

# Investigation of drug release and permeability behavior of different species-specific serum albumin nanoparticles

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## Introduction

Albumin is a versatile, biodegradable drug carrier for numerous therapeutic agents that have poor water solubility, pharmacokinetics, low circulation half-life, inefficient targetability and even instability in vivo. Strategies for applying albumin for drug delivery can be classified broadly into exogenous and in situ binding formulations that utilize covalent attachment, non-covalent association, or encapsulation of the drug in the form of albumin-based nanoparticles (Hoogenboezem et al., 2018). Nasal administration can be a suitable means of transport route for that purpose, moreover it has been reported that the initial formation of Alzheimer's Disease begins in the entorhinal cortex, which region is innervated by olfactory nerves than it progresses according to corresponding pattern. Nano drug delivery systems as albumin-based nanoparticles are able to support bypassing the blood-brain barrier of transported drugs through the trigeminal and olfactory nerves, resulting in higher brain concentration.

## Materials and methods

Meloxicam (MEL) as a model drug was obtained from EGIS Ltd. (Budapest, Hungary). Human serum albumin (HSA), bovine serum albumin (BSA) and rat serum albumin (RSA) (lyophilized powder, purity > 97%) was purchased from Sigma Aldrich Co. Ltd. (Budapest, Hungary). Analytical grade solvents were purchased from Merck KGaA (Darmstadt, Germany). In all experiments,

purified water was purified by the Millipore Milli-Q® Gradient Water Purification System.

The application of different species-specific serum albumins (SSSAs) (human-HSA, bovine-BSA, rat-RSA) may result in different drug delivery properties. Present study aimed to investigate the effect of different SSA-based nanoparticles on drug release and permeability properties. As model drug meloxicam (MEL) a non-steroid anti-inflammatory agent (NSAID) was selected, which can be advantageous in the treatment of neurodegenerative disorders as it has improved anti-amnesic activity through inhibiting lipid peroxidation and acetylcholinesterase activity in the brain (Goverdhan et al., 2012). MEL-SSA nanoparticles were prepared by a modified coacervation method. Briefly, SSSA was dissolved in purified water and the pH was set to 8.5. MEL was dissolved in the albumin solution and incubated for 2 h. Thereafter, certain amount of Ethanol was added to the resultant solution dropwise until the solution become turbid. Various properties such as average hydrodynamic diameter (Z-average), polydispersity index (PdI), zeta potential, albumin binding capacity, in vitro drug release and permeability properties on RPMI 2650 cell-line were characterized.

## Results and discussion

MEL-SSSA binding studies conducted by rapid equilibrium dialysis revealed high protein binding of MEL (>96%), whereas in case of BSA the binding was only ~86%. These results supported, a secondary bond

stabilized complex between MEL and SSSA can be formed during 4.5 h incubation, which suggests adequate drug release after nasal absorption. After the drug binding studies the required amount of Ethanol used for coacervation was optimized in case of different SSSA. The Z-average, PdI and zeta potential was controlled during the precipitation in order to ensure similar colloidal properties for different MEL-SSSA nanoparticles and to exclude differences due to different Z-average, PdI and zeta potential (Table 1).

Table 1. Colloidal properties of MEL-SSSA

SSSA	Z-average (nm)	PdI	Zeta potential (mV)
HSA	218±5	0.236±0.051	-26.4±1.2
BSA	226±3	0.254±0.132	-24.9±1.9
RSA	215±7	0.261±0.09	-27.2±0.8

The colloidal parameters fit the requirement of nasal drug delivery (Z-average < 300 nm; PdI < 0.3), whereas the negative zeta potential hinders the uptake of nanoparticles through macrophages, therefore results in improved retention at the site of action.

*In vitro* drug release study showed MEL-SSSA nanoparticles improved the drug release rate in comparison to initial MEL suspension (Figure 1). Significant differences ( $p < 0.05$ ) were obtained between the different SSSAs, the highest MEL release rate was observed in case of MEL-HAS. Interestingly, RSA nanoparticles showed the lowest drug release tendency, however based on the binding studies the highest drug release rate was expected, as it showed the lowest drug binding efficacy.

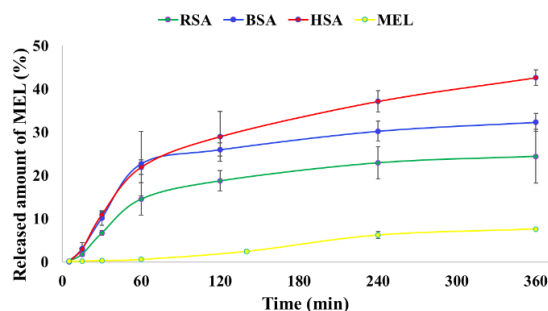


Fig. 1. Drug release profiles of MEL-SSSA nanoparticles in comparison to initial MEL suspension.

*In vitro* blood-brain barrier permeability studies revealed improved flux of MEL-SSSA nanoparticles in comparison in comparison to initial meloxicam solution, which further supports the need of an adequate nanocarrier system for efficient nose-to-brain transport. The highest

flux was obtained in case of MEL-HSA nanoparticles (Figure 2).

*In vitro* cell-permeability studies on RPMI2650 human endothelial cells showed similar results to *in vitro* blood-brain barrier permeability studies, each MEL-SSSA nanoparticles indicated almost two times higher permeability in comparison to initial MEL solution.

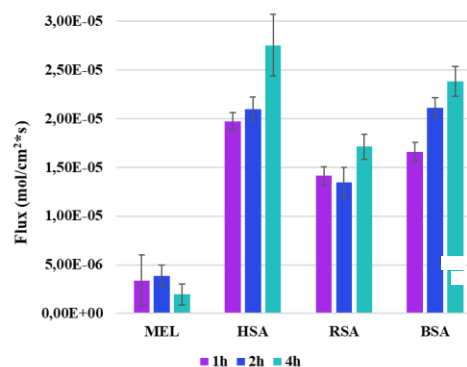


Fig. 2. Blood-brain permeability of MEL-SSSA nanoparticles in comparison to MEL solution.

## Conclusion

These results indicate different SSSA-based nanoparticles have different drug release and permeability properties, for intranasal administration of MEL the HSA-based formulation seemed to be potentially applicable as possible “value-added” product for the treatment of neuroinflammation.

**Acknowledgement:** This work was supported by Project no. TKP2021-EGA-32 implemented with support provided by the Ministry of Innovation and Technology of Hungary from the National Research, Development, and Innovation Fund, financed under the TKP2021-EGA funding scheme and by János Bolyai Research Scholarship of the Hungarian Academy of Sciences (G. Katona, BO/00251/21).

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