The importance of nanosystems in antipsychotic drugs brain targeting

Overview

- Introduction
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- References

PSYCHIATRIC DISORDERS AFFECT TREMENDOUSLY THE WORLD POPULATION AND HAVE A SIGNIFICANT SOCIOECONOMIC IMPACT, MORBIDITY AND MORTALITY.

Introduction

Schizophrenia

Hallucination

Confusion

Delusion

Avolition

Apathy

Flat affect

Weakening of operational memory

Bipolar Disorder

Mania

Depression

Problem

24 and 40 million worldwide

with schizophrenia and bipolar disorder, respectively.

Orally administered antipsychotic drugs have low effectiveness due to their **impaired bioavailability**, **poor drug delivery to the brain** and **severe side effects** .

Problem

Impaired bioavailability

- Poor water-solubility
- High hepatic/ gastrointestinal first-pass metabolism.
- Nonspecific biodistribution.

Poor drug delivery to the brain

- Restrictive properties of the blood-brain barrier (P- glycoprotein efflux).

Severe side effects

- Neuroleptic malignant syndrome.
- Extrapyramidal side effects (drug-induced Parkinsonism, acute dystonia reactions, akathisia...).
- dose dependent weight gain, diabetes.

Intranasal delivery

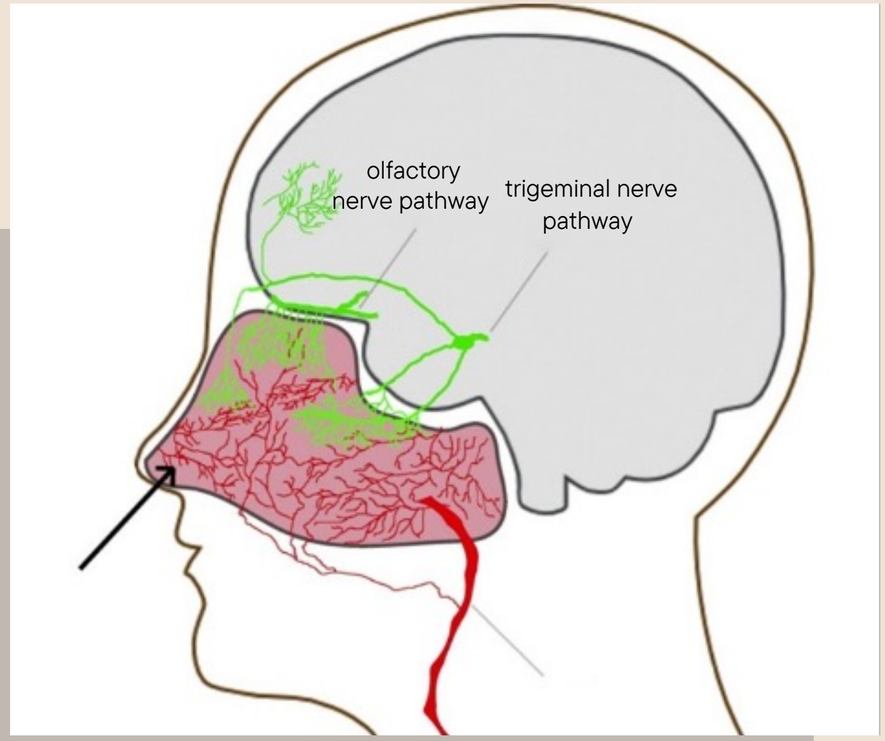
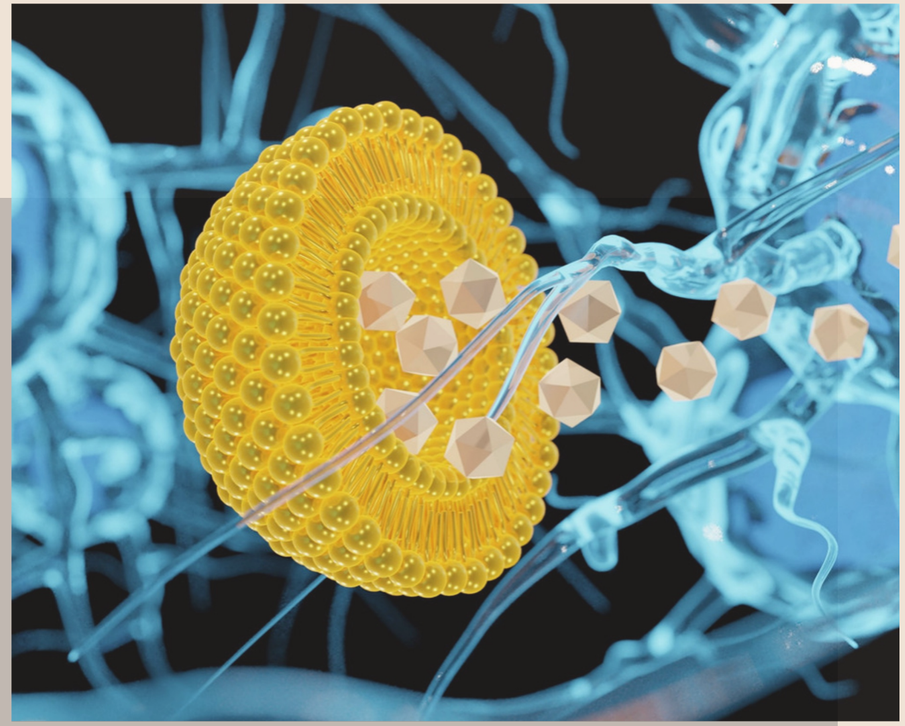


Fig.1 - Direct nose to brain transport. Adapted from Katare, *et al.*

Advantages

- Direct nose to brain transport, bypassing BBB, via neuronal olfactory and trigeminal pathways.
- Enhanced bioavailability due to avoidance of hepatic or GI metabolism.
- Possibility of lowering of doses administered due to targeting/ enhanced bioavailability leading to reduced side effects.

Nanosystems



are described as particles that have one dimension below 1 μm.

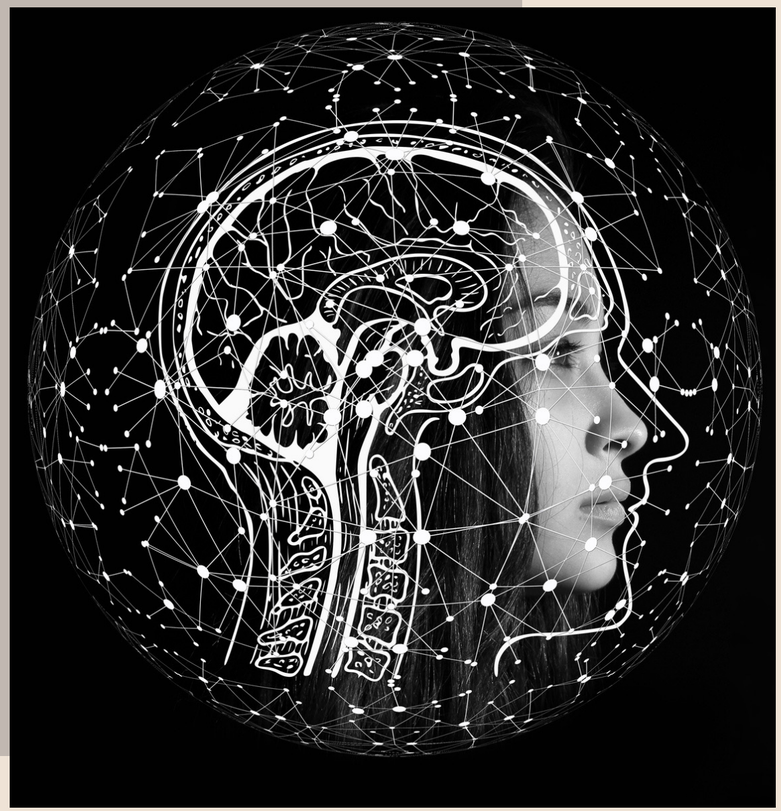
Advantages

- Reduced particle size.
- Enhanced drug solubility.
- Targeted delivery of the drug (improved brain distribution).
- Drug protection from enzymatic degradation.
- Sustained delivery

Gelling agents

Major limitation of intranasal delivery is the faster elimination of the applied formulations due to nasal mucociliary clearance.

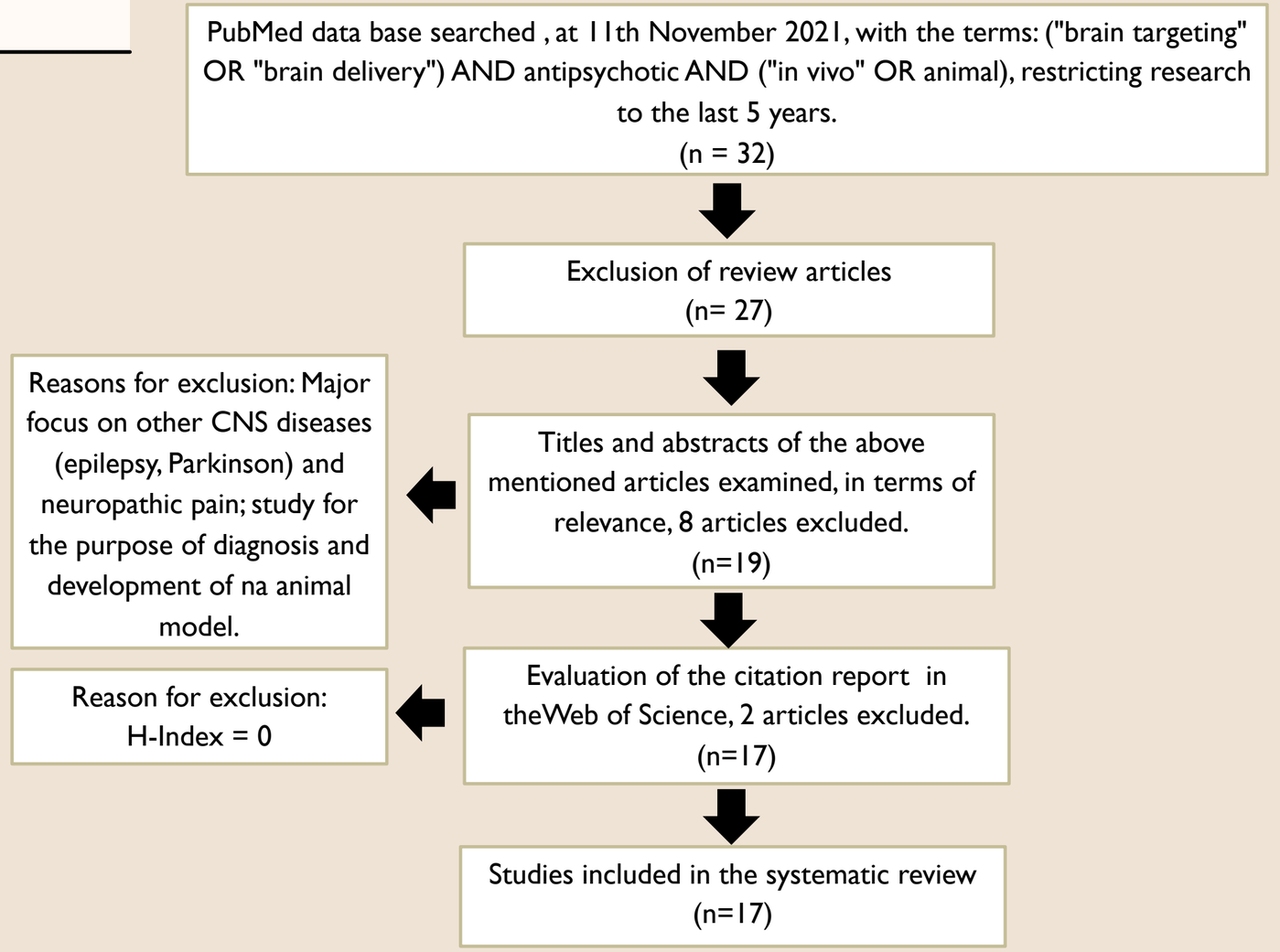
Incorporation of gelling agents (gellan gum, chitosan, poloxamer, Carbopol, etc) in nanosystems could enhance the residence time of formulation in the nasal cavity and permeation of the entrapped therapeutics to the brain.



Objective

Summarize and make a critical analysis of the latest scientific literature, with regard to the efficacy and safety of nanosystems in the brain targeting of antipsychotic drugs.

Methodology



Results

8 out 9

Second generation antipsychotic

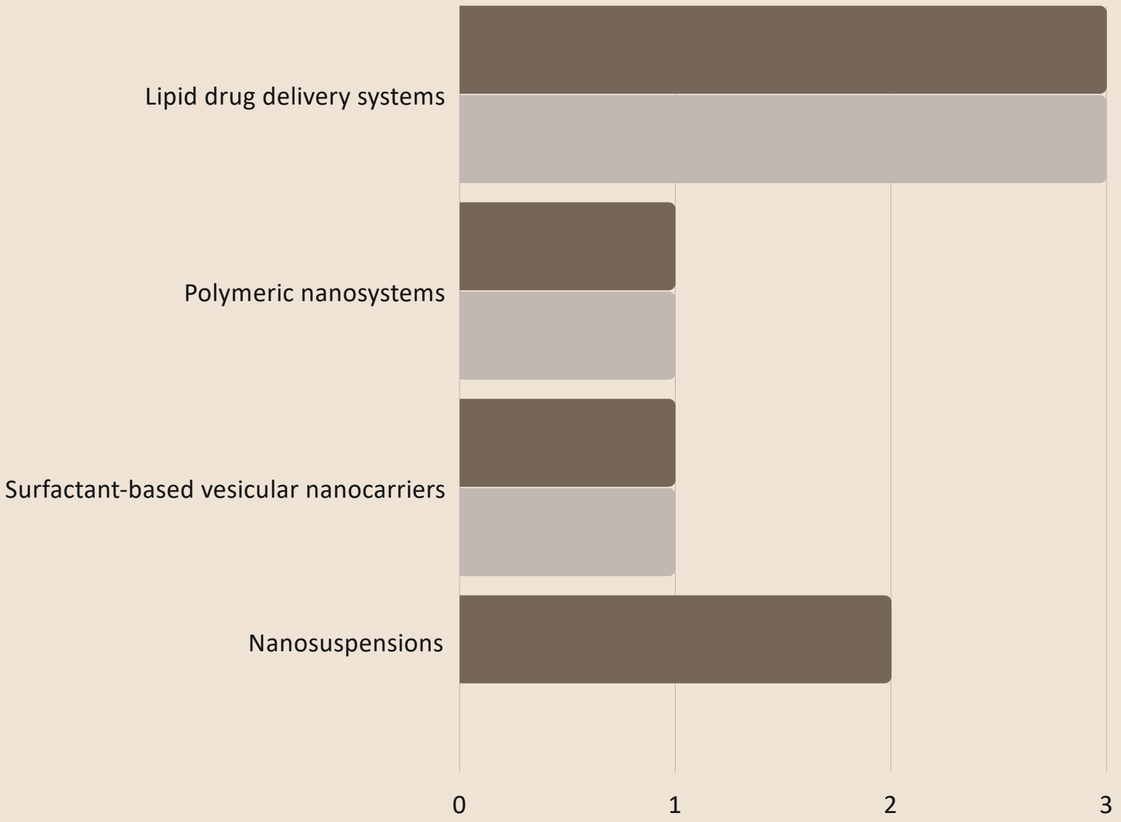
Quetiapine, Olanzapine, Clozapine, Risperidone, Amisulpride, Lurasidone, Asenapine and Perphenazine.

1 out 9

Third generation antipsychotic

Aripiprazole

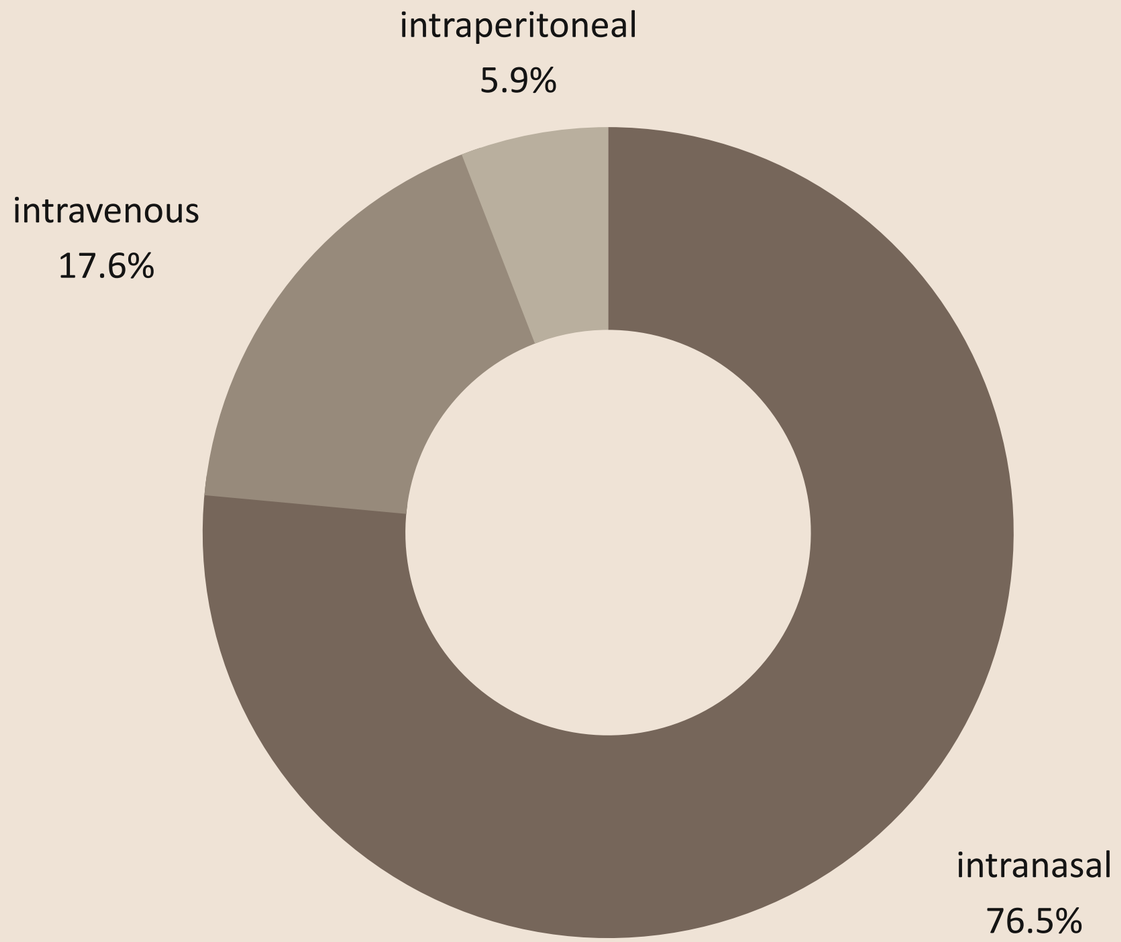
Results



Lipid DDS were the most studied delivery nanosystem group.

Results

Most authors explored the intranasal pathway for brain targeting of nanosystems.



Results

Pharmacokinetic study

I.N. administration of nanosystems were found to be **more effective** in enhancing the bioavailability of antipsychotics in the brain (↑Cmax and AUC) when compared with **IV administration of nanosystems** or **I.N./ IV/ oral administration of solutions**.

Results

Pharmacokinetic study

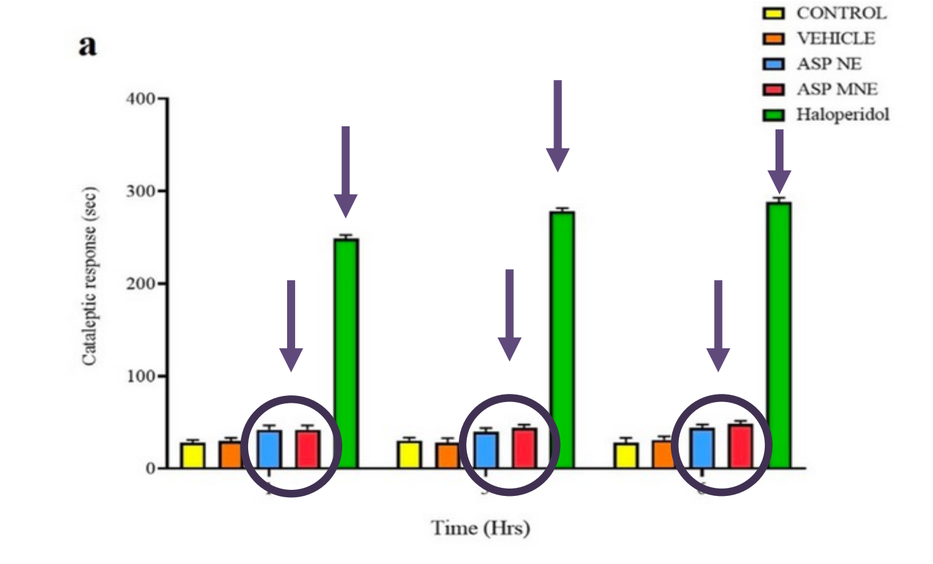
Formulations	Brain		
	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0-\infty}$ (h.ng/mL)
AMS-NG (Intranasal)	220.92 ± 22.41	2.00	2598.62 ± 218.41
AMS-NE (Intranasal)	148.63 ± 14.23	2.00	1414.84 ± 126.93
AMS-NE (Intravenous)	65.01 ± 6.50	2.00	769.34 ± 62.82

Formulations	Brain				
	C_{max} (μg/g)	T_{max} (h)	$T_{1/2}$ (h)	AUC_{0-t} (h.μg/g)	$AUC_{0-\infty}$ (h.μg/g)
ARP MNE	15.19 ± 2.51	1	2.78	79.208 (AUC_{0-24})	79.45
ARP NE (intranasal)	10.57 ± 1.88	1	1.92	36.03 (AUC_{0-12})	36.45
ARP NE (intravenous)	2.52 ± 0.38	2	1.44	11.629 (AUC_{0-12})	11.73

Formulations	Brain		
	C_{max} (ng/g)	T_{max} (h)	AUC_{0-t} (h.ng/g)
ASP-MNE (intranasal)	284.33 ± 19.5	1	2882.7 ± 298.98
ASP-NE (intranasal)	230.23 ± 26.7	1	2357.7 ± 270.40
ASP-NE (intravenous)	79.86 ± 8.20	3	1265.1 ± 181.11

Supported by data from Gadhave et al., 2021, Kumbhar et al., 2021 and Kumbhar et al., 2020

The superior brain pharmacokinetics profile of antipsychotics was recorded with intranasal nanosystems with gelling agents.



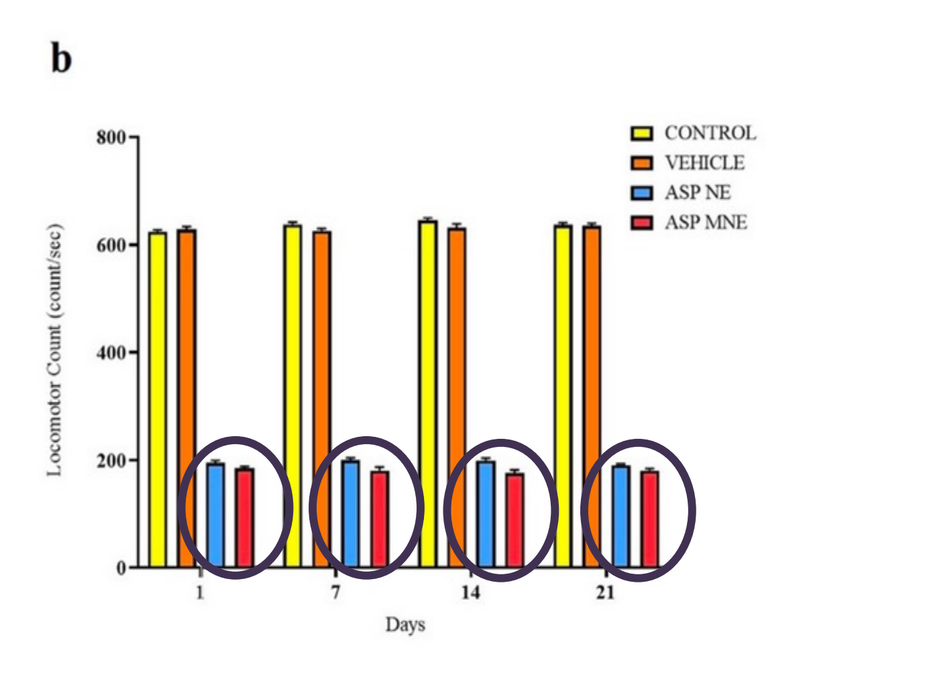


Fig. 9. *In vivo* animal behavioral assessments:(a) Cataleptic response on 21st day in control, vehicle, ASP-NE, ASP-MNE and haloperidol treated groups; (b) Induced locomotor activity, (c) Forelimb retraction response and (d) Hind-limb retraction response in the paw test on 1st, 7th, 14th and 21st day in control, vehicle, ASP-NE, ASP-MNE groups. All values are presented as the mean ± standard deviation (n = 6).

Results

Pharmacodynamic study

Supported by data from Kumbhar et al., 2020

Safe and effective on the targeting of the therapeutic to the brain

Results

Hematotoxicity study

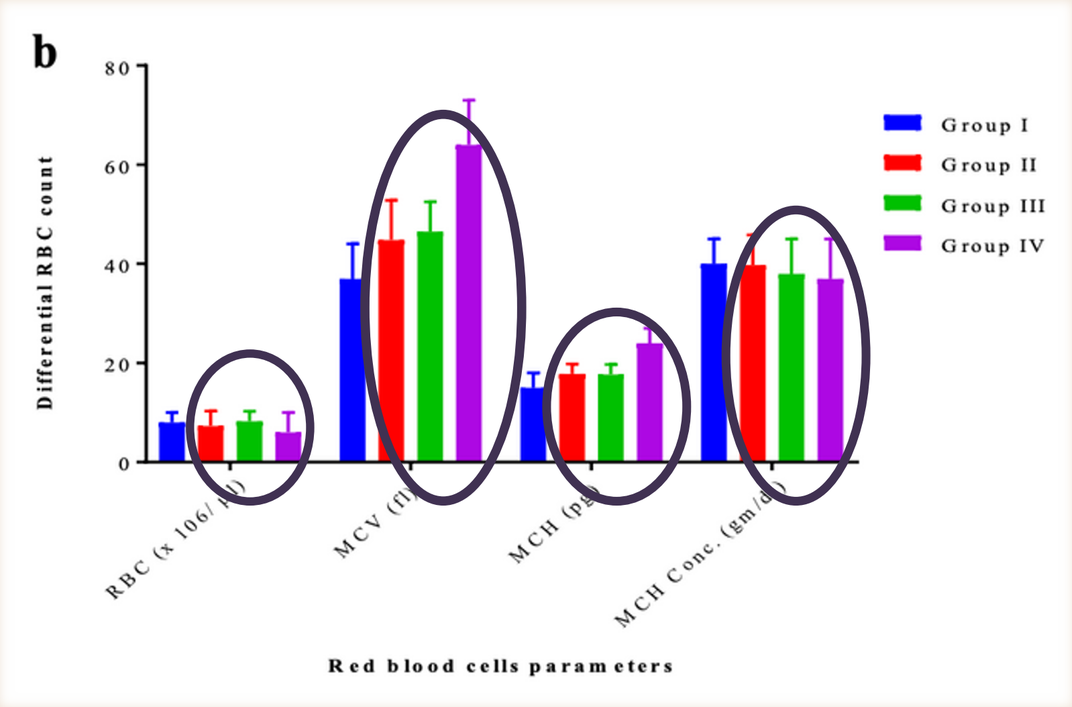


Fig. 7. Effect of OLZ-MNLC (P+H) i.n. formulation on hematological parameters for the different groups: group I (normal control), group II (treated with 1 mg/kg OLZ-MNLC), group III (treated with 2 mg/kg OLZ-MNLC), and group IV (treated with 4 mg/kg OLZ-MNLC) animals. **a** Differential WBC, **b** RBC parameter, and **c** hemoglobin and platelet counts (mean value ± SD, $^{**}p < 0.01$, compared with the control group)

Supported by data from Gadhave et al., 2019

i.n. nanosystems limited the amount of drug that passes into the blood and decreases the risk of hematological toxicity.

Discussion

Nanoemulgels and Nanoemulsions

- Lower globule size
- Higher size homogeneity
- Higher stability
- Higher encapsulation efficiency

Nanosystems are apt carriers for effective nose-to-brain delivery of antipsychotics, bypassing the blood-brain barrier.

Conclusion

Nanosystems have a great prospect for a safe and effective delivery of antipsychotics agents in the treatment of CNS disorders.

It is essential to continue research in this field, so that the true potencial of these formulations can be assessed and a transposition into the pharmaceutical industry is someday possible.

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Thank you