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Abstract:

Trans-resveratrol, due to its antioxidant property, has the potential to be successfully applied in the prevention and the treatment of neurological disorders (Parkinson's and Alzheimer's disease). Nevertheless, its traditional administration (intravenous, oral) and bioavailability are limited by its physical-chemical characteristics (solubility, chemical instability, sensitivity to heat, UV-light and pH). The 'nose-to-brain' application, as an alternate administration route, represents a way to reach the brain without the limitations of the blood-brain barrier, while the use of nano-sized drug delivery systems, like the liposomes, can overcome the developmental and therapeutic issues of the formulations.

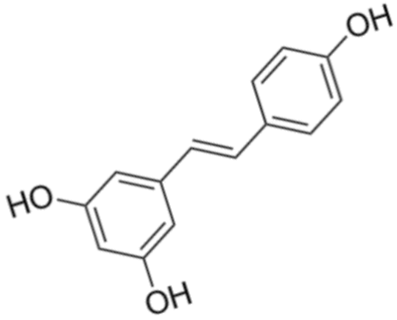

Figure 1. Structural formula of trans-resveratrol

This research paper shows the application of Risk Assessment, the key element of the Quality by Design mindset, in the development of a liposomal resveratrol-containing formulation with brain target and nasal administration.

The study intends to demonstrate the definition of the quality target product profile, the selection of the critical factors, and the application of the RA to get a detailed view on the critical parts of the development process.

On these terms, the factors with the most significant impact on the product quality among the critical material attributes (phospholipids, active pharmaceutical ingredient (API) content, cholesterol ratio, surface modification), furthermore the production process (temperature, oxidation and light protection) were identified; subsequently, an RA-based liposome preparation process was described.

The formulation procedures of 'nose-to-brain' liposomal systems loaded with drugs with many limiting factors meet several risks; however, the adaption of the QbD tools helps to focus on the aimed final product quality and achieve effective experimental designs.

Keywords: liposome; resveratrol; nose-to-brain; Quality by Design; Risk Assessment

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Results and Discussion

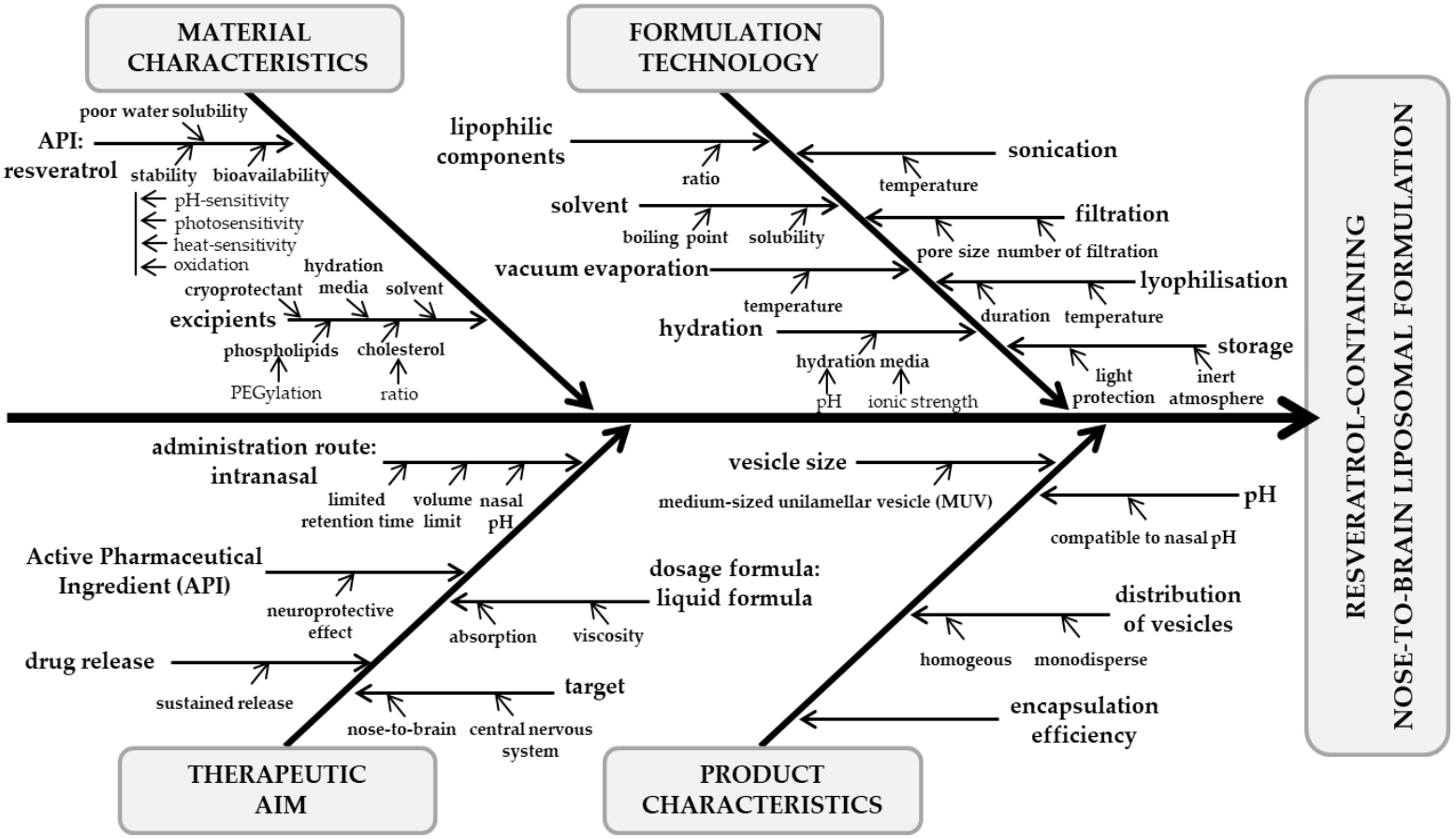

Figure 2. Ishikawa diagram for the evaluation of the cause-and-effect relationships in the trans-resveratrol containing ‚nose-to-brain' liposomal formulation

An Ishikawa diagram was designed to organise the knowledge and the requirements what are needed to execute a successful experimental design. The fishbone diagram collects the most important material quality and formulation requirements, furthermore the therapeutic and target product-oriented aspects.

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Results and Discussion

QTPP	details	CQAs	details
indication	neuroprotection	morphology of liposomes	spherical conventional vesicles
target patient population	ageing population	size of vesicles	medium-sized unilamellar vesicles (MUV)
route of administration	"nose-to-brain"	surface modification	polyethylene glycol (PEG) chains
dosage form	aqueous solution; lyophilised plaques	polydispersity	monodisperse formulation
drug target	dopaminergic neurons; β-amyloid plaques	zeta potential	highly charged
drug release	sustained release	phase transition temperature	formulation-suitable, trans-resveratrol decreases the value
viscosity	enough but not too viscous	API content	trans-resveratrol -containing vesicles
osmolarity	tolerable	position of the API	in the lipophilic double membrane
pH	suitable for intranasal administration and trans-resveratrol stability	encapsulation efficiency	high value
stability	stable formulation		
homogeneity	homogenous formulation		

Table 1. QTPP and CQAs of the trans-resveratrol-containing "nose-to-brain" liposomal formulation

The profile of the target product (QTPP) and the quality requirements of the formulation (CQAs) are summarised in Table 1. The QTPP depends mainly on the therapeutic or clinical aims and requirements, the characteristics of the drug substance, the administration route and the dose of the drug. This collection of the properties is always unique for a formulation. The CQAs of the product are the physical, chemical, biological and microbiological properties that should reach the indicated quality, range or limit to ensure the consistent end-product quality. For example, the features of liposomes, the size, the size distribution and the surface charge of the vesicles, furthermore the API-related properties of the formulation can be a part of the CQAs. These factors are also always unique for the preparation and depend on the QTPP.

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Results and Discussion

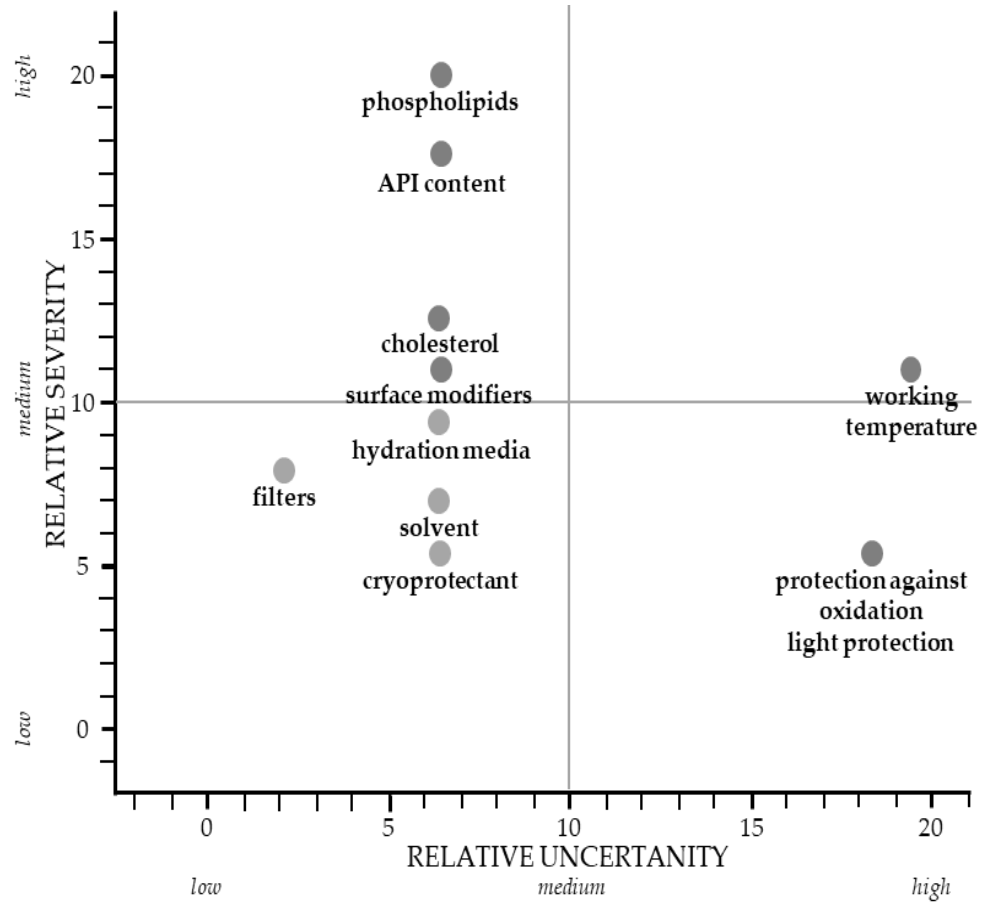

Figure 3. Relative severity-relative uncertainty diagram presenting the CMAs and CPPs of the formulation as a result of the RA

The relative severity-relative uncertainty diagram, as a result of the RA, has shown that the liposome wall-forming agents, the quality of the hydration media and the solvent used in the formulation, the applied temperature, the oxidation and the protection against light are the riskiest steps and factors during the manufacturing process and should get the most attention. The results also mean that the quality of the product can be influenced the easiest by changing the parameters related to the wall-forming agents (ratio, quality) and the trans-resveratrol-content. At the same time, the most critical point of the manufacturing process is the working temperature, because its change has a great impact on the outcome.

The effect of the CMAs and CPPs can be accurately investigated if some of the values are set on the same level, while the ones under the scope of the study are being changed according to the Design of the Experiment.

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Conclusions

Even though trans-resveratrol displays several health-beneficial properties and possesses remarkably strong antioxidant activity, its positive effects are restricted by the characteristics of the compound itself. The paper showed the opportunities of a liposomal formulation containing trans-resveratrol as an active ingredient, designed for the "nose-to-brain" administration route, the technological challenges of development and their possible solutions by applying the QbD approach during the design phase of the research. As a conclusion, we can say that the RA highlights the critical points of the formulation process, and in this way helps to achieve the targeted quality for the product. Applying the QbD approach to design pharmaceutical formulations is a functioning way to improve the development process of the pharmaceutical formulations by collecting the proper information, optimising and rationalising the required experiments and measurements. The determination of the critical features and parameters (QTPPs, CQAs, and CPPs) provides a holistic network of information that can be useful to achieve a more effective experimental design.

Acknowledgments

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