Improving brain targeting efficiency by nose-to-brain delivery of lipidic and polymeric nanoparticles: a focus on depression and anxiety treatments

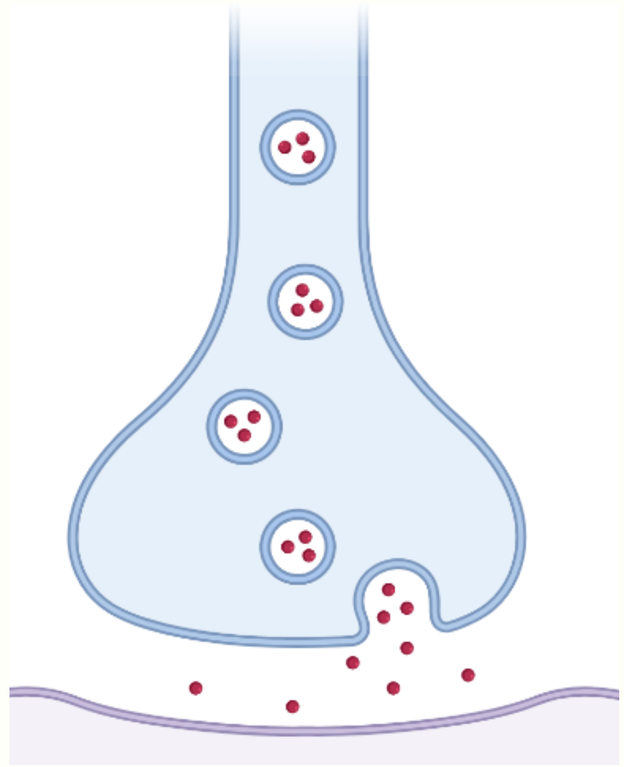
Margarida Alberto[1] , Ana Cláudia Paiva-Santos[1,2], Francisco Veiga[1,2], Patrícia C. Pires[1,2,3*]

1. Faculty of Pharmacy (FFUC-UC), University of Coimbra, Azinhaga de Santa Comba, 3000-548 Coimbra, Portugal
2. REQUIMTE/LAQV, Group of Pharmaceutical Technology, Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal
3. Health Sciences Research Centre (CICS-UBI), University of Beira Interior, Av. Infante D. Henrique, 6200-506 Covilhã, Portugal
*Corresponding author: patriciapires93@gmail.com or patriciapires@ff.uc.pt.

INTRODUCTION: DEPRESSION AND ANXIETY

The most accepted theory for the pathogenesis of depression is based on a monoaminergic transmission disorder due to the complex interaction of several social, psychological and biological factors.
Most drugs used in the treatment of depression increase the availability of these neurotransmitters in the synaptic cleft.

Anxiety is associated with the inhibition of the synaptic transmission of γ-aminobutyric acid (GABA). Pharmacological treatment of anxiety includes anxiolytic drugs such as benzodiazepines.



TREATMENT: DEPRESSION AND ANXIETY

Root of administration used for the treatment

Disadvantages of oral administration of drugs:

- Exposition of the drug to the first pass hepatic metabolism;
- Regular administrations needed to ensure the constant presence of the drug at the site of action;
- The amount of drug that reaches the site of action is restricted by the action of the blood brain barrier and blood-cerebrospinal fluid that act as a barrier,
- Fluctuations in plasma concentrations lead to side effects and loss of efficacy

INTRANASAL ADMINISTRATION:

A possible alternative for the treatment of depression and anxiety

Advantages:

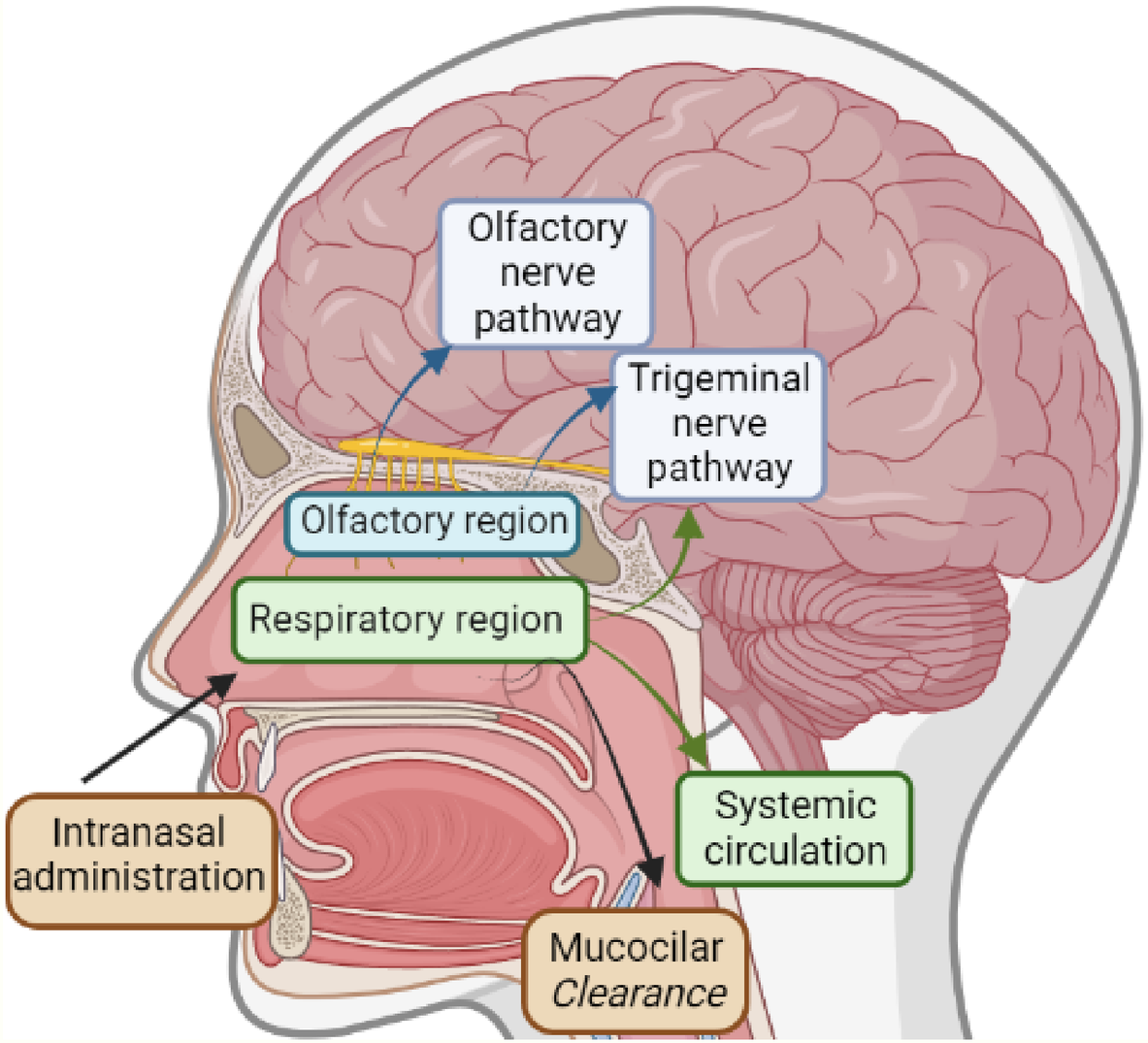
- Overcome the blood brain barrier,
- Avoid the first pass hepatic metabolism;
- Minimize the side effects caused by drugs administered though the systemic circulation;
- Reduce the dosage necessary to achieve the therapeutic effect;
- Direct the active molecule to the site of action;
- Direct contact with the CNS.

INTRANASAL ADMINISTRATION:

A possible alternative for the treatment of depression and anxiety

Disadvantages:

- Physical removal of the drug from the nasal cavity by mucociliary clearance mechanisms;
- Enzymatic degradation in the mucus and nasal epithelium layer;
- Volume of formulation that can be administered that is limited to 25 – 200 µl, which turns this route of administration more appropriate for potent drugs.



NASAL CAVITY ANATOMY AND TRANSPORT

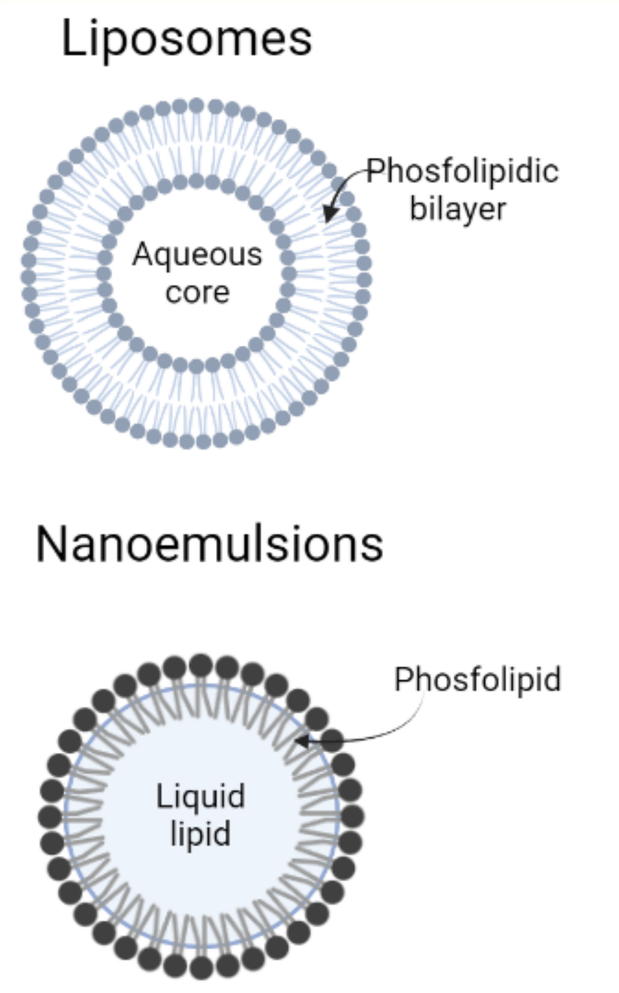
There is a direct connection between the nasal cavity and the CNS, which allows the transport of several substances to the brain, being the only place in the human body where the nervous system is in direct contact with the surrounding environment.

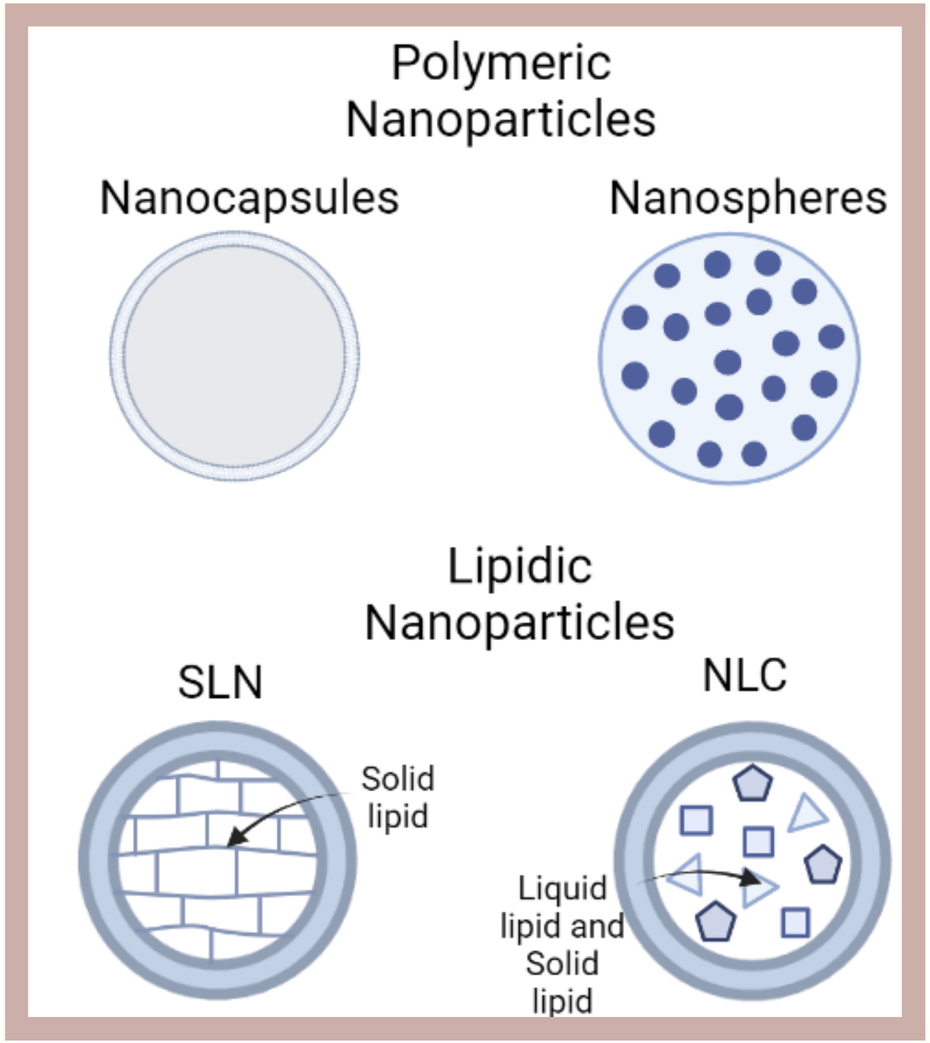
NANOMETRIC DRUG TRANSPORT SYSTEMS

Nanometric drug transport systems are formulations that help transporting the drug to the place of action, allowing to modulate the time and quantity of drug released.

Main types of nanometric systems:

- Liposomes,
- Nanoemulsions,
- Polymeric nanoparticles (nanocapsules and nanospheres)
- Lipidic nanoparticles (solid lipid nanoparticles (SLN) and nanostructured lipid transporters (NLC)).





PURPOSE OF THE WORK

This work approaches, in summary, studies already developed with the goal of formulating nanoparticles for intranasal administration of drugs for the treatment of these pathologies.

METHODS

On 10 of August of 2022, a pubmed database review with the keywords "nanoparticle AND (depression OR anxiety) AND (intranasal OR nasal)" revealed 28 results. Applying exclusion criteria 12 articles of fundamental research were included in this work.

IN VIVO PHARMACOKINETIC STUDIES

Different parameters were calculated:

$$Entrapment\ efficiency\ (EE\%) = \frac{(Total\ drug - free\ drug)}{Total\ drug} \times 100$$

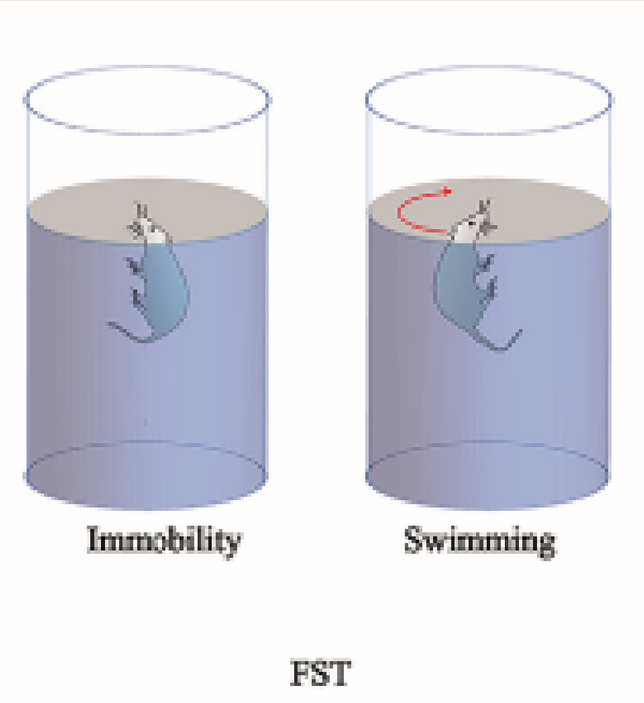
$$Drug\ loading\ (DL\%) = \frac{(Total\ drug - free\ drug)}{Total\ weight\ of\ nanoparticles} \times 100$$

$$Drug\ targeting\ efficiency\ (DTE\%) = \frac{\left(\frac{AUCbrain}{AUCblood}\right) i.n}{\left(\frac{AUCbrain}{Aucblood}\right) i.v} \times 100$$

$$Direct\ transport\ percentage\ (DTP\%) = \frac{Di.n - ((\text{Di. v.}/\text{Pi. v.}) \times \text{Pi. n.})}{Di.n.} \times 100$$

$D_{i.v.}$ is the AUC_{0-72h} (brain) intravenous route.
$P_{i.v.}$ is the AUC_{0-72h} (blood) intravenous route.
$D_{i.n.}$ is the AUC_{0-72h} (brain) intranasal route.
$P_{i.n.}$ is the AUC_{0-72h} (blood) intranasal route

IN VIVO PHARMACODYNAMIC STUDIES



FST

1) Forced Swim Test (FST)

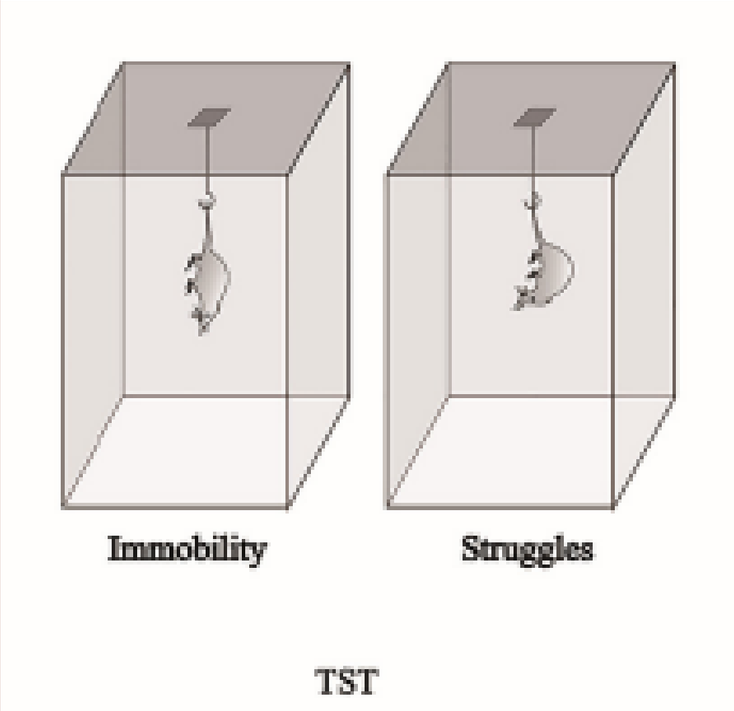
Analyses the response of the animal model to the treat of drowning.

It measures:

- Immobility time
- Climbing time
- Swimming time
- Locomotor activity

The results allow to assess the efficacy of the antidepressive drug.

IN VIVO PHARMACODYNAMIC STUDIES



TST

2) Tail suspension test (TST)

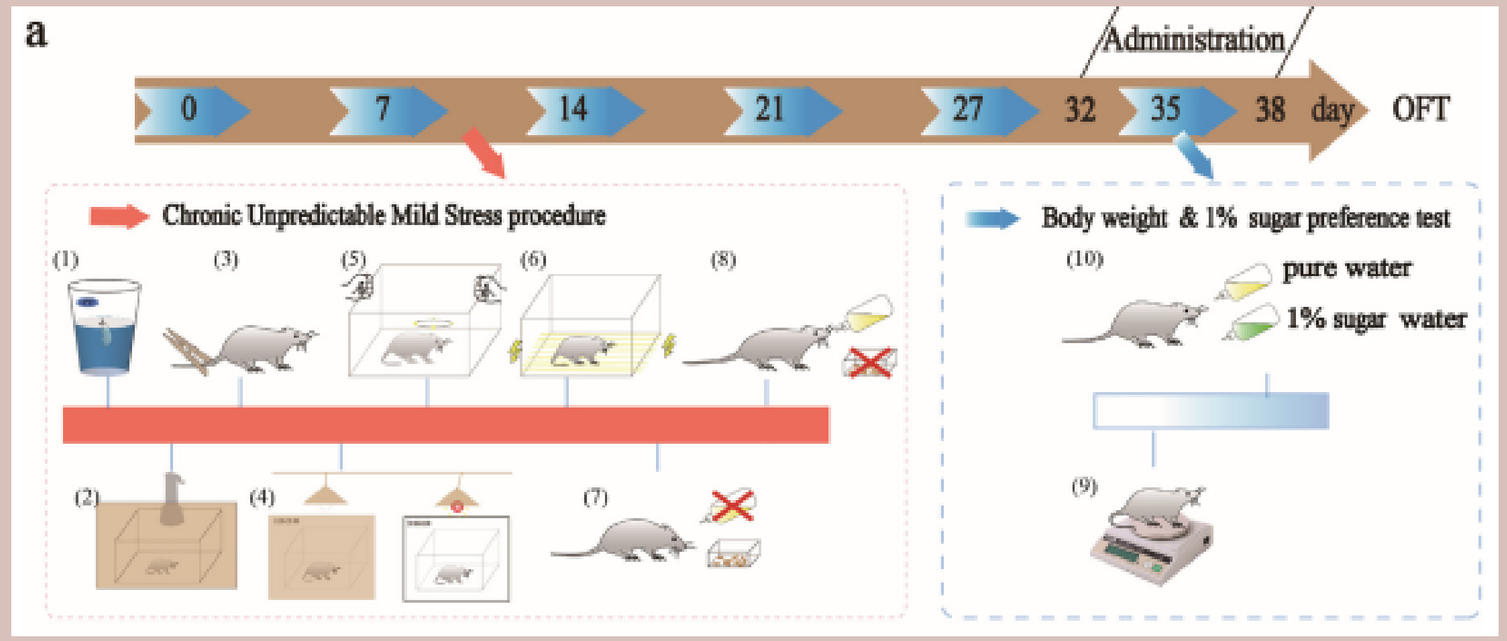
Analyses the response of the animal model when they are suspended and can not escape.

It measures:

- Immobility time
- Locomotor activity

The results allow to assess the efficacy of the antidepressive drug.

IN VIVO PHARMACODYNAMIC STUDIES



3) Chronic Unpredictable Mild Stress model (CUMS model)

This model submits the animal to different stressful situations, leading to the loss of body weight and reducing the sugar preference of the animal.

The results allow to assess the efficacy of the antidepressive drug.

RESULTS AND DISCUSSION

The analysis of the studies revealed that several drugs have been researched in order to verify the efficacy of intranasal administration of nanoparticles for the treatment of depression and anxiety.

The results of the analyzed articles are described in summary form and for each drug, the most relevant results will be presented.

ICARIIN AND ALBIFLORIN

Icariin:

Particle size: 73,80 nm

PDI: 0,15

Zeta potencial: -19,2mV

Albiflorin:

Particle size: 45,6 nm

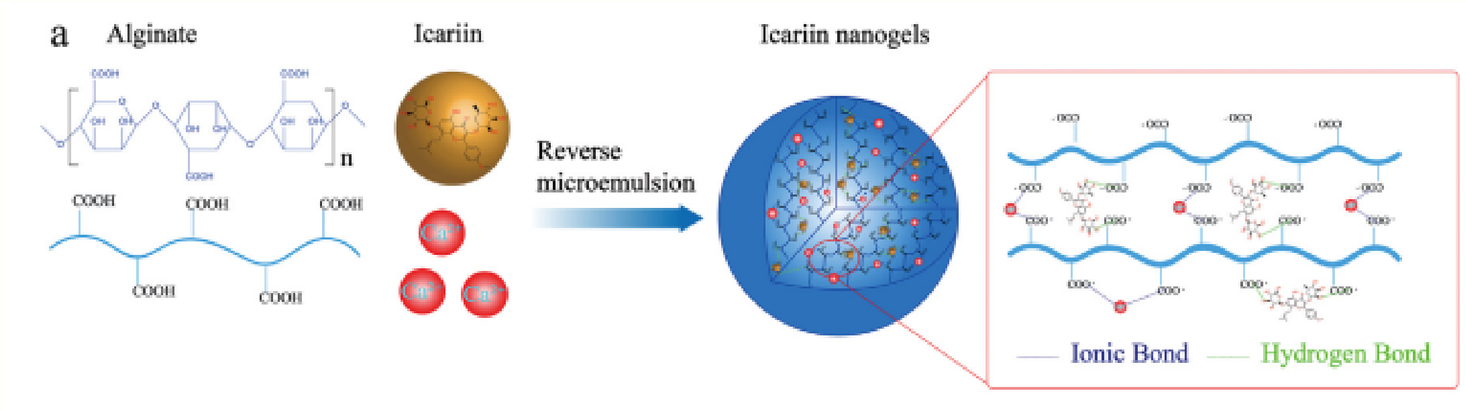
PDI: 0,20

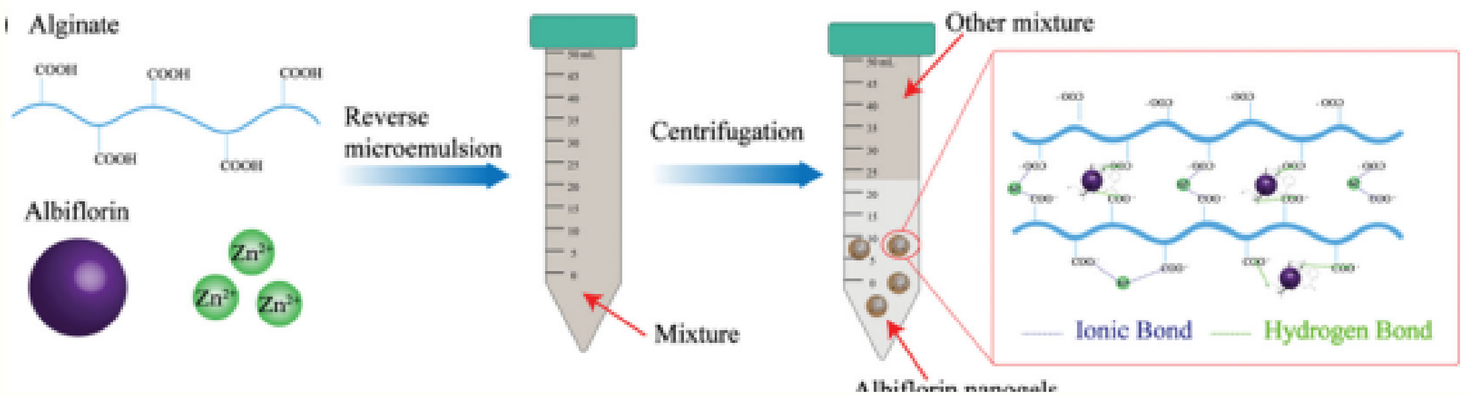
Zeta potencial: -19,8 mV

Composition of the nanoparticules:

Alginate- Polymer

Poloxamer- Surfactant





In both studies the FST, TST and CUMS model were applied.

For all the tests performed, the nanoparticules developed, when administrated via intranasal, obtained better results.

FLUOXETINE

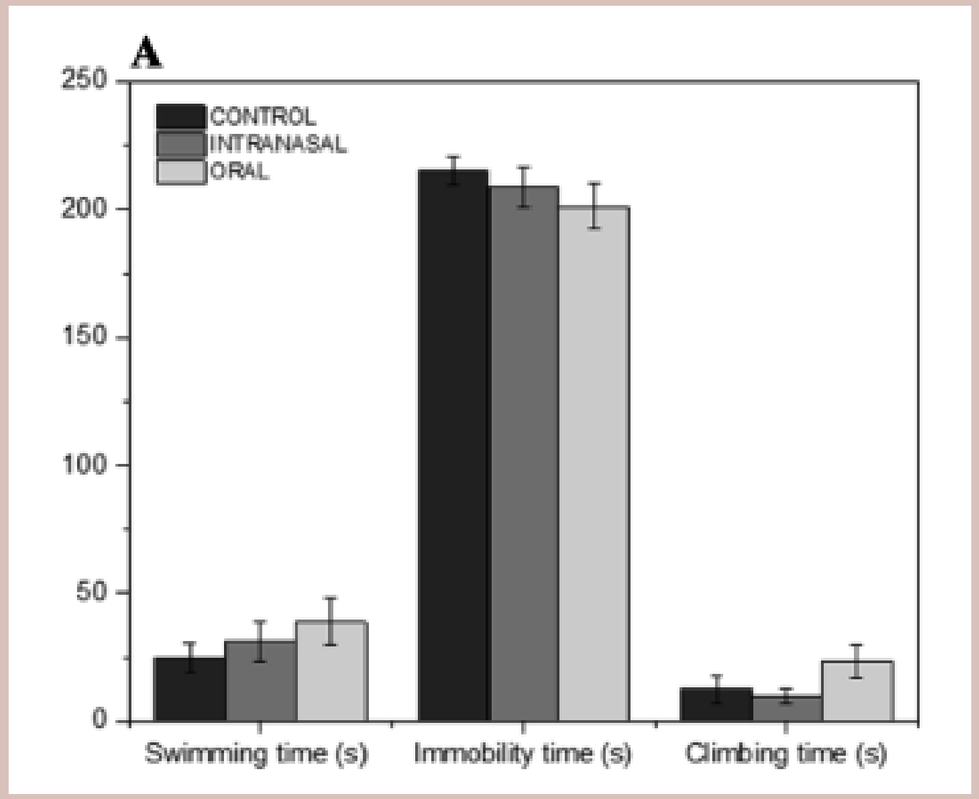
Composition of the nanoparticles:

Glyceryl palmitostearate- Solid lipid
Propylene glycol monocaprylate (type I)- Liquid lipid
Polysorbate 80- Surfactant

RESULTS

Particle size: 154 nm
PDI: 0,514
Zeta potencial: 19,7 mV
EE%: 74%
DI%: 12,9%

FST applied to mice when treated with an **oral** solution vs **intranasal** nanoparticles:



Although there is no comparative superiority, the formulation can be used when the oral route is not available (vomits, intubation, convulsions...).

AGOMELATINE

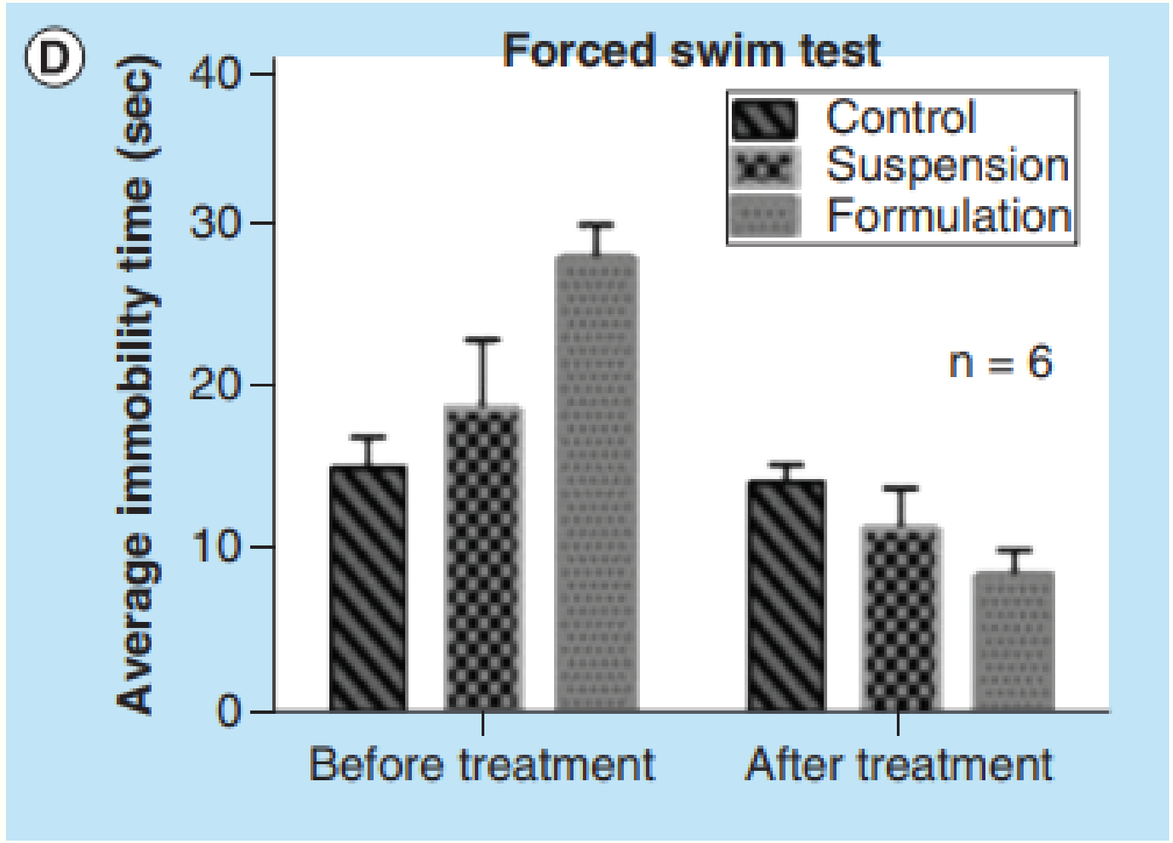
Composition of the nanoparticles:

PLGA (poly-lactic-coglycolic acid)- Polymer
Poloxamer 407- Surfactant

RESULTS

Particle size: 116,06 nm,
PDI: <0,3
Zeta potencial: -22,7 mV.
EE%: 98,3%
DL% 49,15%

FST applied to rats when treated with an **oral** suspension vs **intranasal** nanoparticles:



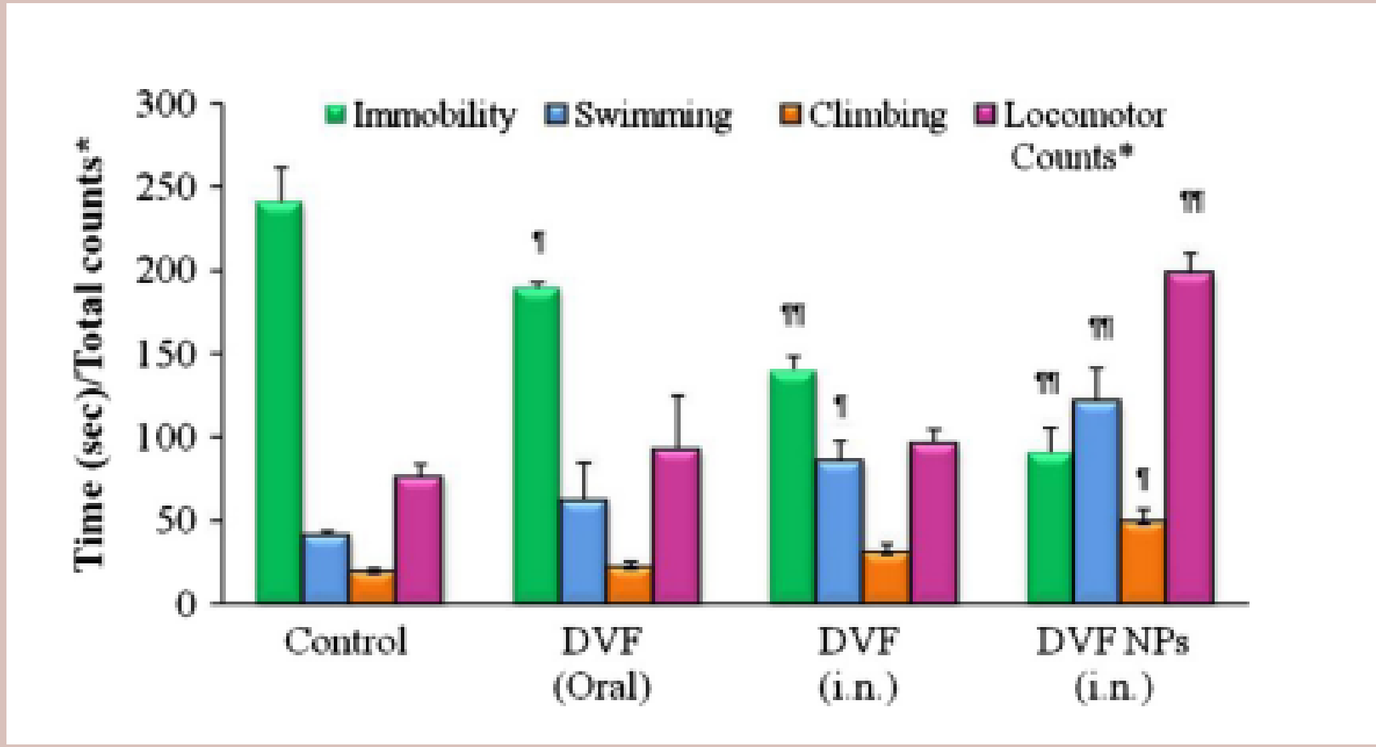
DESVENLAFAXINE

Composition of the nanoparticles:
PLGA- Polymer
Chitosan- Polymer
Polyvinyl alcohol- Surfactant

RESULTS

Particle size 172,5 nm
PDI: 0,254
Zeta potencial: +35,63 mV
EE%: 98,3%
DL%: 49,15%
DTE%: 554,23%
DTP%: 81,62%

FST applied to rats when treated with an **oral** solution vs **intranasal** solution vs **intranasal** nanoparticles:



VENLAFAXINE

3 studies developed formulations with venlafaxine:

1

CHITOSAN TPP

Particle size: 167 nm
PDI: 0,367
Zeta potential : +23,83 mV

EE%: 79,3%
DL%: 32,25%
DTE%: 508,59%
DTP%: 80,34%

2

ALGINATE CHITOSAN

Particle size: 173,7 nm
PDI: 0,391
Zeta potential: +37,4 mV

EE%: 85,6%
DL%: 26,74%
DTE%: 425,77%
DTP%: 76,52%

In vivo pharmacokinetics studies compared results of AUC, concentration and semi-life time of three different formulations:

- Nanoparticles (i.n.)
- Solution (i.v.)
- Solution (i.n.)

The best results were obtained after intranasal administration of the nanoparticles.

3

PLGA

Particle size: 206,3 nm
PDI: 0,190
Zeta potential: -26,5 mV
EE%: 48 - 50%
DL%: 10 - 12%

PLGA + TF*/ PLGA + TFRP**

Particle size: 218,6/ 216,3 nm
PDI: 0,078 / 0,067
Zeta potential: -19,5/ -19,6 mV
EE%: 48 - 50%
DL%: 10 - 12%

The ligands were used in order to modify the surface of the nanoparticles and improve their interaction with mucosal cells, favoring absorption and permeability through the mucosa.

30 minutes after intranasal administration of the 3 formulations, the higher concentration of drug in the brain was obtained with simple nanoparticles, which allowed to conclude that functional nanoparticles take longer to reach the brain.

*transferin receptor
** specific peptide against Tf receptor

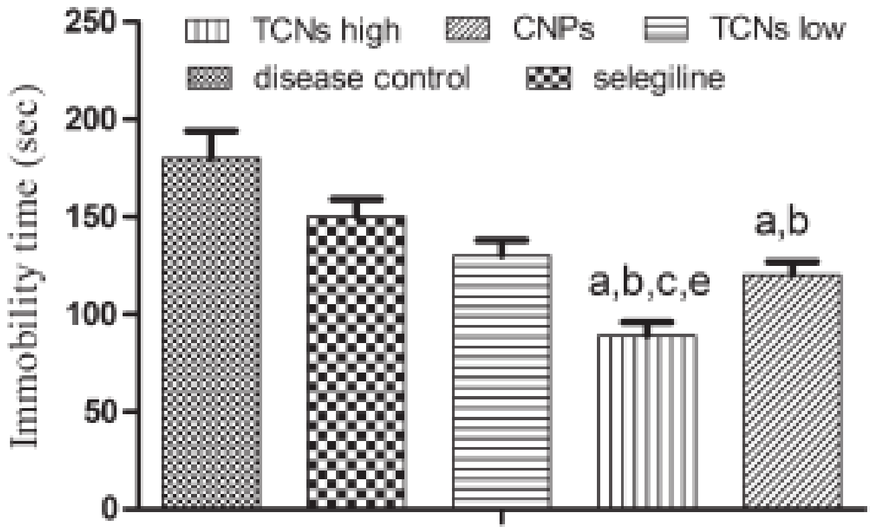
SELEGILINE

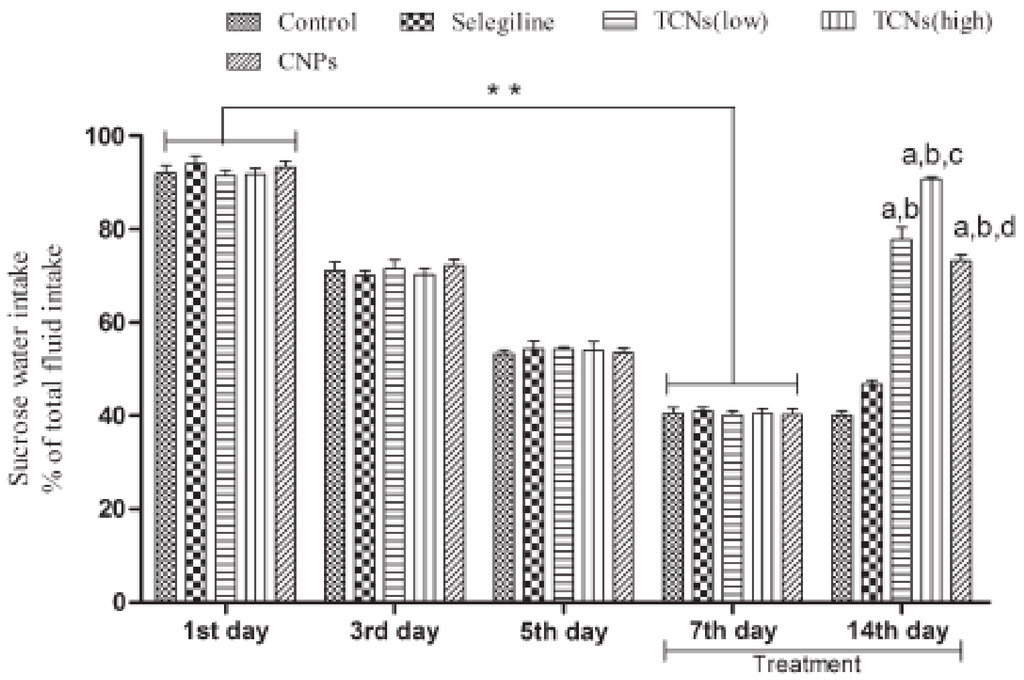
Composition of the nanoparticles:

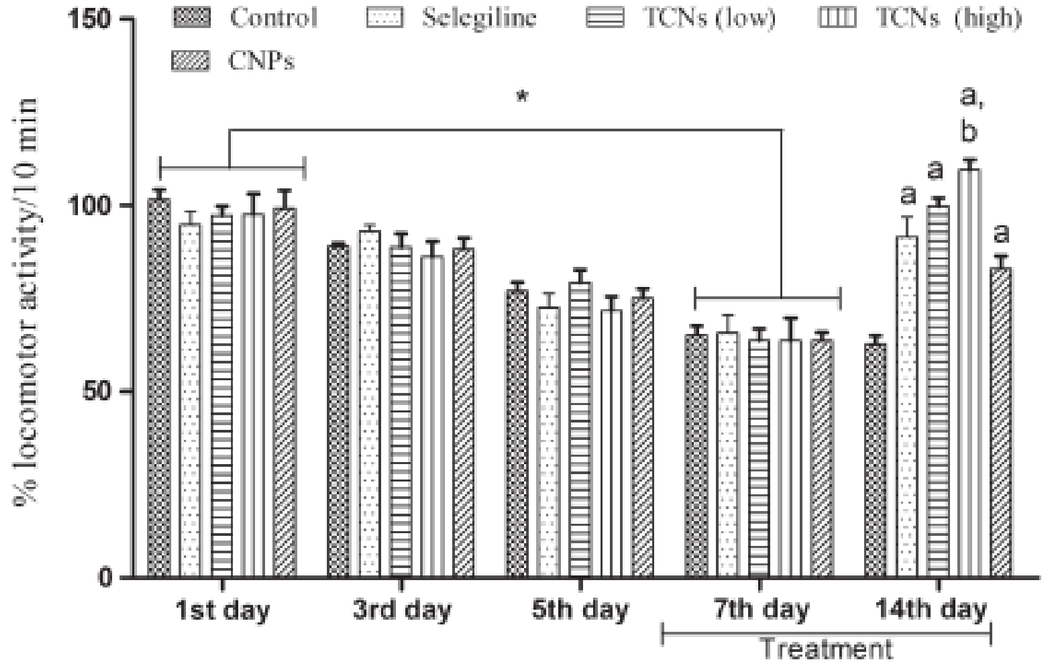
Chitosan or tiolated chitosan- Polycation
Tripolyphosphate (TPP)- Polyanion

RESULTS (for thiolated chitosan nanoparticles)

Particle size: 215 nm
PDI: 0,214
Zeta potential: +17,06 mV
EE%: 70%







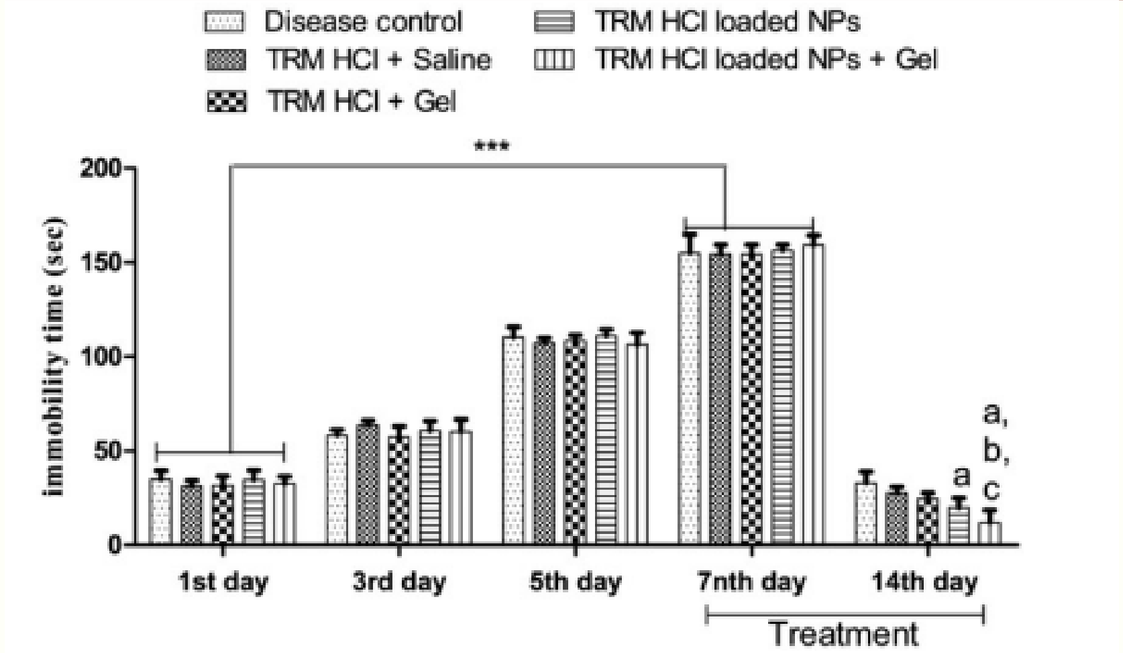
TRAMADOL

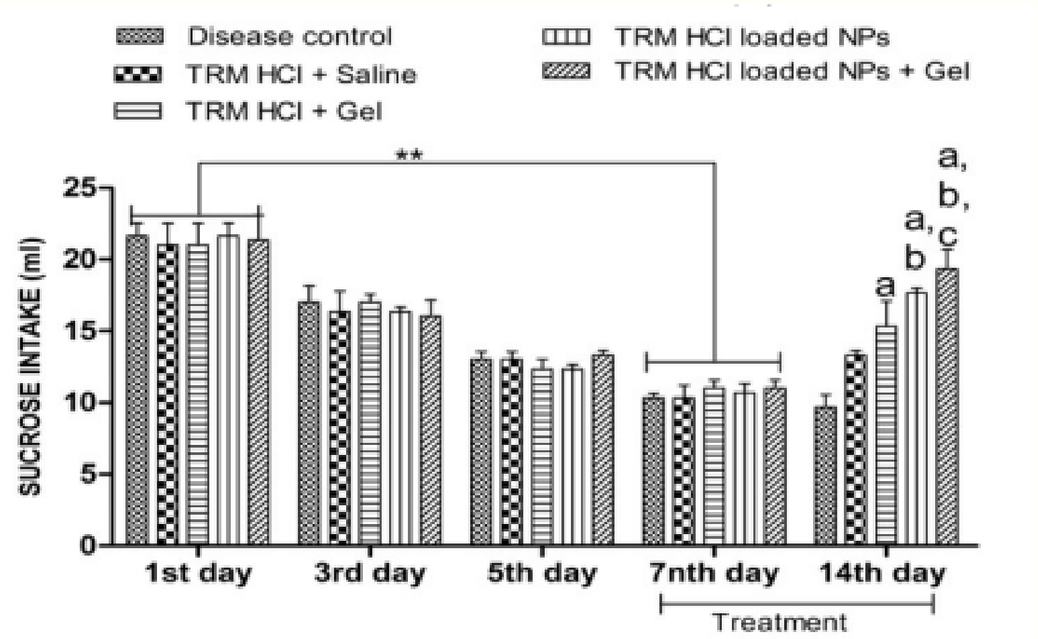
Composition of the nanoparticles:

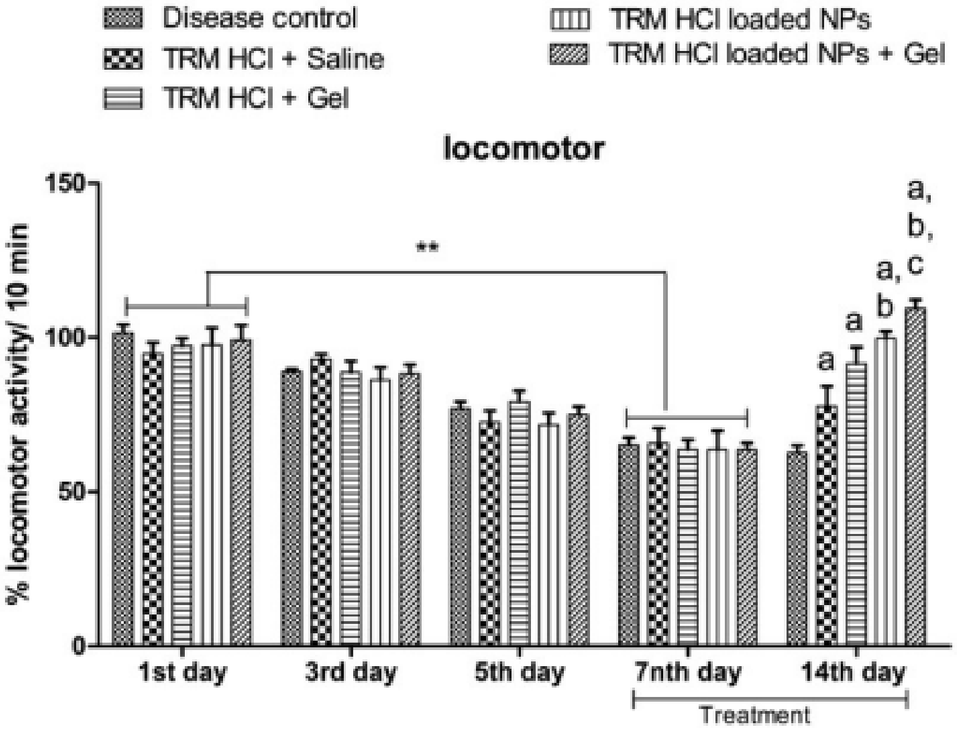
Chitosan- Polymer
TPP- Surfactant
Poloxamer 407- Surfactant
HPMC K15M- Polymer
Benzalkonium chloride- Stabilizer, cationic surfactant

RESULTS

Particle size: 152 nm
PDI: 0,143
Zeta potential: +31 mV
EE%: 85%







BUSPIRONE

Composition of the nanoparticles:

Chitosan- Polymer

Cross-linker (alginate + TPP)

Results

Particle size: 195,7 nm

PDI: 0,367

Composition of the nanoparticles:

Thiolated chitosan- Polymer

Cross-linker (alginate + TPP)

Results

Particle size: 208,3 nm

PDI: 0,253

DTE%: 95,97%

DTP%: 78,94%

In vivo pharmacokinetics studies results:

Formulation	Organ/tissue	C_{max} (ng/ml)	T_{max} (h)	$AUC_{0-480\ min}$ (ng min/ml)	$AUC_{0-\alpha\ min}$ (ng min/ml)
BUH(i.v.)	Brain	384.15 ± 13.42	2	1151.01 ± 54.78	1253.01 ± 10.32
BUH (i.n.)	Brain	417.77 ± 19.24	2	2036.9 ± 51.62	3941.26 ± 26.99
BUH TCS-NPs (i.n.)	Brain	797.46 ± 35.76	2	4048.29 ± 28.35	6057.21 ± 52.3

BUH - Buspirone BUH TCS-NPs- Thiolated chitosan nanoparticles

RILUZOL

Composition of the nanoparticles:

Chitosan- Polycation

TPP- Polianion

Results

Particle size: 173,6 nm

PDI: 0,264

Composition of the nanoparticles:

Chitosan- Polycation

TPP- Polyanion

Tf- ligand

Results

Particle size: 207,0 nm

PDI: 0,406

DTE%: 1138,46%

DTP%: 91,21%

***In vivo* pharmacodynamics Elevated plus maze test:**

- Confirmed the anxiolytic potential of riluzol

***In vivo* pharmacokinetics studies results:**

- Suspension (i.v.)
- Suspension (i.n.)
- Chitosan Tf nanoparticles (i.n.)

Best results obtained after intranasal administration of nanoparticles with Tf.

CONCLUSIONS

- Pharmacokinetics and pharmacodynamic results are very promising
- Polymeric nanoparticles were the preferred nanometric drug transport systems
- Chitosan and alginate were the polymers most used due to their mucoadhesive properties

CONCLUSIONS

In the future it is important to compare these results with studies performed in humans in order to confirm the true potential of the intranasal administration of nanoparticles for the treatment of depression and anxiety

Bibliography

1. WORLD HEALTH ORGANIZATION - Mental Health [Consult. 17 jul. 2022]. Available in: http://www.who.int/health-topics/mental-health#tab=tab_1
2. VITORINO, Carla et al. - QbD-driven development of intranasal lipid nanoparticles for depression treatment. European Journal of Pharmaceutics and Biopharmaceutics. ISSN 09396411. 153:2020) 106–120. doi: 10.1016/j.ejpb.2020.04.011.
3. SNS24 - Depressão [Consult. 15 ago. 2022]. Available in: http://www.sns24.gov. pt/tema/saude-mental/depressao/#sec-4
4. TONG, Gui-Feng; QIN, Nan; SUN, Li-Wei - Development and evaluation of Desvenlafaxine loaded PLGA-chitosan nanoparticles for brain delivery. Saudi Pharmaceutical Journal. ISSN 13190164. 25:6 (2017) 844–851. doi: 10.1016/j.jsps.2016.12. 003.
5. CUF - Depressão [Consult. 26 jul. 2022]. Available in: https://www.cuf.pt/saude-a- z/depressao
6. NORMAN, Trevor R.; OLVER, James S. - Agomelatine for depression: expanding the horizons? Expert Opinion on Pharmacotherapy. ISSN 1465-6566. 20:6 (2019) 647–656. doi: 10.1080/14656566.2019.1574747.
7. BARI, Naimat Kalim et al. - Brain delivery of buspirone hydrochloride chitosan nanoparticles for the treatment of general anxiety disorder. International Journal of Biological Macromolecules. ISSN 01418130. 81:2015) 49–59. doi: 10.1016/j.ijbiomac.2015. 07.041.
8. PENNINX, Brenda WJHet al. - Anxiety disorders. The Lancet. ISSN 01406736. 397:10277 (2021) 914–927. doi: 10.1016/S0140-6736(21)00359-7.
9. CUF - Ansiedade [Consult. 26 jul. 2022]. Available in: https://www.cuf.pt/saude-a- z/ansiedade
10. COSTA, C. et al. - Nose-to-brain delivery of lipid-based nanosystems for epileptic seizures and anxiety crisis. Journal of Controlled Release. ISSN 01683659. 295:2019) 187– 200. doi: 10.1016/j.jconrel.2018.12.049.
11. SOYKA, Michael - Treatment of Benzodiazepine Dependence. New England Journal of Medicine. ISSN 0028-4793. 376:12 (2017) 1147–1157. doi: 10.1056/NEJMra1611832.
12. LOMBARDO, Rosamaria et al. - Nanotechnologies for intranasal drug delivery: an update of literature. Pharmaceutical Development and Technology. ISSN 10979867. 26:8 (2021) 824–845. doi: 10.1080/10837450.2021.1950186.
13. SINGH, Devendra et al. - Pharmacological evaluation of nasal delivery of selegiline hydrochloride-loaded thiolated chitosan nanoparticles for the treatment of depression. Artificial Cells, Nanomedicine, and Biotechnology. ISSN 2169-1401. 44:3 (2015) 1–13. doi: 10.3109/21691401.2014.998824.
14. BAHADUR, Shiv; PATHAK, Kamla - Physicochemical and physiological considerations for efficient nose-to-brain targeting. Expert Opinion on Drug Delivery. ISSN 1742-5247. 9:1 (2012) 19–31. doi: 10.1517/17425247.2012.636801.
15. MISRA, Ambikanandan et al. - Recent Patents Review on Intranasal Administration for CNS Drug Delivery. Recent Patents on Drug Delivery & Formulation. ISSN 18722113. 2:1 (2008) 25–40. doi: 10.2174/187221108783331429.

Bibliography

16. SELVARAJ, Kousalya;GOWTHAMARAJAN, Kuppusamy; KARRI,Veera Venkata Satyanarayana Reddy - Nose to brain transport pathways an overview: potential of nanostructured lipid carriers in nose to brain targeting. Artificial Cells, Nanomedicine and Biotechnology. ISSN 2169141X. 46:8 (2018) 2088–2095. doi: 10.1080/21691401.2017. 1420073.
17. PARDESHI, Chandrakantsing Vijaysing; BELGAMWAR, Veena Shailendra - Direct nose to brain drug delivery via integrated nerve pathways bypassing the blood–brain barrier: an excellent platform for brain targeting. Expert Opinion on Drug Delivery. ISSN 1742-5247. 10:7 (2013) 957–972. doi: 10.1517/17425247.2013.790887.
18. PIRES, Patrícia C.; SANTOS, Adriana O. - Nanosystems in nose-to-brain drug delivery: A review of non-clinical brain targeting studies. Journal of Controlled Release. ISSN 01683659. 270:2018) 89–100. doi: 10.1016/j.jconrel.2017.11.047.
19. MARA MAINARDES, Rubiana et al. - Liposomes and Micro/Nanoparticles as Colloidal Carriers for Nasal Drug Delivery. Current Drug Delivery. ISSN 15672018. 3:3 (2006) 275– 285. doi: 10.2174/156720106777731019.
20. CUNHA, S. et al. - Lipid Nanoparticles for Nasal/Intranasal Drug Delivery. Critical ReviewsTM in Therapeutic Drug Carrier Systems. ISSN 0743-4863. 34:3 (2017) 257–282. doi: 10.1615/CritRevTherDrugCarrierSyst.2017018693.
21. SCHERLIESS, Regina - Nasal formulations for drug administration and characterization of nasal preparations in drug delivery. Therapeutic Delivery. ISSN 2041-5990. 11:3 (2020) 183–191. doi: 10.4155/tde-2019-0086.
22. BATTAGLIA, Luigi et al. - Lipid nanoparticles for intranasal administration: application to nose-to-brain delivery. Expert Opinion on Drug Delivery. ISSN 1742-5247. 15:4 (2018) 369–378. doi: 10.1080/17425247.2018.1429401.
23. SOOD,Sumeet; JAIN, Kunal;GOWTHAMARAJAN, K. -Intranasal therapeutic strategies for management of Alzheimer's disease. Journal of Drug Targeting. ISSN 1061- 186X. 22:4 (2014) 279–294. doi: 10.3109/1061186X.2013.876644.
24. BEHL, C. R. et al. - Effects of physicochemical properties and other factors on systemic nasal drug delivery. Advanced Drug Delivery Reviews. ISSN 0169409X. 29:1–2 (1998) 89– 116. doi: 10.1016/S0169-409X(97)00063-X.
25. PIRES, Anaísa et al. - Intranasal Drug Delivery: How, Why and What for? Journal of Pharmacy & Pharmaceutical Sciences. ISSN 1482-1826. 12:3 (2009) 288. doi: 10.18433/J 3NC79.
26. TENCHOV, Rumiana et al. - Lipid Nanoparticles—From Liposomes to mRNA Vaccine Delivery, a Landscape of Research Diversity and Advancement. ACS Nano. ISSN 1936-0851. 15:11 (2021) 16982–17015. doi: 10.1021/acsnano.1c04996.

Bibliography

27. GOMEZHENS, A.; FERNANDEZROMERO, J. - Analytical methods for the control of liposomal delivery systems. TrAC Trends in Analytical Chemistry. ISSN 01659936. 25:2 (2006) 167–178. doi: 10.1016/j.trac.2005.07.006.

28. XU, Jingying; TAO, Jiangang; WANG, Jidong - Design and Application in Delivery System of Intranasal Antidepressants. Frontiers in Bioengineering and Biotechnology. ISSN 22964185. 8:2020). doi: 10.3389/fbioe.2020.626882.

29. SINGH, Yuvraj et al. - Nanoemulsion: Concepts, development and applications in drug delivery. Journal of Controlled Release. ISSN 01683659. 252:2017) 28–49. doi: 10.1016/j. jconrel.2017.03.008.

30. XU, Dong et al. - Intranasal delivery of icariin via a nanogel-thermoresponsive hydrogel compound system to improve its antidepressant-like activity. International Journal of Pharmaceutics. ISSN 03785173. 586:2020) 119550. doi: 10.1016/j.ijpharm.2020.119550.

31. XU, Dong et al. - Alginate nanogels-based thermosensitive hydrogel to improve antidepressant-like effects of albiflorin via intranasal delivery. Drug Delivery. ISSN 1071- 7544. 28:1 (2021) 2137–2149. doi: 10.1080/10717544.2021.1986604.

32. JANI, Parva et al. - Formulation of polymeric nanoparticles of antidepressant drug for intranasal delivery.Therapeutic Delivery. ISSN2041-5990. 10:11 (2019)683–696. doi: 10.4155/tde-2019-0060.

33. HAQUE, Shadabul et al. - Venlafaxine loaded chitosan NPs for brain targeting: Pharmacokinetic and pharmacodynamic evaluation. Carbohydrate Polymers. ISSN 01448617. 89:1 (2012) 72–79. doi: 10.1016/j.carbpol.2012.02.051.

34. HAQUE, Shadabul et al. - Development and evaluation of brain targeted intranasal alginate nanoparticles for treatment of depression. Journal of Psychiatric Research. ISSN 00223956. 48:1 (2014) 1–12. doi: 10.1016/j.jpsychires.2013.10.011.

35. CAYERO-OTERO, M.D. et al. - Invivo biodistribution ofvenlafaxine-PLGA nanoparticles for brain delivery: plain vs. functionalized nanoparticles. Expert Opinion on Drug Delivery. ISSN 1742-5247. 16:12 (2019) 1413–1427. doi: 10.1080/17425247.2019. 1690452.

36. KAUR, Prabhjot et al. - Brain delivery of intranasal in situ gel of nanoparticulated polymeric carriers containing antidepressant drug: behavioral and biochemical assessment. Journal of Drug Targeting. ISSN 1061-186X. 23:3 (2015) 275–286. doi: 10.3109/1061186X. 2014.994097.

37. ABDELNABI, Dina M.; ABDALLAH, Marwa H.; ELGHAMRY, Hanaa A. - Buspirone Hydrochloride Loaded In Situ Nanovesicular Gel as an Anxiolytic Nasal Drug Delivery System: In Vitro and Animal Studies. AAPS PharmSciTech. ISSN 1530-9932. 20:3 (2019) 134. doi: 10.1208/s12249-018-1211-0.

38. NABI, Bushra et al. - Riluzole-loaded nanoparticles to alleviate the symptoms of neurological disorders by attenuating oxidative stress. Drug Development and Industrial Pharmacy. ISSN 0363-9045. 46:3 (2020) 471–483. doi: 10.1080/03639045.2020.1730396