# Hybrid nanoparticles for possible Nose-to-brain delivery of Ropinirole Hydrochloride

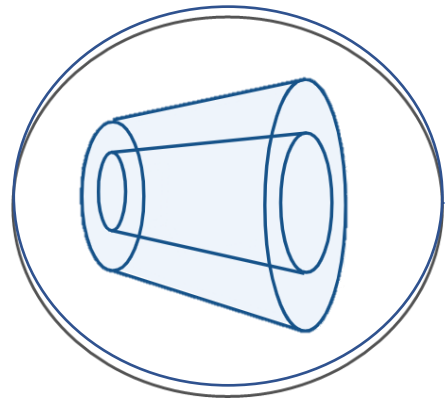Elmina-Marina Saitani[1], Natassa Pippa[1], Stergios Pispas[2], Georgia Valsami[1]

[1]Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece

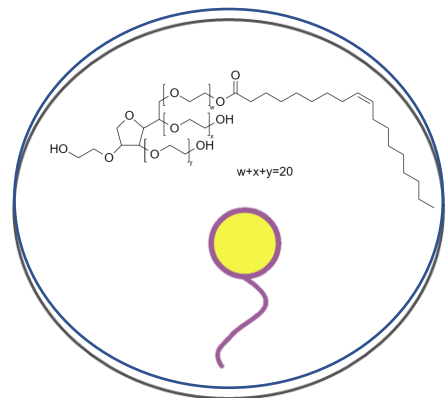[2]Theoretical and Physical Chemistry Institute, National Hellenic Research Foundation, Athens, Greece
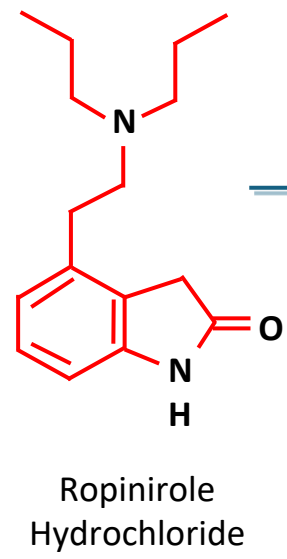
1. Background-Aim
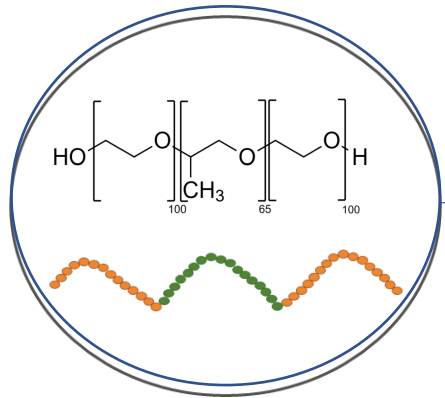
Poloxamer 407
PEO$_{100}$-PPO$_{65}$-PEO$_{100}$
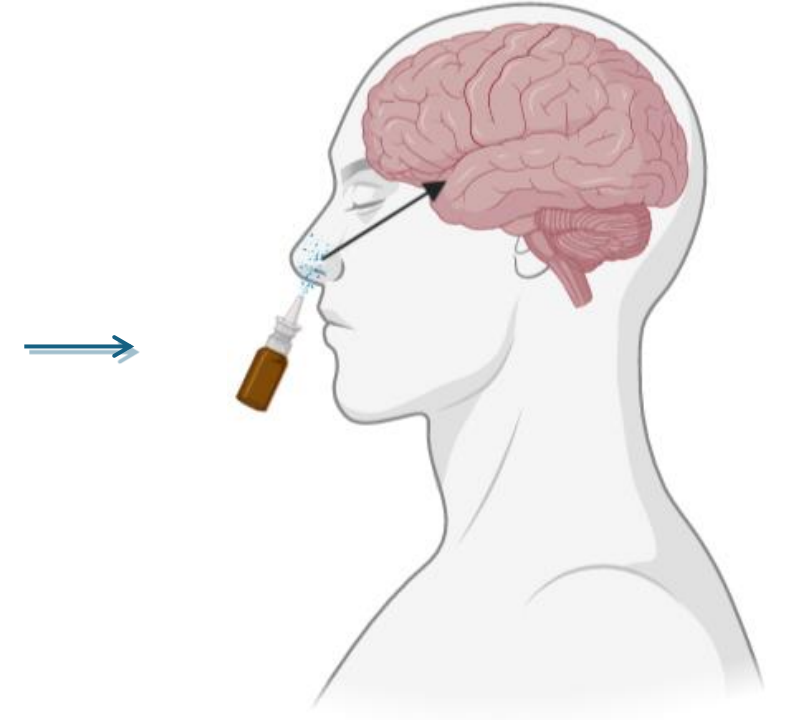
Cyclodextrin

Polysorbate 80
(Tw80)
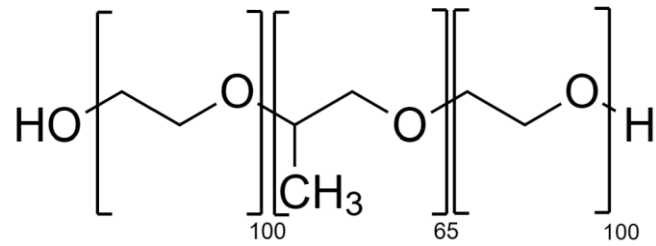
Ropinirole
Hydrochloride
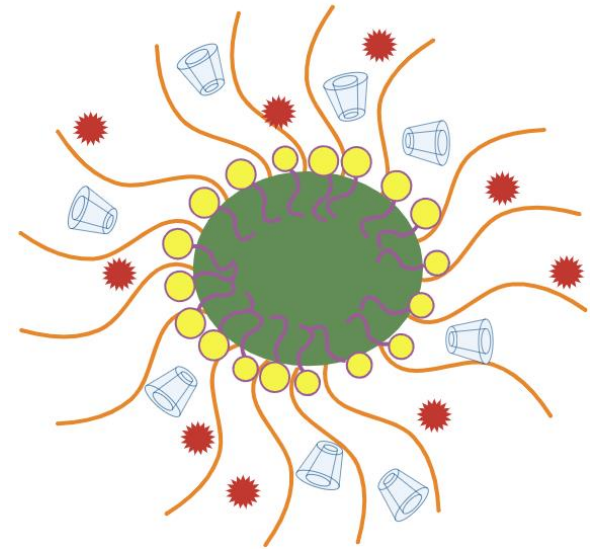
2.1 Materials & Methods

Block copolymers

HO─(CH₂CH₂O)₁₀₀─(CH(CH₃)CH₂O)₆₅─(CH₂CH₂O)₁₀₀─H

Poloxamer 407

Surfactant

w+x+y=20
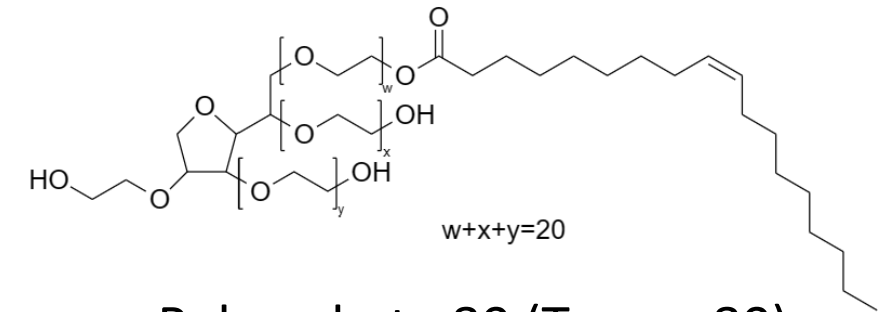
Polysorbate 80 (Tween 80)

Cyclodextrins

R=H, CH₃

Methyl-β-CD

R=H, ⟨OH⟩

Hydroxy-propyl-β-CD

CHCl₃ solution

H₂0 HPLC-grade
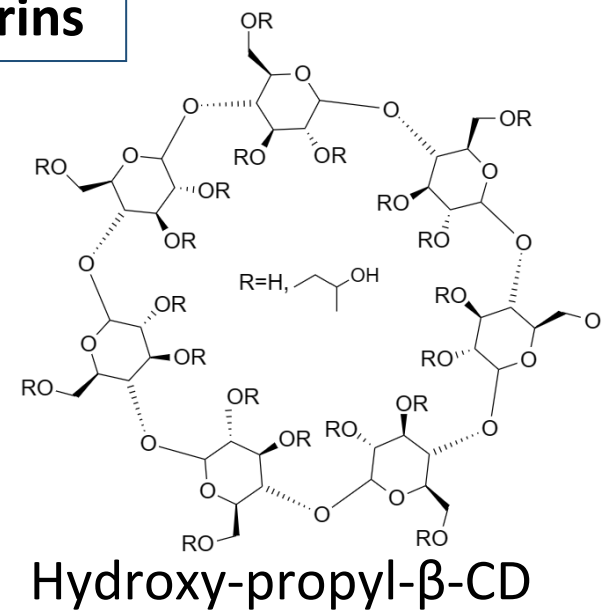
Thin-film hydration method

Under vacuum (40 ˚C)   (40 ˚C, slow rotation)   C=10 mg/mL
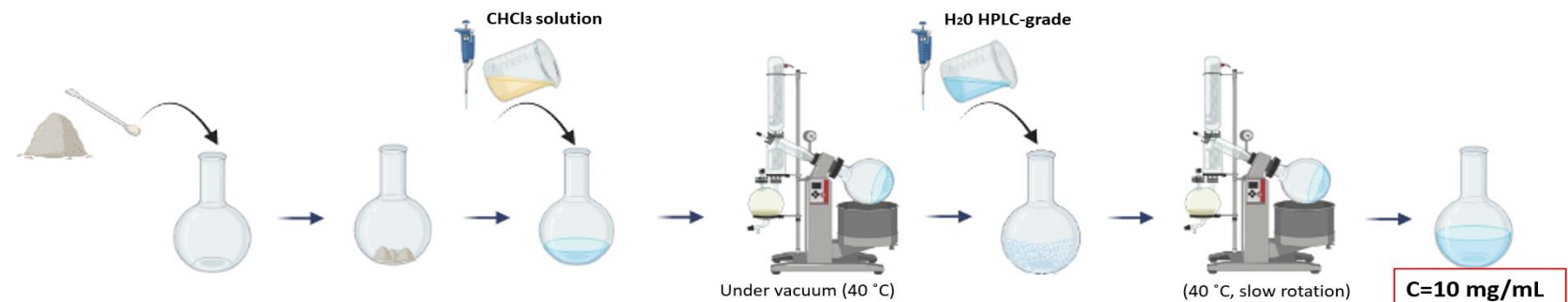
2.2 Added value of CD – block copolymer systems

New biomaterials and supramolecular structures, which encompass the physicochemical and thermotropic properties of both classes of materials.

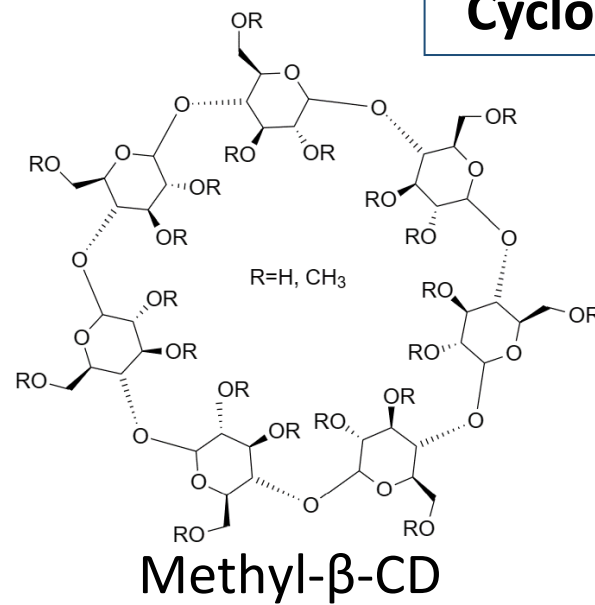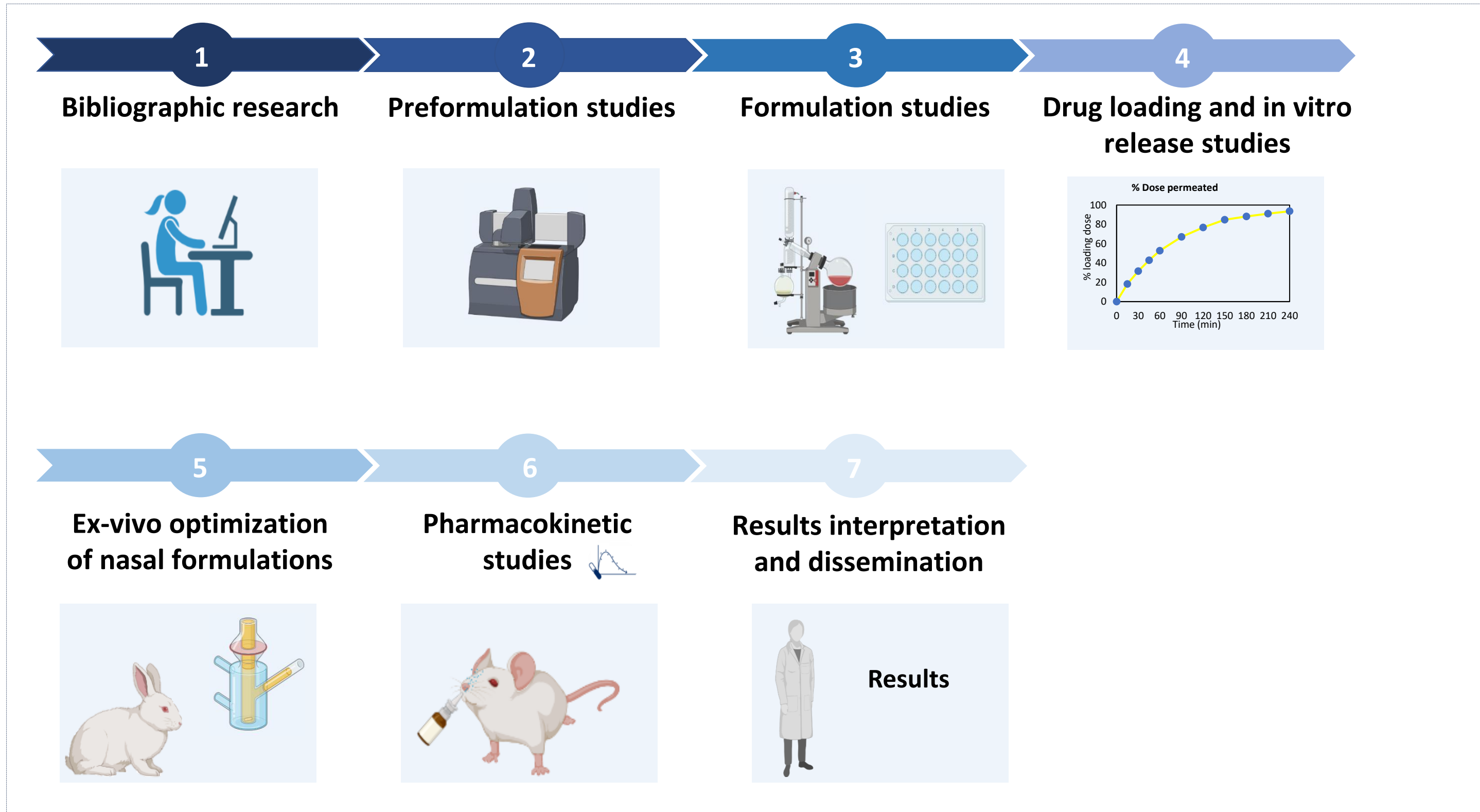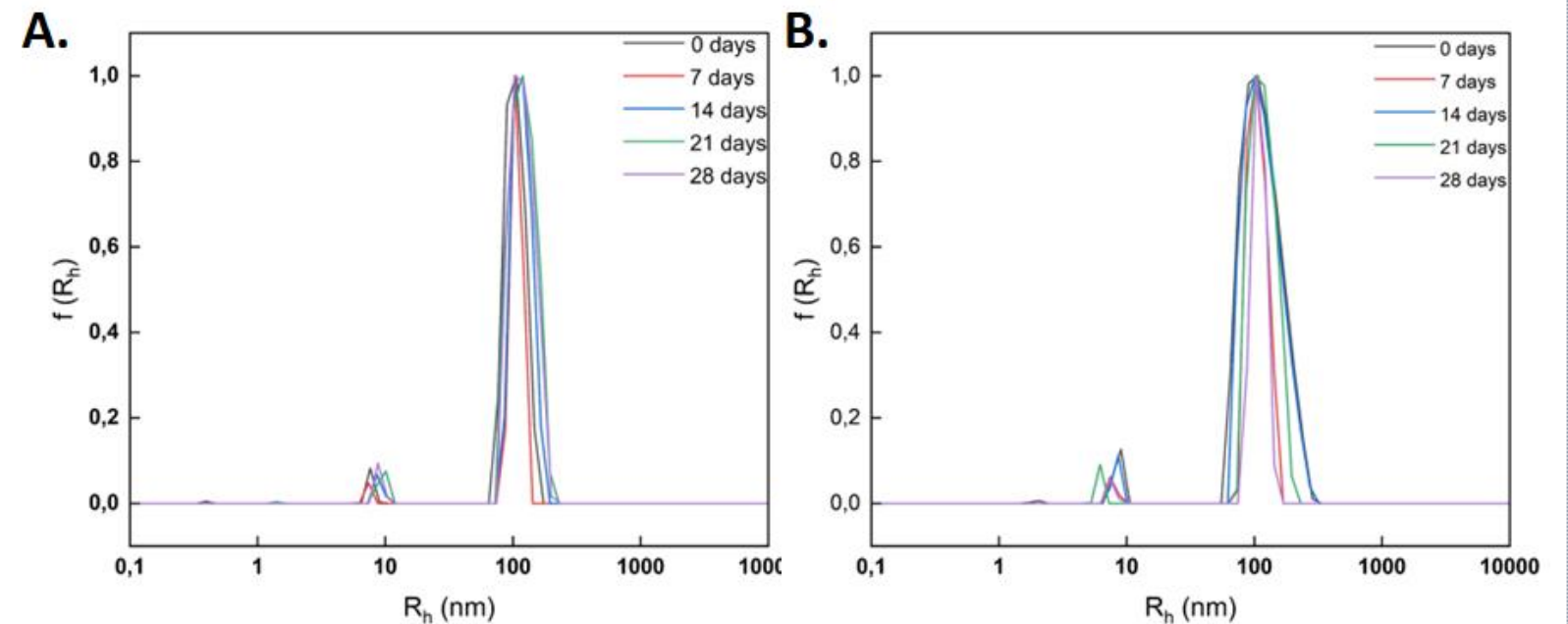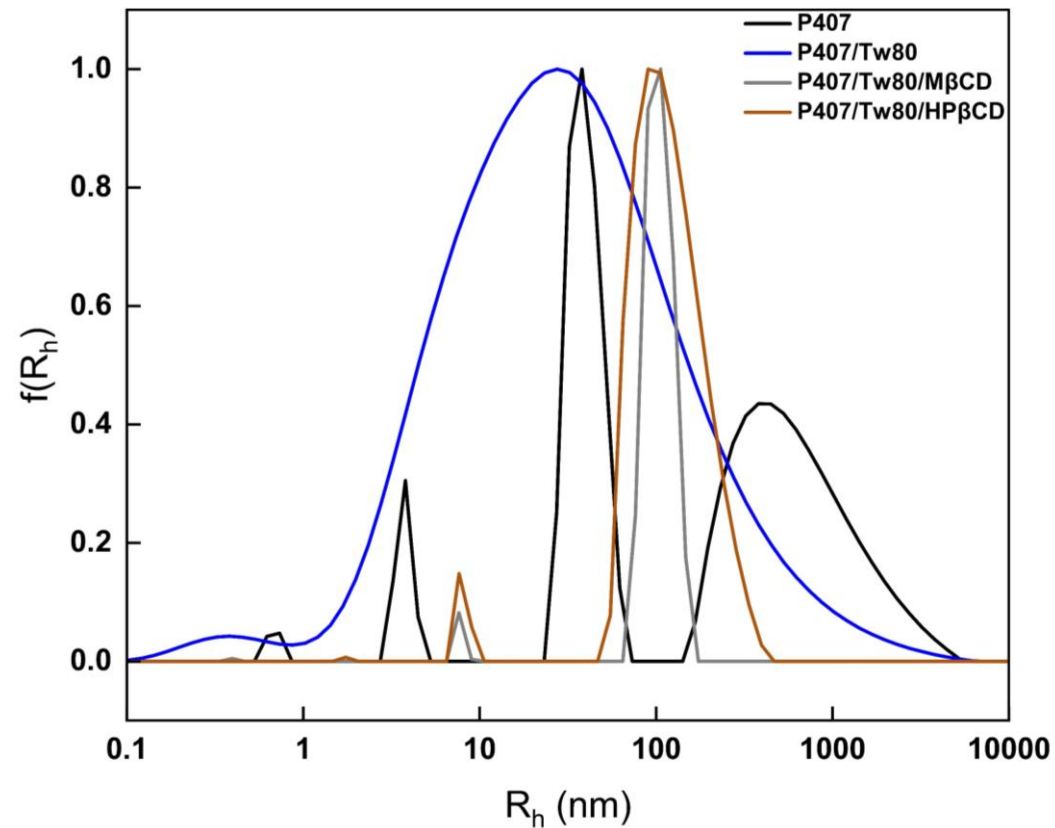| Formulation	Block copolymer	CD	APIs	Added value
Micelles	PEG-b-PLA	α-CD	Doxorubicin	· Sustained and controlled release rate of DOX from SMGel
				· Enhanced and prolonged inhibition efficacy against tumor cells in vitro compared to the free DOX
				· Biocompatibility
				· Superior rheological characteristics
NPs/ Micelles	PCL-b-PDMAEMA	β-CD	· Dexamethasone · Genes	· Superior transfection efficiency compared to the most popular nonviral gene transfection reagent
Micelles	· PDMAEMA · PCL		Doxorubicin	· High value of (%) encapsulation efficiency
				· pH responsiveness
				· Improved anticancer activity compared to free DOX
Supramolecular assemblies	PEG-PCL	β-CD	· Doxorubicin · Curcumin	· pH-responsive properties
				· Temperature-responsive properties
				· Controlled release rate of DOX and curcumin
				· Biocompatibility
Micelles	PEG-PLA	β-CD	Doxorubicin	· Improved antitumor activity compared to free DOX
				· Decreased cardiotoxicity compared to free DOX
Micelles	PEG-PCL	β-CD	Doxorubicin	·High values of (%) encapsulation efficiency and drug loading
Micelles	·poly(N-isopropylacrylamide) ·PEG	β-CD	Doxorubicin	· Thermoresponsive properties
				· Biocompatibility of blank micelles
				· Improved antitumor efficacy compared to free DOX
Hydrogelated micelles	PEG-b-PAA	α-CD	Cisplatin	· Sustained and controlled release rate of Cisplatin

2.3 Research implementation

1 Bibliographic research

2 Preformulation studies

3 Formulation studies

4 Drug loading and in vitro release studies

5 Ex-vivo optimization of nasal formulations

6 Pharmacokinetic studies

7 Results interpretation and dissemination

Results

*Stability assessment of **A.** P407/Tw80/MβCD and **B.** P407/Tw80/HPβCD systems.*

| Colloidal dispersions	w/w	R_h (Cumulant) (nm)[1]	PDI[2]	Number of peaks	R_h (Contin) (nm)[3]	Weight of peak (%)	z-potential (mV)
P407	-	97	0.4_9	3	1) 4 2) 39 3)598	1) 6% 2) 38% 3) 55%	-20.5±6.0
P407:Tw80	70:30	18	0.5_2	1	29	100%	-6.1±2.0
(P407:Tw80):MβCD	80:20	106	0.3_2	2	1) 8 2) 104	1) 3% 2) 97%	-12.9±12.0
(P407:Tw80):HPβCD	80:20	100	0.3_0	2	1) 9 2) 114	1) 3% 2) 97%	-6.9±8.4

[1] R_h of three replicates of each sample measured by the Cumulant method
[2] PDI indicates average polydispersity index
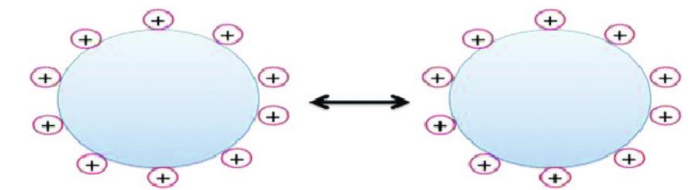[3] R_h of three replicates of each sample measured by the Contin method
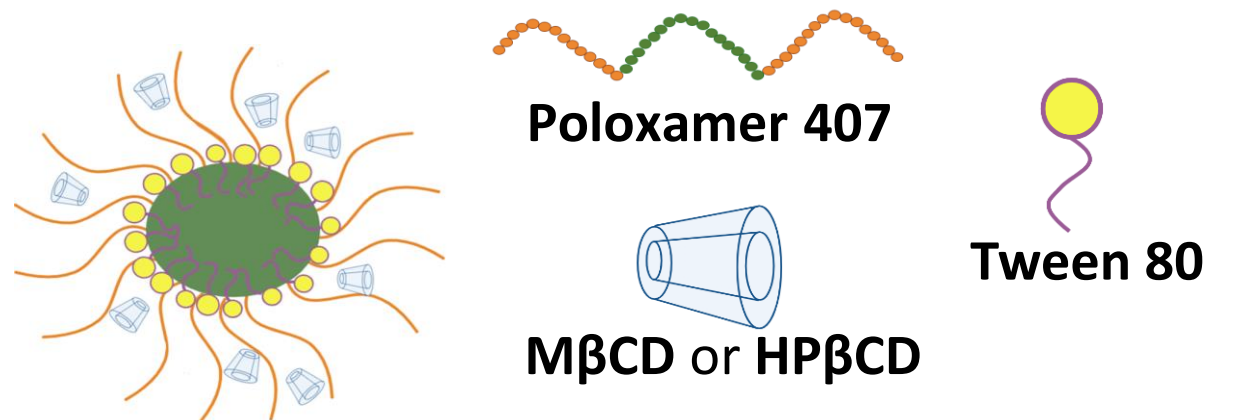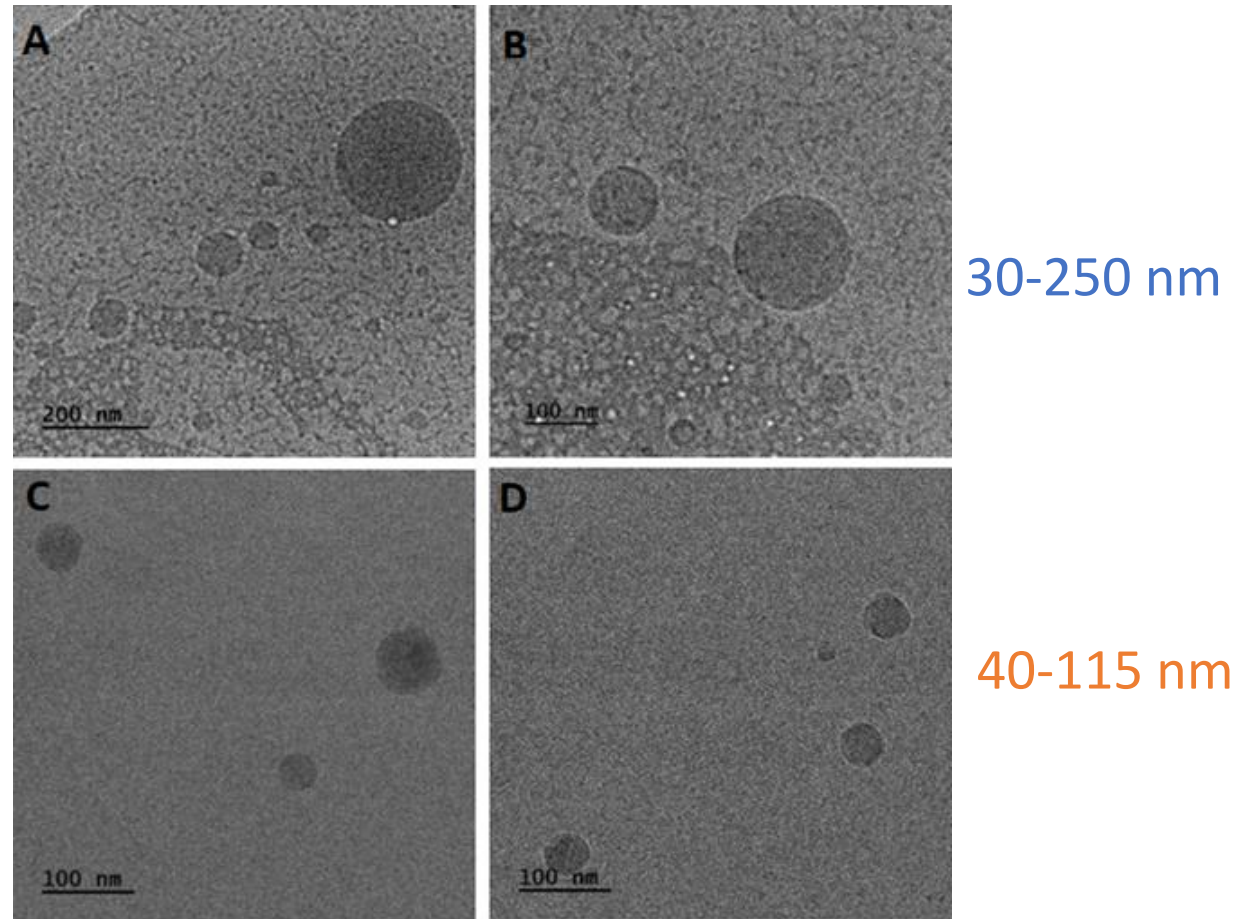
30-day stability study

STABLE systems ✓
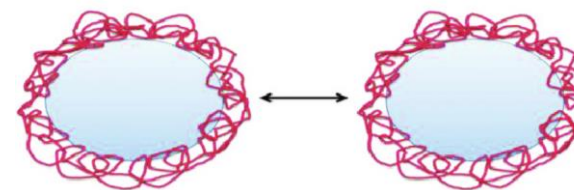
Steric repulsion

Electrostatic interactions

3.2 Morphological characterization and in vitro cytotoxicity assessment

Cryo-TEM micrographs of hybrid P407/Tw80/MβCD (A, B) and P407/Tw80/HPβCD (C, D) systems.

30-250 nm

40-115 nm

Poloxamer 407

MβCD or HPβCD

Tween 80

MTT cell viability assay on HEK-293 of hybrid colloidal systems: pure P407, P407/Tw80, P407/Tw80/MβCD and P407/Tw80/HPβCD systems. Cell viability is expressed as % cell viability ± SD between two experiments.
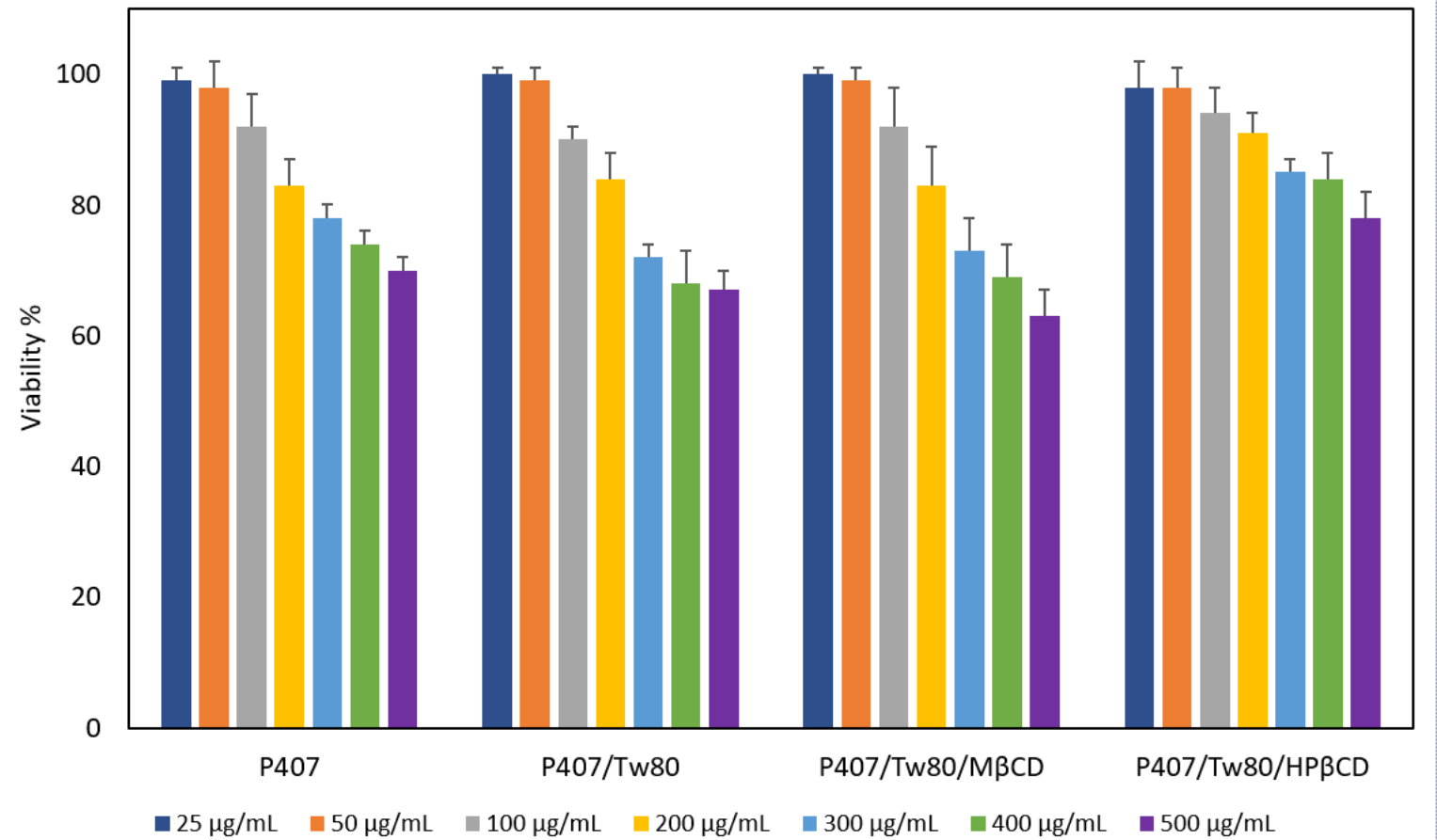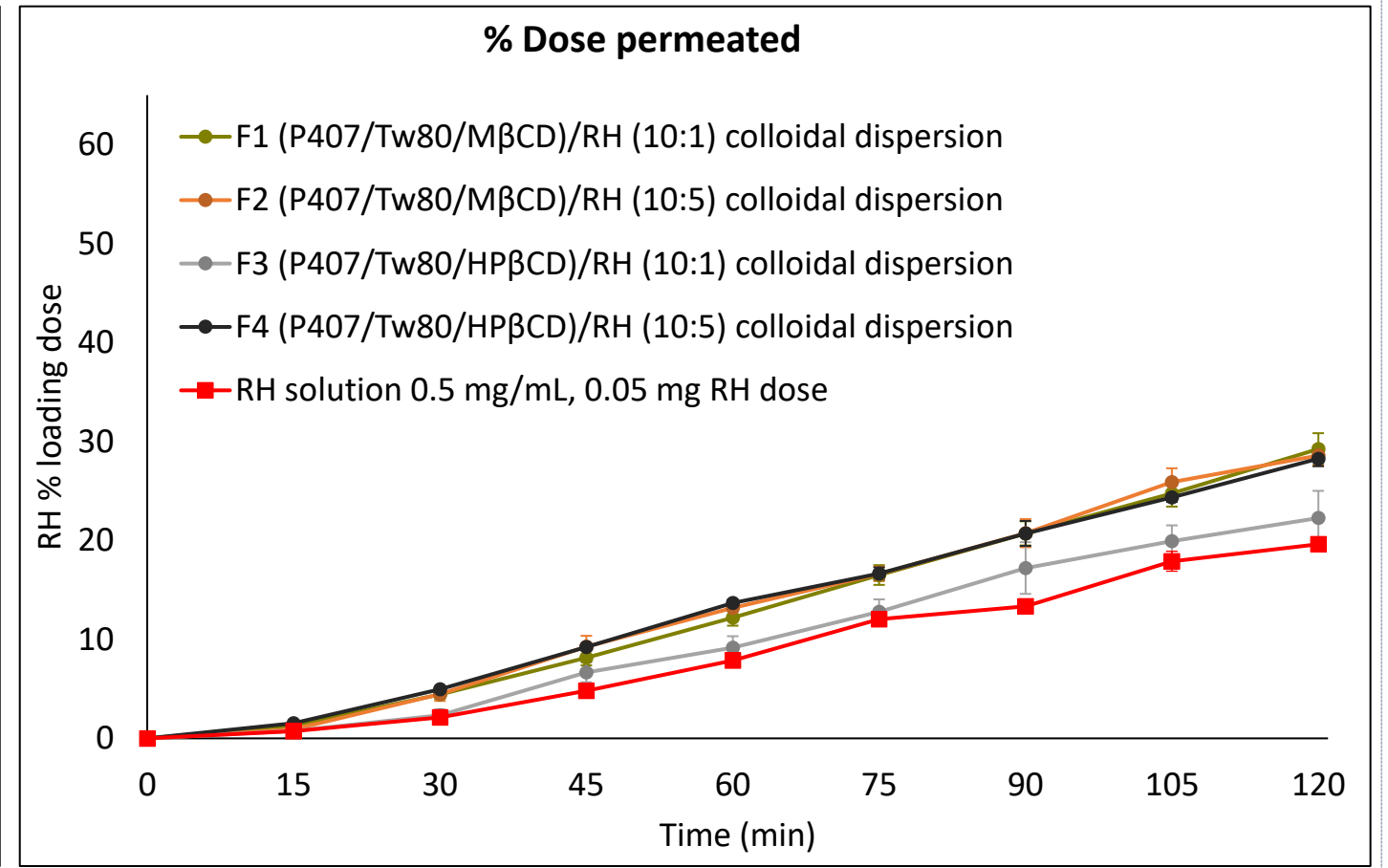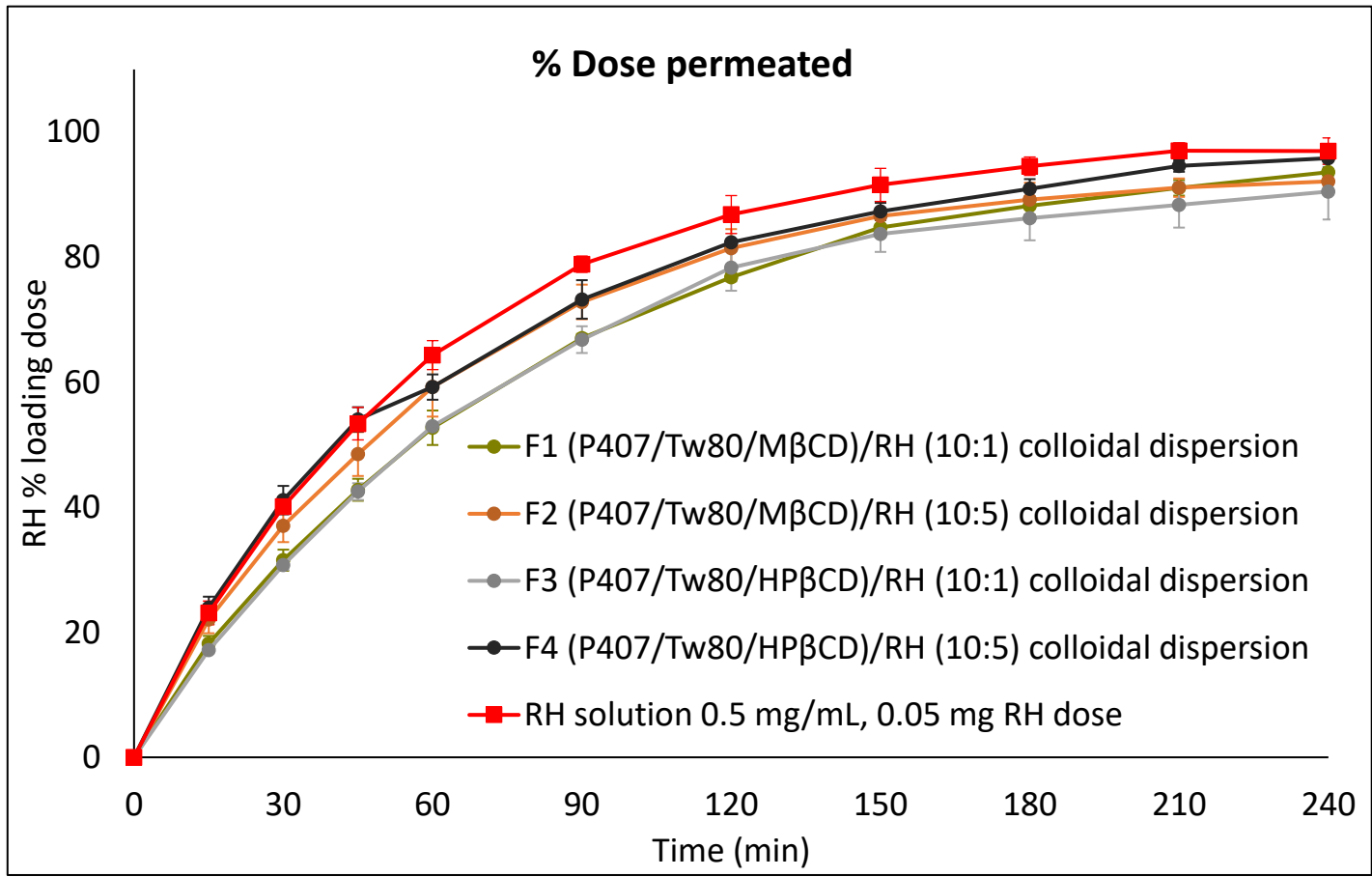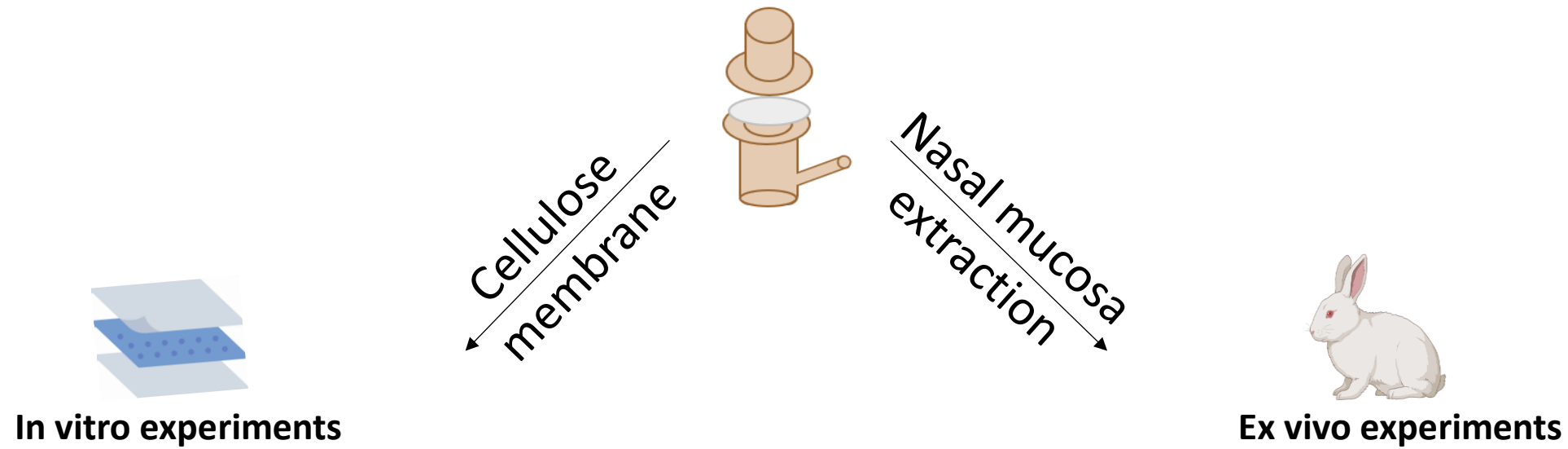

Dose-dependent toxicity   Material-dependent toxicity

3.3 In vitro and ex vivo experiments results

4. Conclusions

- The development of strong interactions between polymer, surfactant and CD may be possibly associated with the formation of an inclusion complex

- The structures visualized in cryo-TEM images had spherical configurations.

- RH release > 90% in all cases, with the drug release exhibiting a progressive increase over the duration of the experiment.

- Ex vivo permeation studies revealed a significant increase in the percentage of RH loading dose permeated through rabbit nasal mucosa compared to pure RH solution.

- Further studies are ongoing to evaluate the in vivo serum and brain pharmacokinetic profiles after nasal administration of the developed formulations.

Article

Fabricating Polymer/Surfactant/Cyclodextrin Hybrid Particles for Possible Nose-to-Brain Delivery of Ropinirole Hydrochloride: In Vitro and Ex Vivo Evaluation

Elmina-Marina Saitani [1], Natassa Pippa [1], Diego Romano Perinelli [2], Aleksander Forys [3], Paraskevi Papakyriakopoulou [1], Nefeli Lagopati [4,5], Giulia Bonacucina [2], Barbara Trzebicka [3], Maria Gazouli [4], Stergios Pispas [6] and Georgia Valsami [1,*]