IECP 2020
The 1st International Electronic Conference on Pharmaceutics
01–15 DECEMBER 2020 | ONLINE
Chaired by DR. ANDREA ERXLEBEN and PROF. DR. ELISABETTA GAVINI
pharmaceutics
MDPI

Fakhara Sabir [1], Gábor Katona [1], Ruba Ismail [1] and Ildiko Csoka [1]

[1] Faculty of Pharmacy, Institute of Pharmaceutical Technology and Regulatory Affairs, University of Szeged, H-6720 Szeged, Hungary

* Corresponding author: csoka@pharm.u-szeged.hu, Tel.+36-62-546-116

SZTE UNIVERSITY of SZEGED HUNGARY

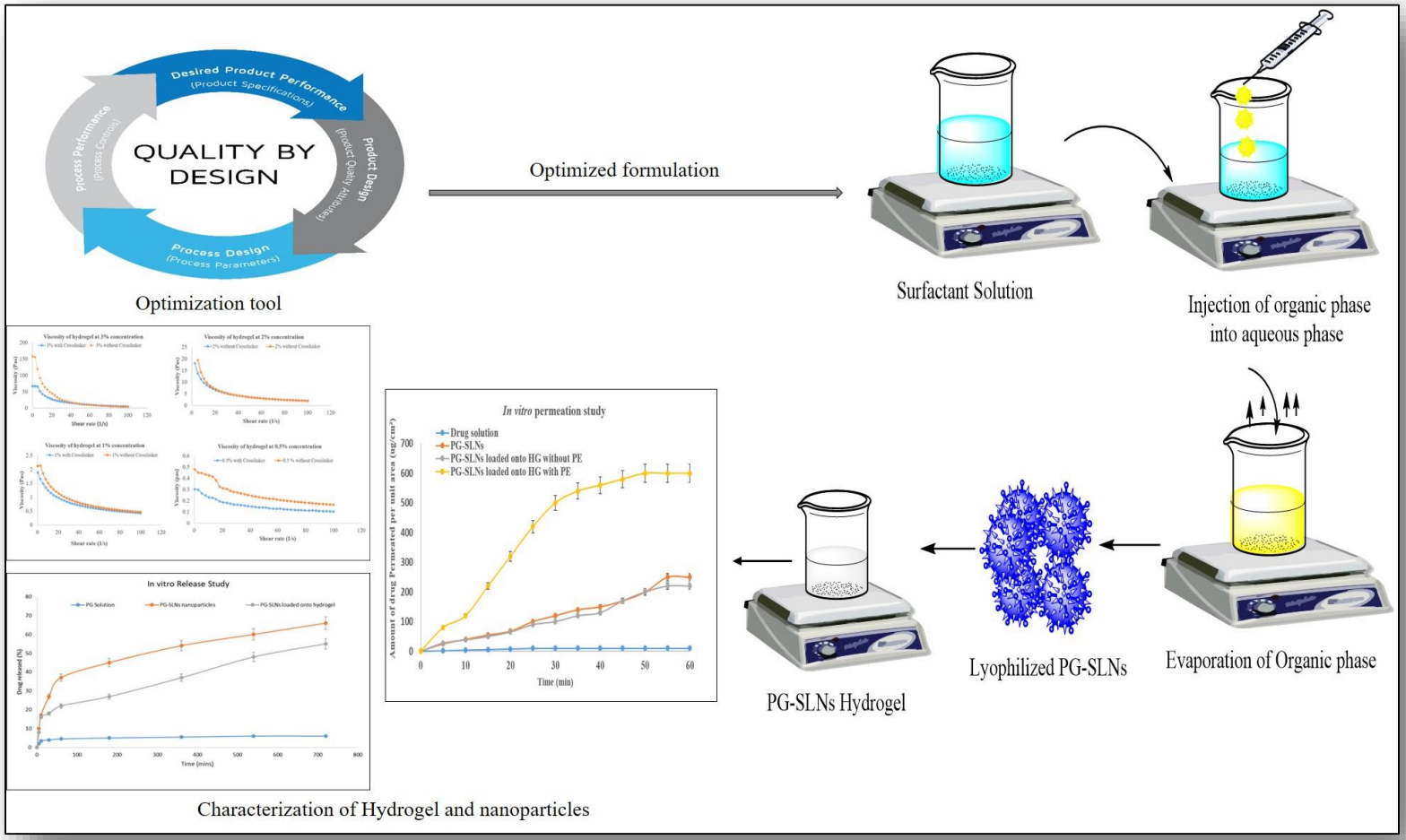
Development and Optimization of N-Propyl gallate Encapsulated Hyaluronic Acid Based Hydrogel for Nose to Brain Delivery by Applying Quality by Design Methodology

Abstract: The aim of this research work was to develop *n*-propylgallate encapsulated solid lipid nanoparticles (PG-SLNs) and load them into a Hyaluronic acid (HA) based hydrogel (HG) for intranasal delivery. Simple modified solvent injection technique was used for the preparation of the PG-SLNs via the Quality-by Design (QbD) approach. The optimized PG-SLNs with an average hydrodynamic diameter of 103±46.04 nm with polydispersity index (PDI) of 0.16±0.001 and zeta potential of -36±4.78 mV of were obtained. The percentage yield of PG-SLNs was found to be 80.78±0.1% with an encapsulation efficiency of 84±0.5% and loading capacity of 60±0.1%. In vitro drug release from the hydrogel containing PG-SLNs showed sustained release profile with a lower burst effect (less than 20%) and controlled release to a greater extent within 720 mints following diffusion based release kinetics. The in vitro permebility studies showed the total permeation of PG from HG was 600 µg/cm^2 within 60 mints that showed significant permeation of PG. Findings of this work strongly emphasize that PG-SLNs loaded hydrogel and permeation enhancer holds significant potential to be delivered through intranasal route.

Keywords: nose to brain; n-propylgallate; SLN; hydrogel; Quality by Design

IECP 2020

Graphical Abstract



IECP 2020

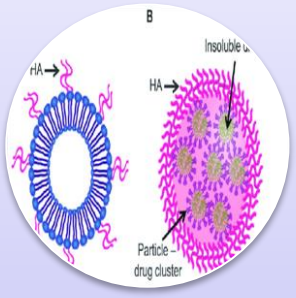
Aims and Objective of study

- Development and loading of PG-SLNs into chemically linked HA hydrogel with permeation enhancer (Transcutol-P) and crosslinker glutaraldehyde suitable for nose to brain delivery by applying QbD.
- Characterization of developed nanoparticles encapsulated with PG and PG loaded HA-hydrogel for intranasal delivery.

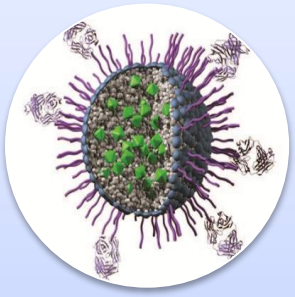
IECP 2020

Methodology

Application of QbD design and DOE for development of PG-SLNs



Development of Optimized PG-SLNs via Solvent injection method



Development of PG-SLNs loaded HA based Hydrogel

Characterization of NPs and Hydrogel

Particle size,Zeta potential,PDI,mucoadhesivity,viscosity,permeability, release studies

IECP 2020

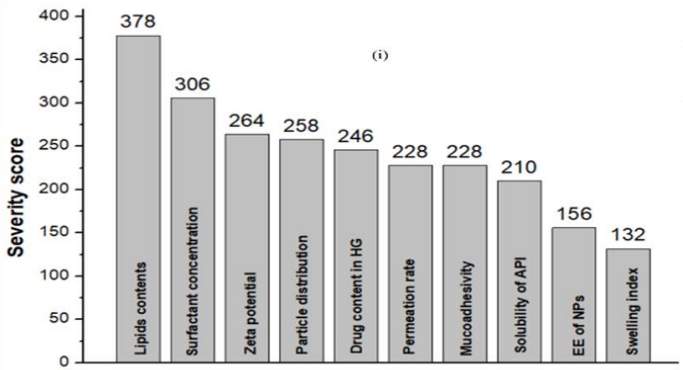
Results and Discussion

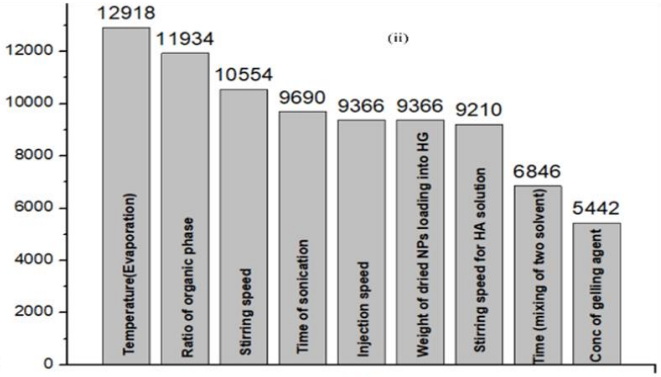
Risk Assessment

CQA / CPP	Ratio of organic phase (Preparation of lipid solution)	Sonication time (Preparation of lipid solution)	Stirring speed (Preparation of surfactant solution)	Injection speed (Mixing of organic and aqueous phase)	Stirring speed (Mixing of organic and aqueous phase)	Temperature (Evaporation)	Stirring speed(Hydrogel preparation) (Preparation of HA Solution)	Weight of dried PG-SLNs added (Preparation of HA Solution)	Time in hours for mixing (Addition of GA and phenolethanolamine)
Particle size	High	High	High	High	High	High	Low	Low	Low
Zeta potential	Low	Low	Medium	Medium	Medium	Medium	Low	Low	Low
Permeation rate	Low	Low	Low	Medium	Low	Medium	Medium	Medium	High
Mucoadhesivity	Medium	Low	Low	Low	Low	Low	High	High	High
Swelling index	Low	Low	Low	Low	Low	Low	Medium	High	High
Drug contents of HG	Low	Low	Low	Low	Low	Low	Medium	Medium	High
EE of NPs	Medium	Medium	Medium	Medium	Medium	High	Low	Low	Low
Viscosity of gel	Low	Low	Low	Low	Low	Low	High	High	High
Lipids contents	High	Medium	Medium	High	Medium	High	Low	Low	Low
Surfactant concentration	High	Medium	High	High	High	High	Low	Low	Low

CQA / QTPP	Route of administration	Dissolution profile	Stability	Therapeutic indication	Permeation	Brain distribution
Particle size	High	High	High	High	High	High
Zeta potential	Medium	Low	High	High	High	High
Permeation rate	High	High	Medium	Low	High	High
Mucoadhesivity	High	High	Medium	Low	High	Medium
Swelling index	Low	Medium	Low	Low	High	Medium
Drug contents of HG	Low	High	Medium	High	High	High
EE of NPs	Low	High	Medium	Medium	High	High
Viscosity of gel	High	High	Medium	Medium	High	Medium
Lipids contents	High	High	High	Medium	High	High
Surfactant concentration	High	High	High	Medium	High	High

Process	CPP	Occurrence
Preparation of lipid solution	Ratio of organic phase	High
Preparation of lipid solution	Sonication time	Medium
Preparation of surfactant solution	Stirring speed	Low
Mixing of organic and aqueous phase	Injection speed	High
Mixing of organic and aqueous phase	Stirring speed	Low
Evaporation	Temperature	High
Preparation of HA Solution	Stirring speed(Hydrogel preparation)	Medium
Preparation of HA Solution	Weight of dried PG-SLNs added	Medium
Addition of GA and phenolethanolamine	Time in hours for mixing	High

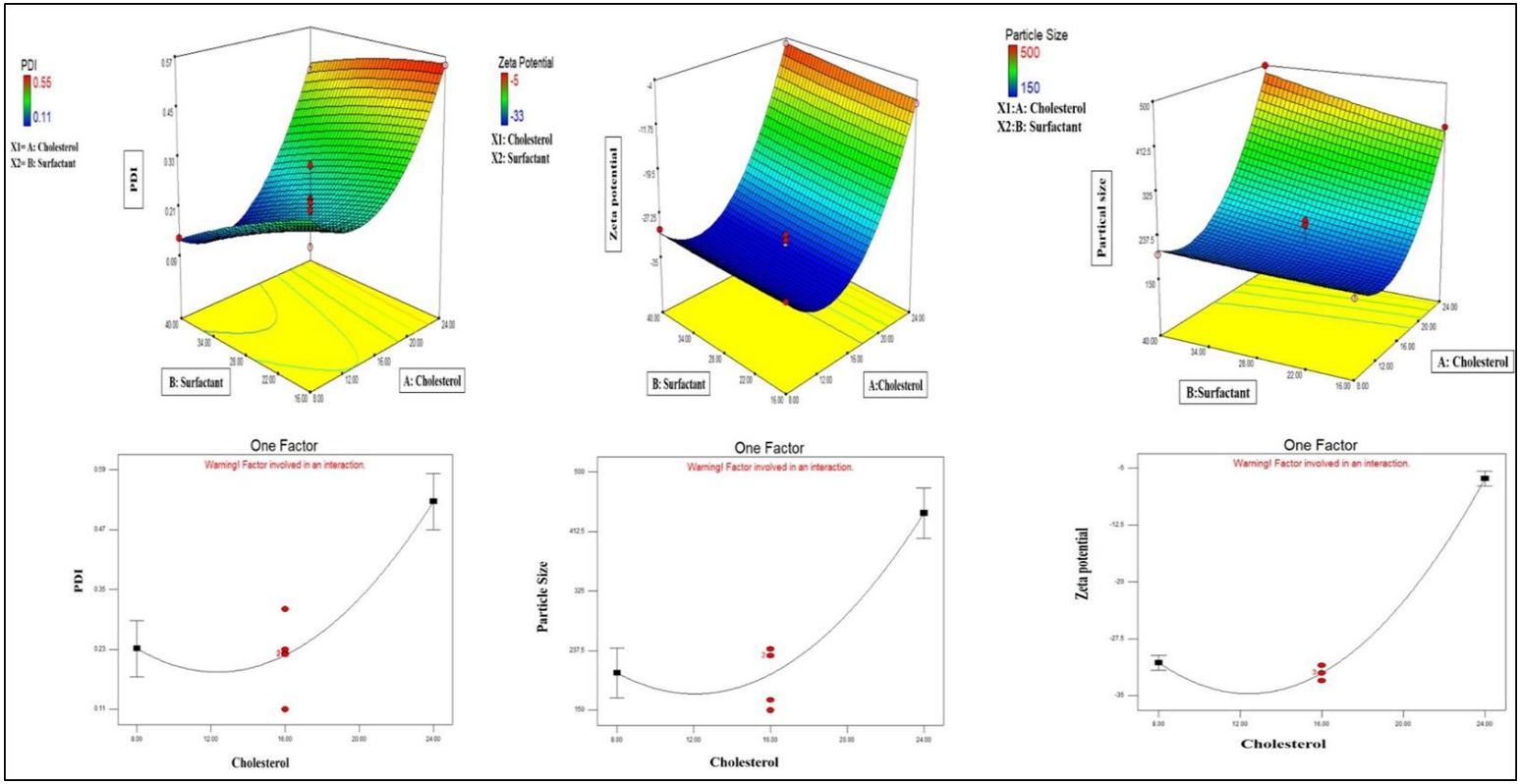




****Interdependence rating and estimation of the QTPP and CQAs and CQAs-CPPs, and Pareto charts showing the severity/impact among selected

IECP 2020

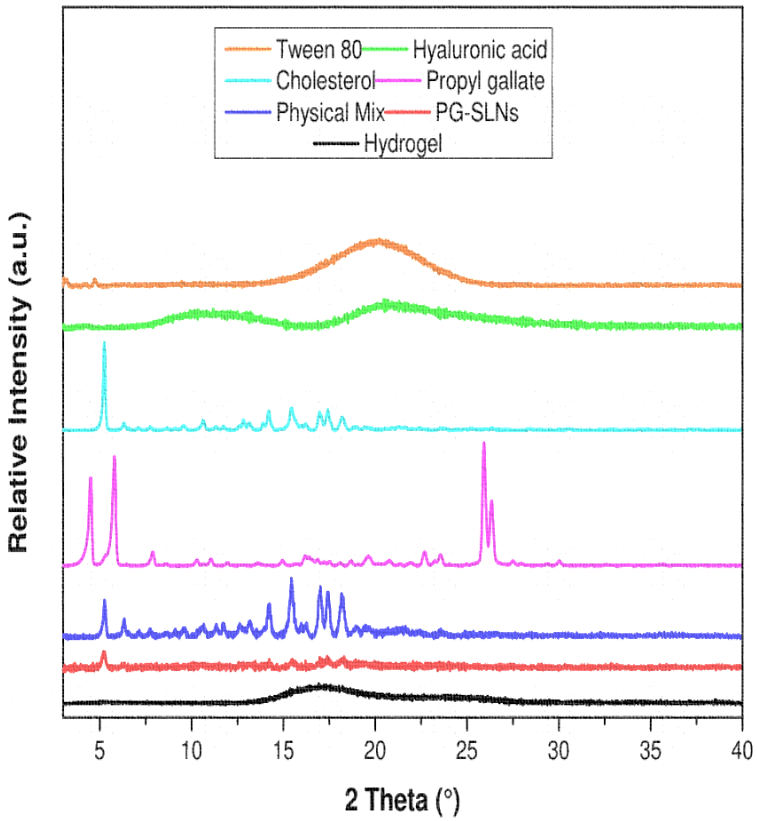
Results and Discussion
Response Surface Quadratic Model

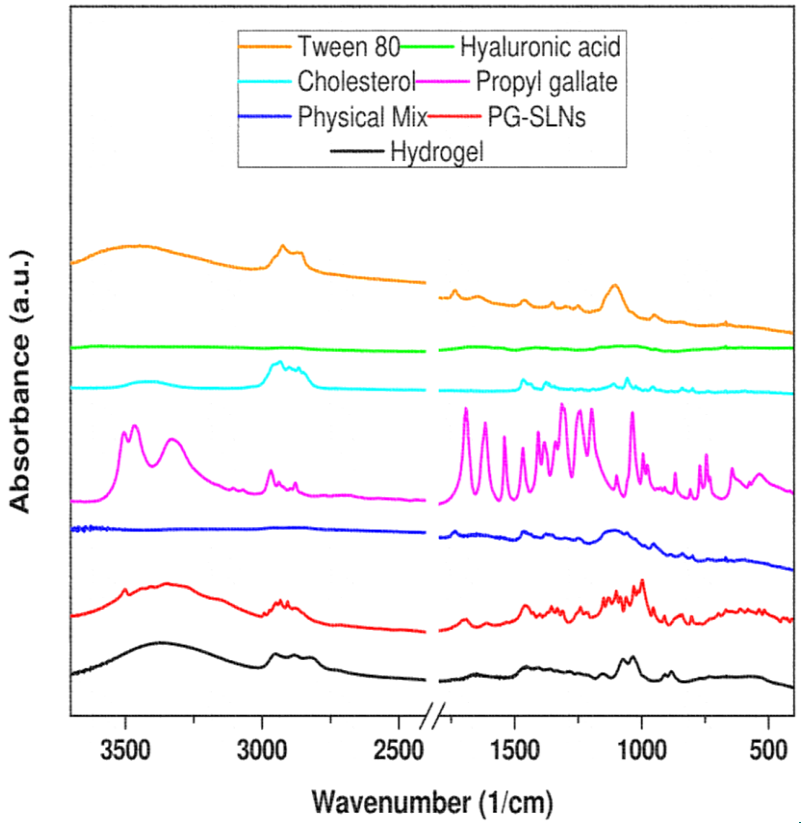


3D surface plot show combine effect of cholesterol and surfactant on Particle size,PDI and Zeta potential.
One factor interaction plot showed Cholesterol was significantly invovled in effecting the all studies factors under obervation.

IECP 2020

Results and Discussion
FTIR and XRPD

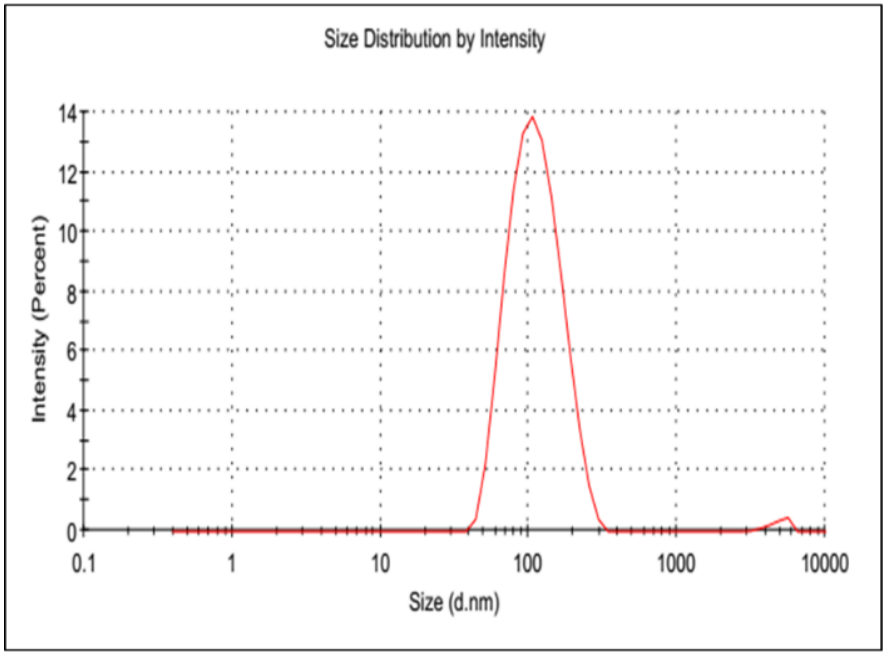


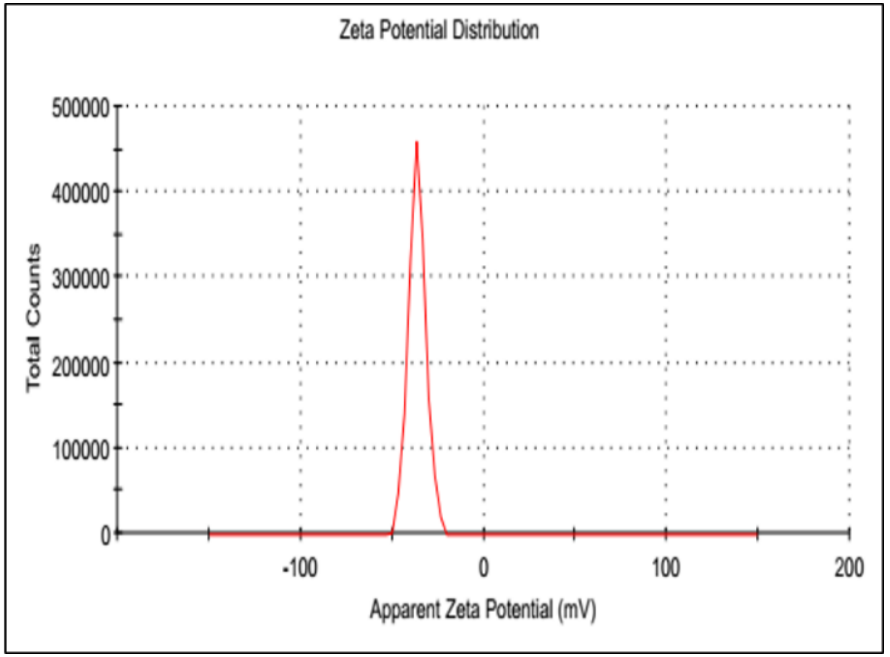


****No interaction was found between the formulation component and final formulation, XRPD results show conversion of crystalline form of PG into amorphous form in PG-SLNs

IECP 2020

Results and Discussion
Particle Size, Zeta Potential, PDI



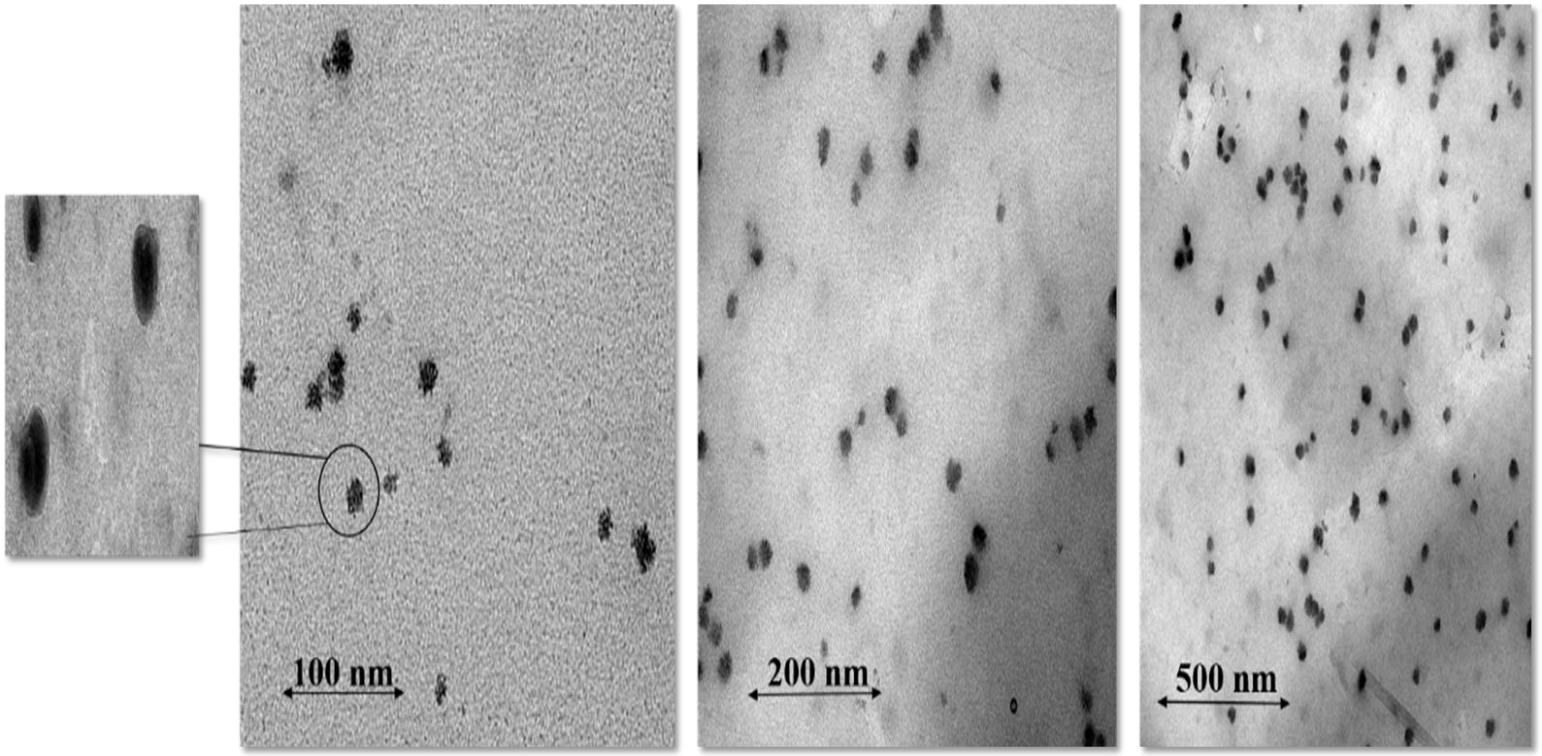


Zeta sizer were used for analysis

PG-SLNs with an average size of 103±46.04 nm,PDI of 0.16±0.001, Zeta potential of -36±4.78 mv

IECP 2020

Results and Discussion
Morphological study (TEM analysis)



***Particles were spherical in shape and within nanorange
And results were comparable with particle size analysis of zeta sizer

IECP 2020

Results and Discussion
Characterization of Hydrogel

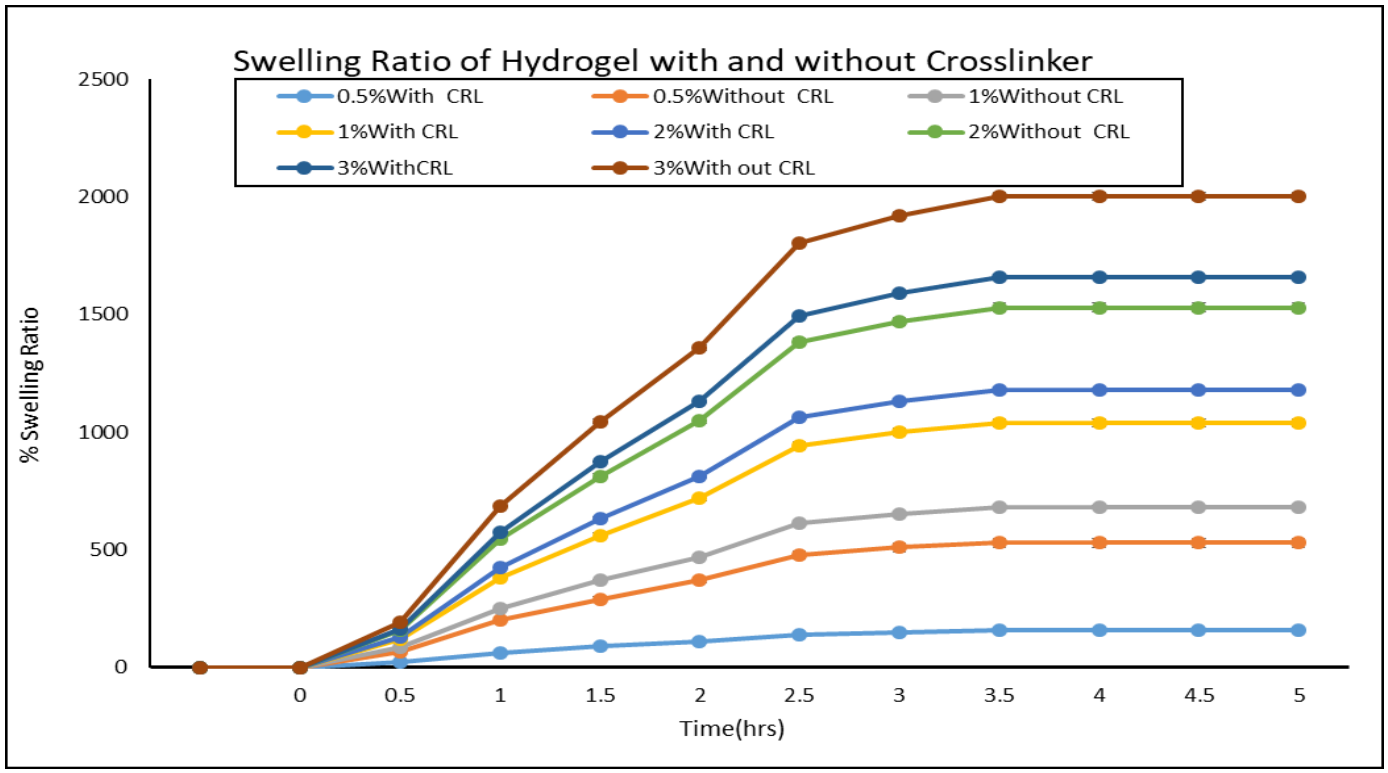
Conc. Hydro gel	pH value of different conc of HA-Hydrogel	% Swelling ratio	% Drug Contents	Spread ability mm^2	Muco-adhesivity	Viscosity with CL(Pas)	Viscosity without CL(Pas)
0.5	5.3±0.2	400	78± 2.5	222.45 ± 0.22	***	0.112	0.181
1	5.2±0.3	900	82±3.3	360±0. 33	Good	1.88	2.11
2	5.5±0.4	1300	80±1.4	320±0. 44	Good	14.29	15.45
3	5.9±0.6	2000	79±4.2	340±0. 012	Good	66.34	157

***The hydrogel at concentration 1% show best results in all performed studies. We selected this concentration for further in vitro release and permeation testing

IECP 2020

Results and Discussion

Swelling study results showed that hydrogel without cross linker showed greater swelling index. it can be concluded that by adding cross-linker, mechanical strength of hydrogel enhances and has more precise control on release of nano-carrier from gel matrix as compare to simple hydrogel which is mechanically fragile that can get fractured easily thus larger pores may be created through which nano-carriers can easily escape with initiating a burst release

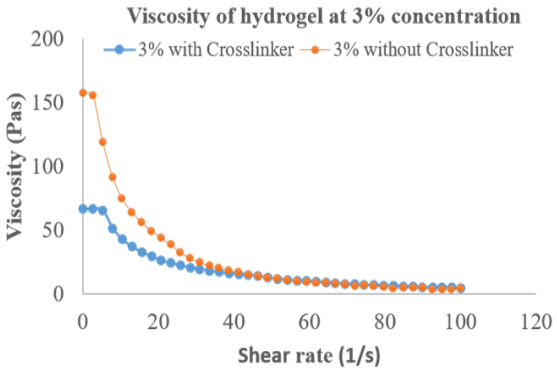


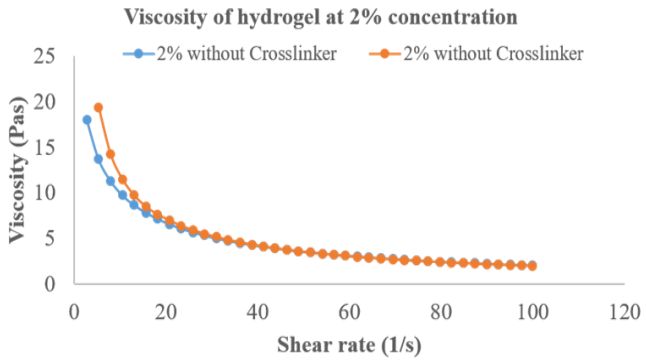
IECP 2020

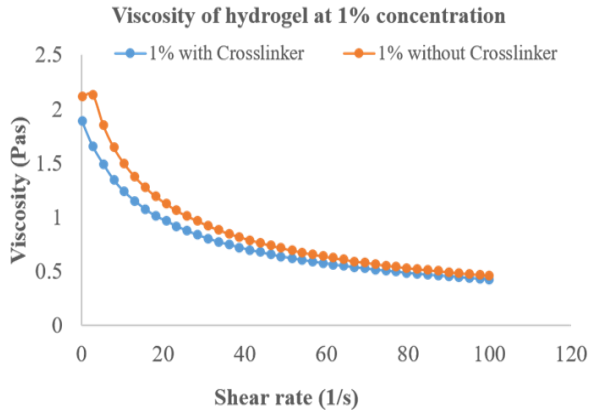
Results and Discussion

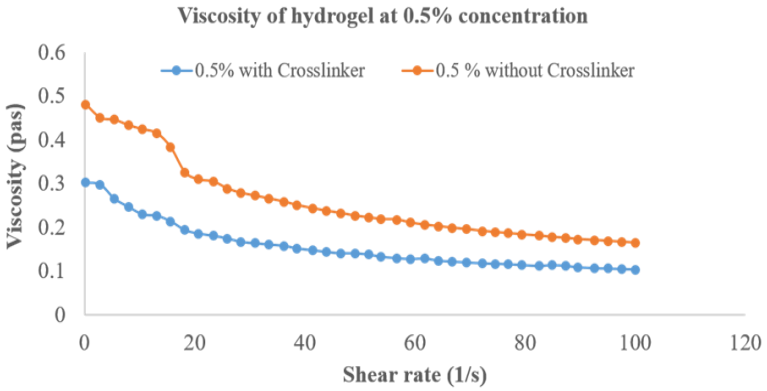
Viscosity measurement

At different concentration of hyaluronic acid viscosity of hydrogel was measured to get optimized concentration suitable for intranasal administration





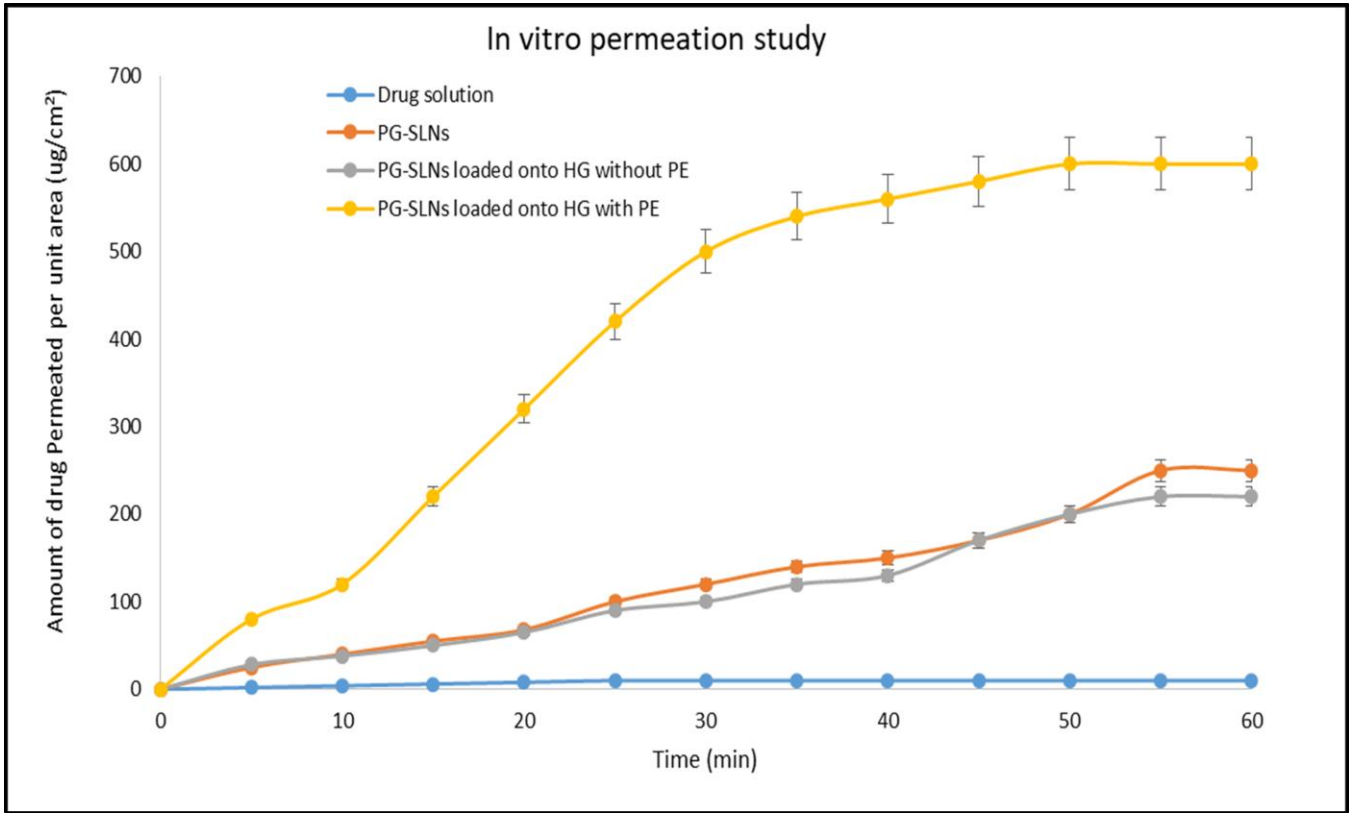




IECP 2020

Results and Discussion

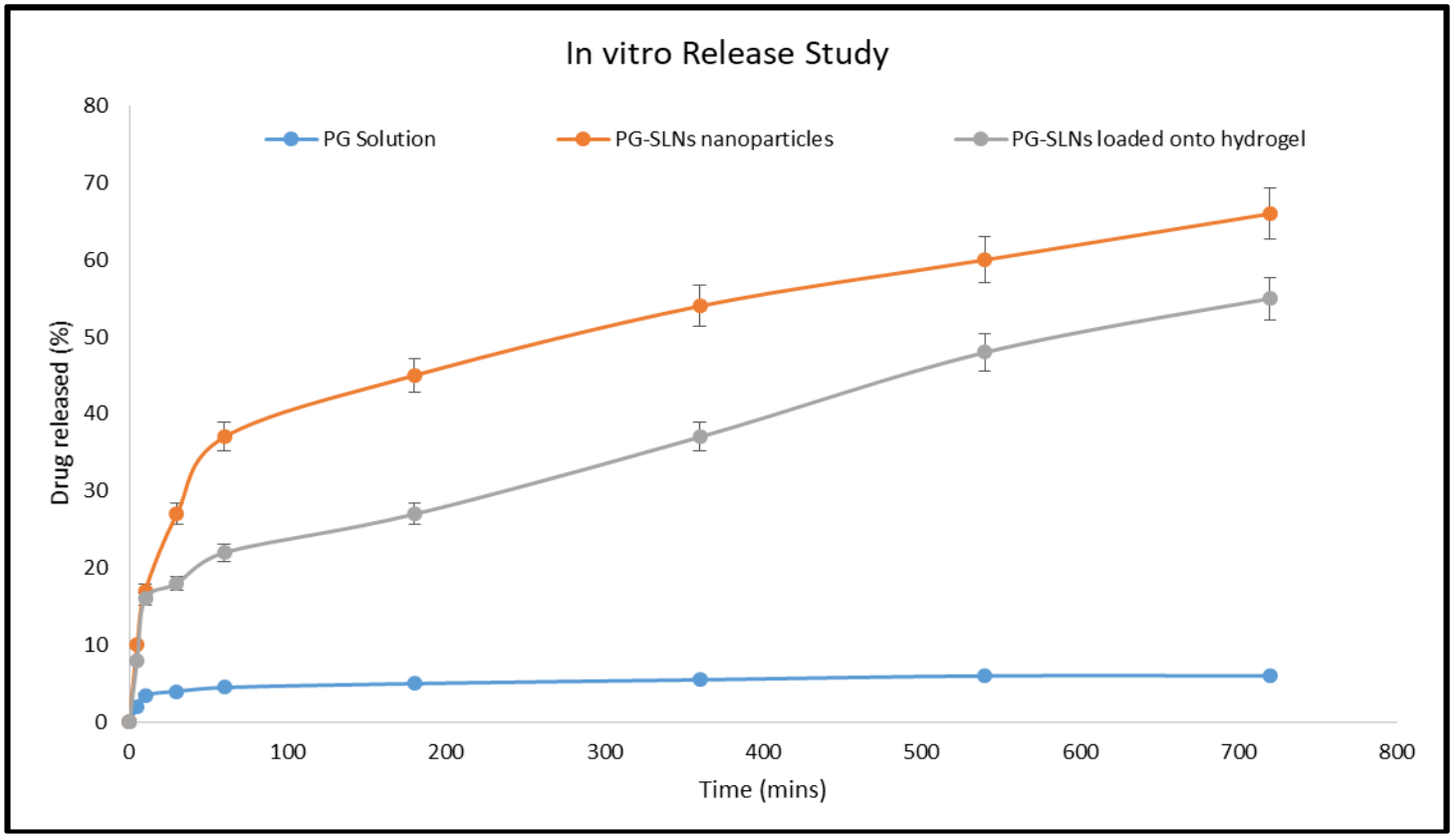
For In vitro permeability study of nano-formulation and hydrogel Side bi side equipment was used for permeation study



IECP 2020

Results and Discussion

In vitro Release study of Nano-formulation and Hydrogel showed initial burst released in case of hydrogel has been slower and controlled to a greater extent



IECP 2020

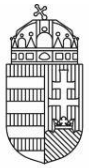
Conclusions

- PG-SLNs were successfully prepared in this study using the modified injection method. For the optimization of formulation and process parameters, initial risk assessment study was applied as a part of QbD approach.
- The PG-SLNs showed an average size of roughly 100 nm with a homogenous distribution, negative surface charge, drug release reaching roughly 60% and high EE (> 80%) (complying with the predefined QTPP).
- The viscosity and mucoadhesivity results reflect enhanced adherence property of optimized HA-HG loaded with PG-SLNs. Compared to PG-SLNs, in vitro permeation studies showed the superiority of the PG-SLNs loaded into HA-HG and transuctol-P system with a less initial burst effect and more sustained release.
- The optimized platform provides in vitro proof of the potential of combining the advantages of lipid based NPs with HG as a promising intransal delivery system.

IECP 2020

Acknowledgments

The authors want to express their acknowledgement to the supporters. This study was supported by the Ministry of Human Capacities, Hungary (Grant 20391-3/2018/FEKUSTRAT) and by the National Research, Development and Innovation Office, Hungary (GINOP 2.3.2-15-2016-00060) projects.



NATIONAL RESEARCH, DEVELOPMENT
AND INNOVATION OFFICE
HUNGARY

IECP
2020

References

1. Mistry, A., S. Stolnik. ; L. Illum, Nanoparticles for direct nose-to-brain delivery of drugs. Int.J.Pharm, 2009. 379(1): p. 146-157.
2. Kumar, M., et al., Evaluation of neuropeptide loaded trimethyl chitosan nanoparticles for nose to brain delivery. Int.J Biol.Macro, 2013. 61: p. 189-195.
3. Gonçalves, J., et al., Nose-to-brain delivery of levetiracetam after intranasal administration to mice. Int.J.Pharm, 2019. 564: p. 329-339.
4. Eskandani, M., et al., Formulation, characterization, and geno/cytotoxicity studies of galbanic acid-loaded solid lipid nanoparticles. Pharm.Bio, 2015. 53(10): p. 1525-1538.

IECP 2020

Dr. Ildiko Csoka

Dr.Gábor Katona

Dr. Pallagi Edina

Dr.Rita Ambrus

Dr. Dorina Gabriella Dobó

Dr. Ruba Ismail

IECP 2020