INSULIN AGGLOMERATES FOR NASAL ADMINISTRATION TO PREVENT ALZHEIMER'S DISEASE

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Purpose

Several recent studies have showed that brain's insulin levels are related with Alzheimer's disease. Insulin is an important neurotrophic and neuroprotective factor in the context of an intact insulin signalling system; increased level demonstrated the capability to reduce β amyloid peptide precipitation and so slowing cognitive decline [1].
Insulin delivered to the brain by nasal route enables direct absorption through olfactory region, bypassing the BBB. The aim of this work was to produce and characterize insulin powder agglomerates containing mannitol and lecithin to prevent Alzheimer's disease.

Methods

A dry powder of recombinant human insulin was prepared by spray drying as previously described [2]. Insulin chimeral agglomerates, with a size suitable for a nasal administration, were obtained by tumbling (40 rpm for 30 min) the micronized insulin spray-dried with micronized excipients (mannitol:lecithin 90:10) in the ratios: 0.25:10 (Ins_A) and 1:10 (Ins_B). Agglomerates with a size 150-750 μm were collected by sieving and further characterized. Drug loading, morphology by SEM and nasal deposition after insufflation with three devices (powder loading=30 mg), were evaluated. *In vitro* dissolution of insulin spray-dried and insulin agglomerates was studied using Franz's cells in a Simulated Nasal Fluid (SNF) [3].

Results

Insulin spray-dried powder had a fine particle size ($d_{v\ 50}$ = 4.0 μm) and required a process to increase the size to address a nasal deposition avoiding powder penetration to the lungs. Thus, agglomerates were easily prepared and SEM showed their peculiar morphology: insulin particles surrounded by spherical particles of excipients.
Powder deposition in the nasal cast after insufflations from MIAT® and Puvlizer®, activated by squeezing, was equal to 81% and 75%, respectively. On the contrary, insulin deposition when the powder was emitted by Monopoudre® was 17% due to its excessive force which broke agglomerates.
In vitro dissolution profiles showed that agglomerates had a slower dissolution than insulin spray-dried. Both agglomerate formulations had a quite similar dissolution profile.

Conclusions

Recombinant human insulin nasal agglomerates have been successfully prepared for an efficacy targeting to the CNS, exploiting the nose to brain route.
The device choice is a critical factor that influence nasal deposition and, then the clinical efficacy.

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[2] A. G. Balducci, S. Cagnani, F. Sonvico, A. Rossi, P. Barata, G. Colombo, P. Colombo, F. Buttini. Pure insulin highly respirable powders for inhalation. Eur J Pharm Sci. Vol. 51 (2014), pp. 110-117.

[3] L. Illum. Nasal drug delivery-possibilities, problems and solutions. J Controlled Rel. Vol. 87 (2003), pp.187-198.