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Short communication

In vivo brain distribution study of dexamethasone encapsulated in polymeric and albumin-based nanocarriers

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Introduction

Nanomedicine is one of the leading fields in the pharma trends of the 21st century. Via utilization of the nano scale particle size, the advantageous properties of the individually applied excipients, value-added pharmaceutical preparations can be formulated. Such value lies in the field of polymer-based drug delivery systems, most specifically, polymeric micelles. These amphiphilic structures can offer high solubilization alongside with permeation enhancement. The same can be claimed about human serum albumin (HSA) nanoparticles where added value also lies in the fact that it reduces the risk of immunogenicity due to its biocompatible nature.

Nasal drug delivery can also be exploited in case of these nanoparticles. Via the direct nose-to-brain drug delivery pathway, the blood-brain barrier can be bypassed. This axonal pathway is manifested through the trigeminal and olfactory nerves. Otherwise, the large vascularized nasal mucosa offers high drug absorption as well.

Our aim in this current research was to develop dexamethasone (DXM)-loaded polymeric micelles and HSA nanoparticles and to characterize the brain distribution of DXM after intranasal administration..

Materials and methods

In case of the polymeric micelle formulation (DXM-PM), as polymeric micelle forming agents Soluplus and TPGS were applied. The formulation was performed via direct freeze-drying. Tert-butyl-alcoholic (t-BuOH) solution of DXM was prepared to which aqueous solution of Soluplus, TPGS and mannitol was added. The freeze-drying was performed after 6 h of freezing at -40°C, followed by 12 h of primary drying at -40°C, 0.013 mbar and later it was finished via the secondary drying at 25 °C, 0.013 mbar for 6 h.

In case of DXM-HSA formulation, the coacervation method was applied. At first, aqueous solution of HSA, Tween 80 was set at pH 8.0 using sodium hydroxide, then ethanolic solution of DXM was added dropwise to the aqueous phase. Later, pure ethanol was added dropwise to the mixture until visible turbidity was achieved. After incubation, the ethanol was rotary evaporated at 40°C, 25 rpm, and 100 mbar for 30 min.

To optimize the DXM-PM formulation, a 3-factor, 3-level Box-Behnken factorial design was evaluated. As independent factors, the amount of TPGS, Soluplus and the volume of the dissolving medium t-BuOH was chosen. As dependent variables, Z-average and polydispersity index (PdI) was investigated.

To optimize the DXM-HSA formulation, a 3^3 full factorial design was applied. As independent variables, the concentration of HSA, the volume of ethanol and the incubation time was chosen. The effect of these factors was investigated on the Z-average and PdI, as dependent factors.

The average hydrodynamic diameter (Z-average), the polydispersity index and the zeta potential of the formulations was measured via dynamic light scattering (DLS) using a Malvern Zetasizer Nano ZS (Malvern Instruments, Malvern, UK). The refractive index of DXm was 1.592 and the measurements took place in 25 °C.

In vivo pharmacokinetic measurements were performed on Sprague-Dawley rats. Intranasal administration was carried out via a pipette, whilst the rats were under isoflurane anesthesia. At predetermined time points, blood plasma was collected alongside with brain samples. The brain was divided into four sections:

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cerebrum, cerebellum, striatum, and olfactory bulb. The concentration was determined via LC-MS/MS technology. All the experiments involving animal subjects were carried out with the approval of the National Scientific Ethical Committee on Animal Experimentation (permission number: IV/1247/2017). The animals were treated in accordance with the European Communities Council Directives (2010/63/EU) and the Hungarian Act for the Protection of Animals in Research (Article 32 of Act XXVIII).

Results and discussion

In both cases, the optimalization processes were successful. After evaluating the factorial design regarding the DXM-PM formulation, the optimized preparation has an average hydrodynamic diameter of 89.92 ± 2.7 nm, which corresponds to the appropriate polymeric micelle size range. The PdI is 0.216 ± 0.014 which represents monodisperse distribution and the relatively high zeta potential value (-19.2 ± 4.5 mV) contributes to colloidal stability.

Regarding the DXM-HSA formulation, the Z-average value is 261.8 ± 11.5 nm, which is optimal in case of API-loaded albumin nanoparticles. The PdI is 0.154 ± 0.011 which also means monodisperse distribution. The zeta potential value is low (-5.85 ± 1.13 mV) which requires that the formulation should be reconstituted in water prior to administration in low dosage volumes.

In Fig. 1. the plasma concentrations of DXM can be seen regarding the reference IV injection compared to the nasal formulations. As it can be seen, there is no significant difference amongst the formulation, which in our case is beneficial, since it represents that the nasal administration can match the direct intravenous administration route with the added value of the nanocarriers.

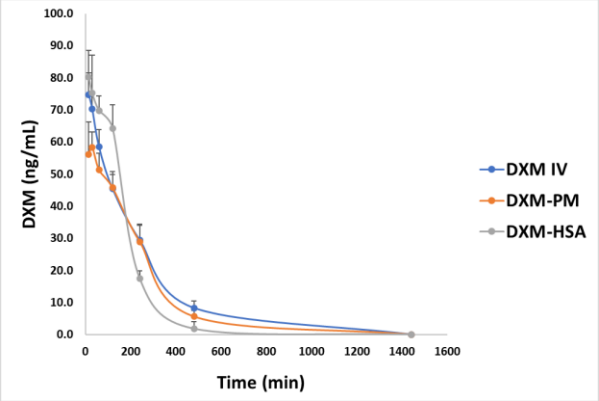

Fig. 1. Measured in vivo plasma concentrations of DXM after nasal administration of the formulations compared to the IV reference (n=5).

In Fig. 2. a sample of the brain DXM concentration studies can be seen. It can be concluded that both formulations exceeded higher brain DXM concentration compared to the IV reference. Regarding the DXM-HSA formulation, it was also significantly higher than the DXM-PM formulation.

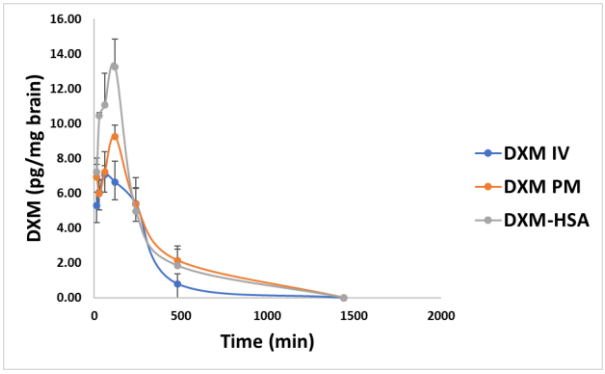

Fig. 2. In vivo cerebellum concentration of DXM from the the applied nasal formulations and the reference IV DXM injection (n=5).

Conclusion

Based on the in vivo results, the optimized nanocarriers provided higher brain concentration of the model drug in all cases which means that the added value of either polymeric or albumin-based carriers is necessary if we want to exploit the nasal drug delivery route.

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