	Yield %
m-MPs I	77,8%
b-MPs I	77,2%
m-MPs II	69,0%
b-MPs II	78,2%

Particle size distribution



Scanning Electron Microscopy



Determination of drug loading amount

Formulation	Drug amount (% w/w)			Encapsulation efficiency (%)		
	PROP	Pr-OH	Pr-Ac	PROP	Pr-OH	Pr-Ac
m-MPs I	0,82 ± 0,06	0,79 ± 0,07	-	82	79	-
b-MPs I	0,86 ± 0,04	0,81 ± 0,04	-	86	81	-
m-MPs II	0,76 ± 0,04	-	0,89 ± 0,03	76	-	89
b-MPs II	0,75 ± 0,01	-	0,81 ± 0,03	75	-	81

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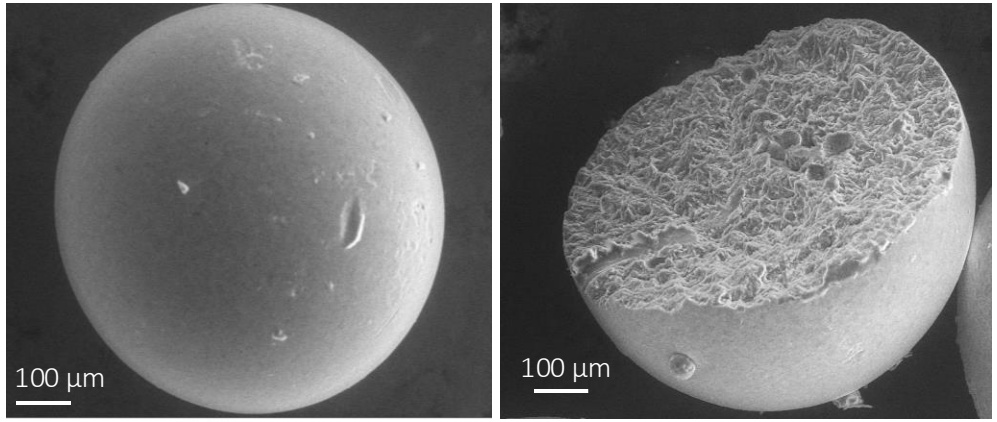
Results: Characterization of MPs

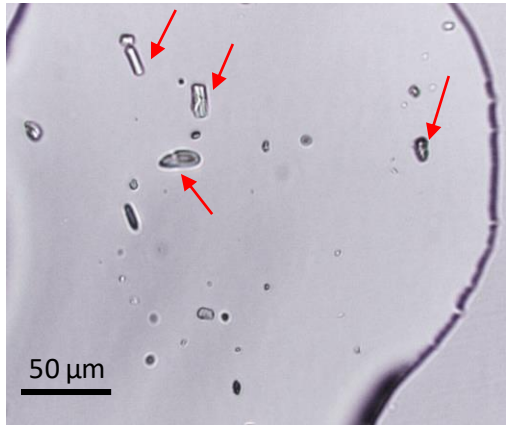
Scanning Electron Microscopy

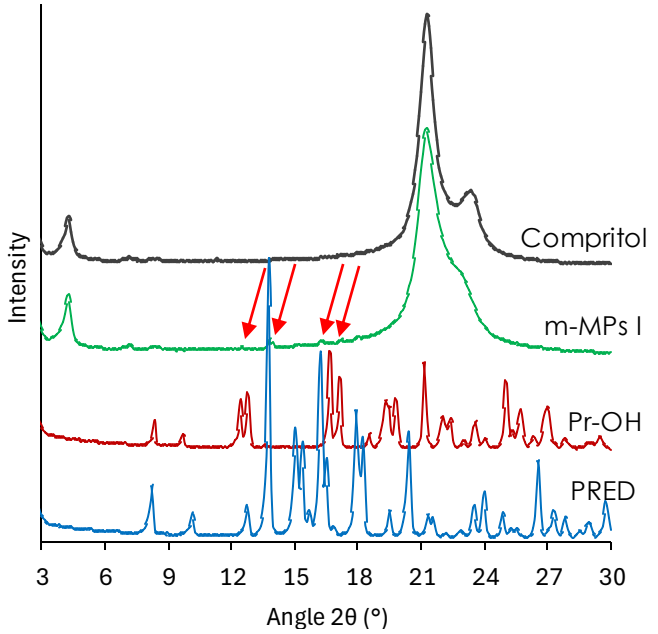
Hot Stage Microscopy

Powder X-Ray Diffraction Analysis

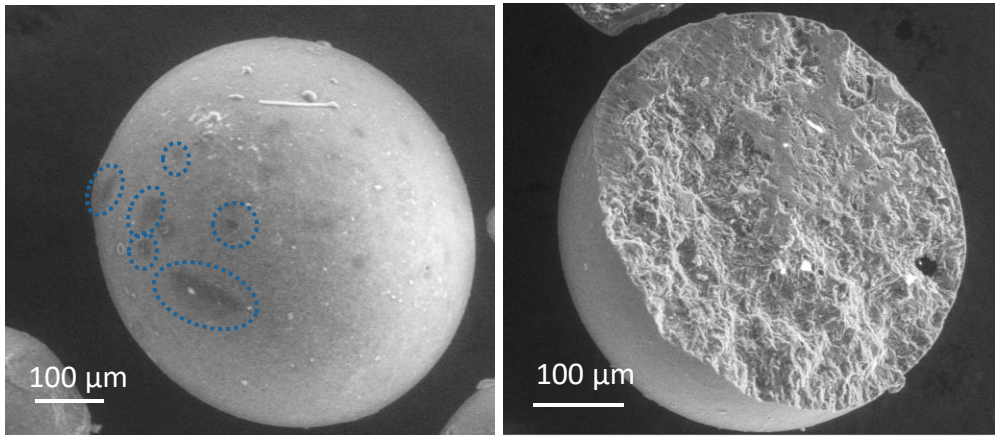
m-MPs I

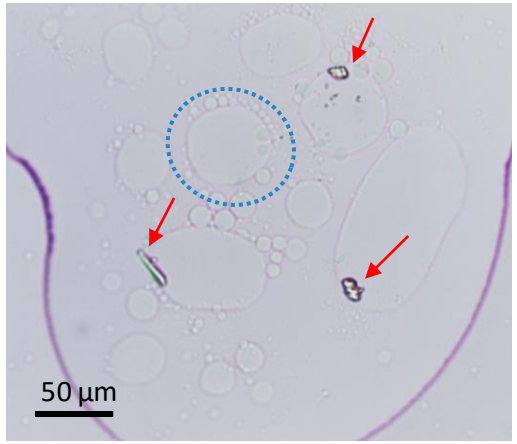


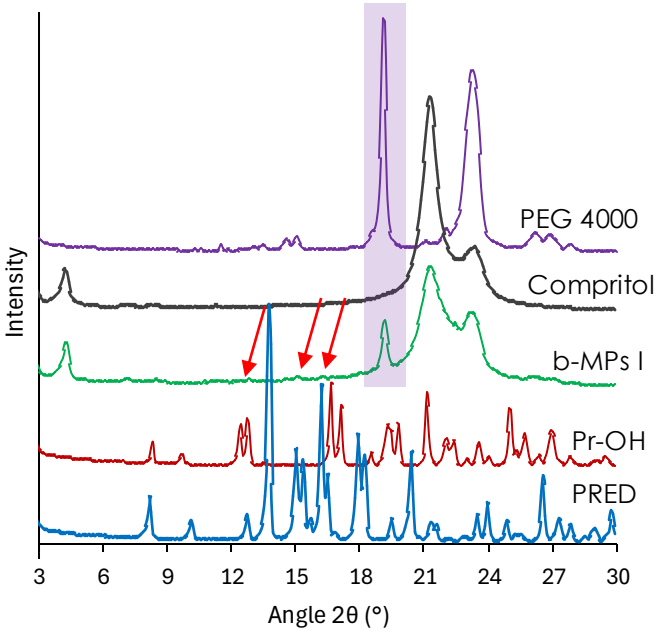




b-MPs I







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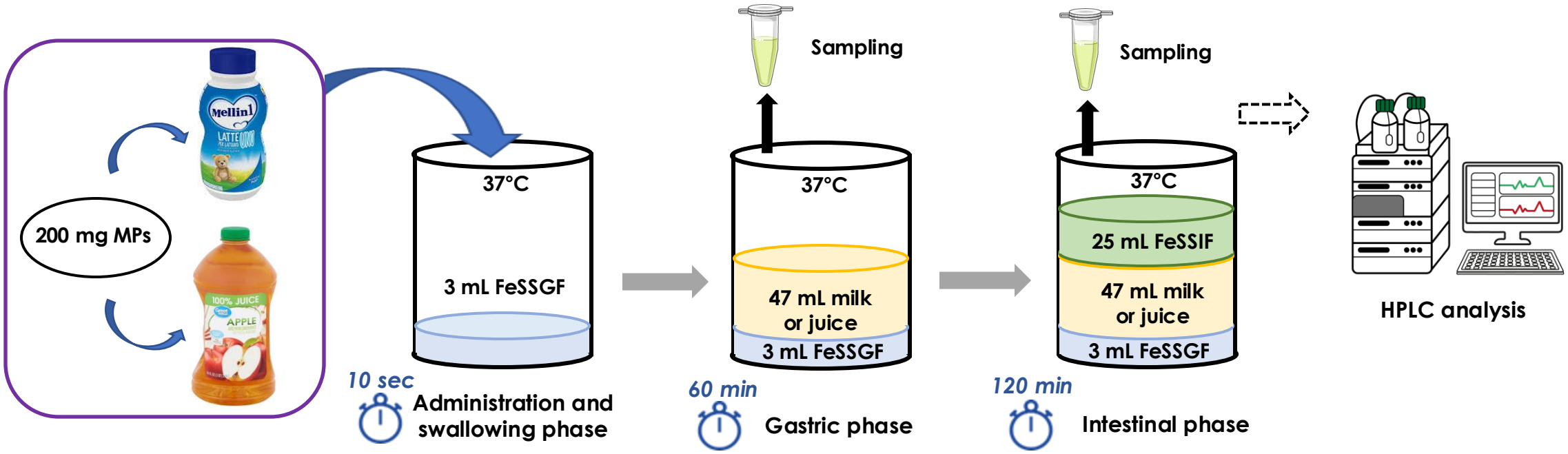
Dissolution studies using newborn/infant *in vitro* model



Gastro-Intestinal media recommended for Newborn and Young Infants:

- Fed State Simulated Gastric Fluid (FeSSGF)
- Fed State Simulated Gastric Fluid (FeSSGF)

Biorelevant Media	Components (mM)					Enzymes (U/ml)			pH
	NaCl	TRIS	Maleic acid	Taurocholic acid	L-a-phosphatidil choline	Gastric lipases	Pepsin	Pancreatic lipases	
FeSSGF	3	2	2	-	-	17	30	-	6.4
FeSSIF	89.5	2	2	1	0.2	-	-	50	6.5

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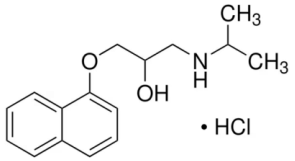
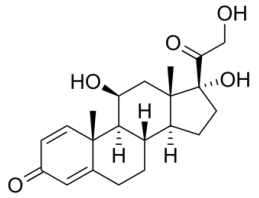
Klitgaard, et al. Eur. J. Pharm. Sci. 109, 191-199 (2017)

Results: Combination I



PROP

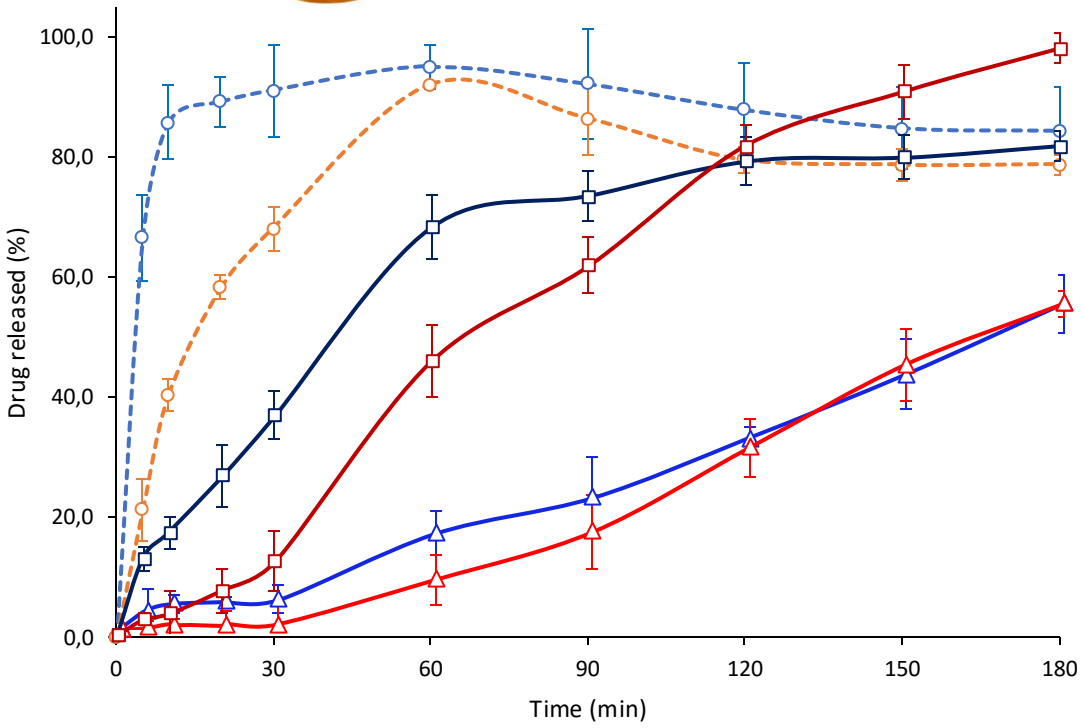


PR-OH

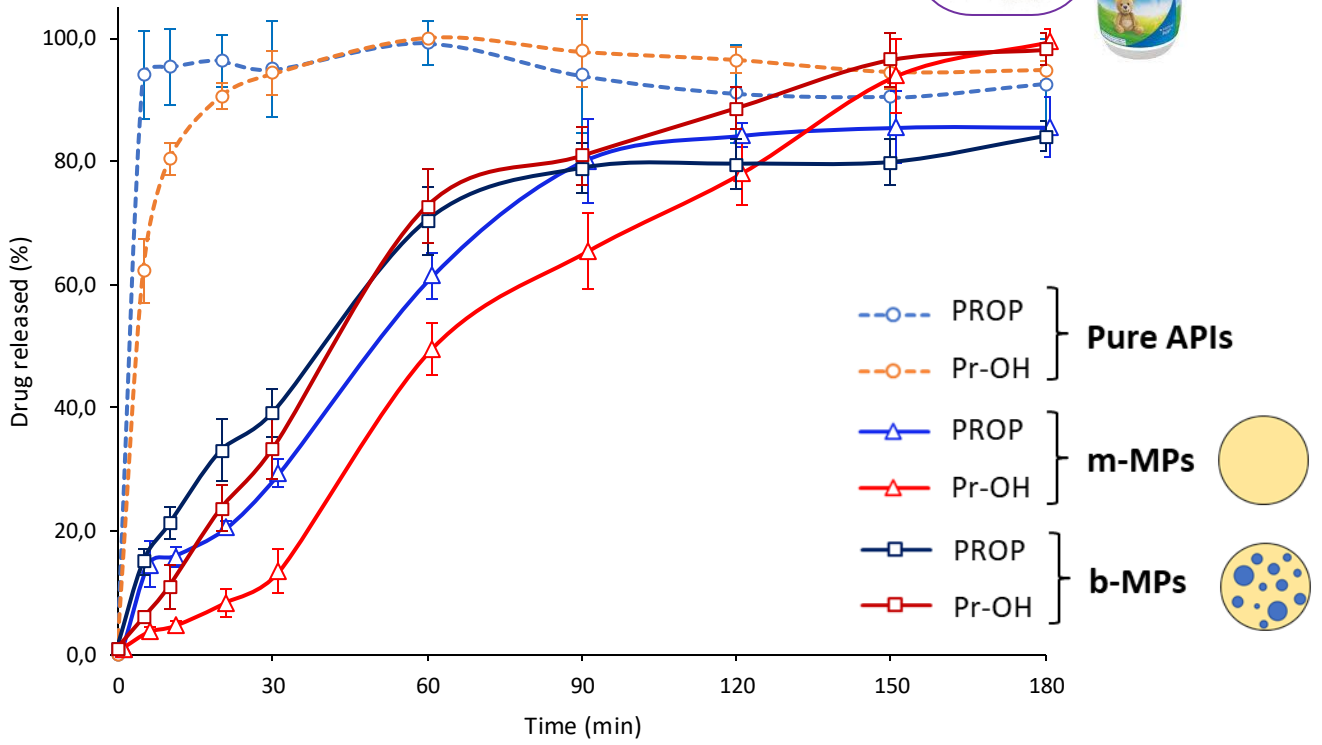
Solubility (mg/L)

Phosphate buffer: 532 ±41
Apple juice: 557 ± 22
Baby-milk: 617 ± 64

Apple juice



Baby-milk



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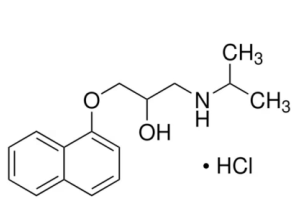
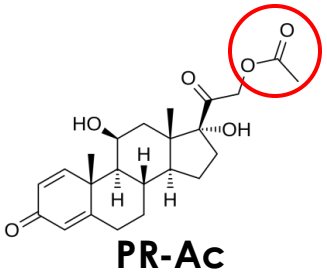
Results: Combination II



PROP

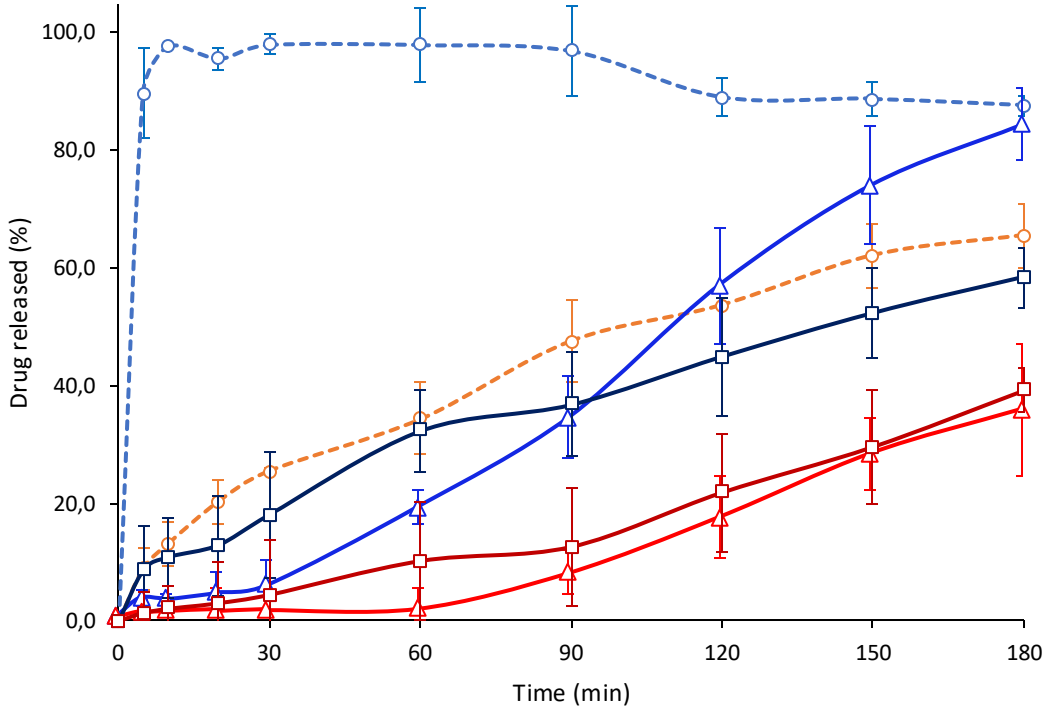


PR-Ac

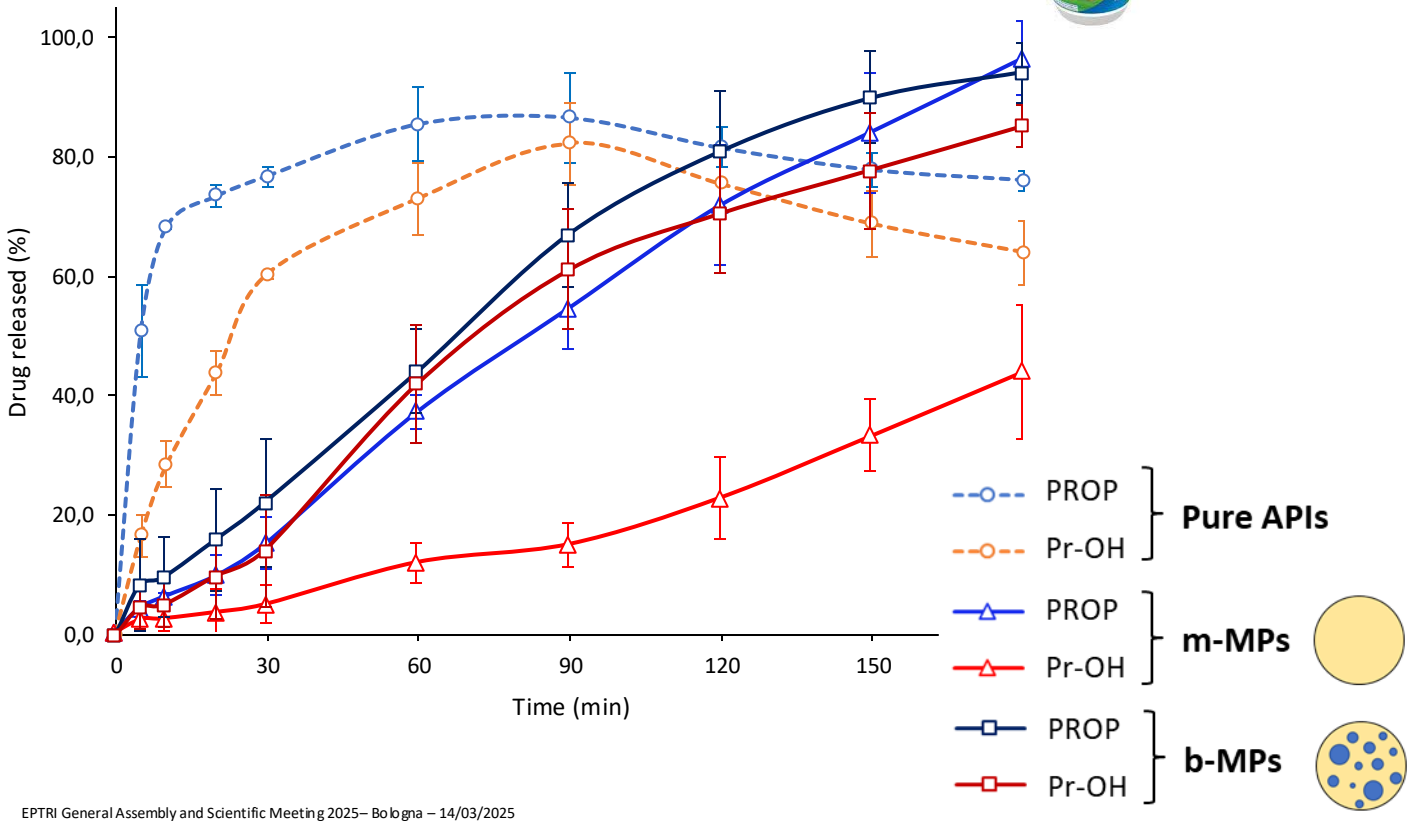
Solubility (mg/L)

Phosphate buffer: 45 ± 8
Apple juice: 35 ± 6
Baby-milk: 48 ± 16

Apple juice



Baby-milk



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Conclusion

Allow oral administration of a **combination of two drugs** (PROP and a corticosteroid) for the treatment of complicated IH.

Are a **suitable dosage form for newborns/infants**: precise dosing and easy administration

Enable **prolonged drug release**, with fewer variations depending on the type of drink used for administration (milk or juice).

Acknowledgments

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