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Glabridin smartPearls – selection of appropriate mesoporous particles & optimization of production conditions

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Glabridin can be extracted from the roots of Glycyrrhiza glabra. It efficiently inhibits the tyrosinase activity [1], therefore, can be used either in cosmetics against pigment disorders as a whitening agent with natural origins or in pharmaceutics as an API against melanoma. The obstacle for practical use of glabridin is its insufficient dermal bioavailability due to its poor solubility, e.g. in water. Attempts have already been made to increase its water solubility, for example chemical modifications [2]. However, the tyrosinase inhibiting properties drastically decreased. Also using another solvent, e.g. alcohols or high surfactant concentrations are not suitable for skin application. Therefore, up to now no satisfying solution were found.
One approach to increase the glabridin solubility in water and thus its dermal bioavailability without reducing its efficacy is the use of smartPearls as dermal delivery system. smartPearls are mesoporous silica particles in which an active can be loaded and long-term stabilized in amorphous state. Compared to the crystalline active, the solubility is pronouncedly increased [3]. In addition, pore sizes are in nm range. Consequently, the active is nano-dispersed, showing the same solubility increasing effects as for nanocrystals.
Therefore, aim of this study was to find appropriate mesoporous silica particles as well as suitable conditions to produce stable glabridin loaded smartPearls.

Silica particles with different pore sizes (3, 6, 10, 17 nm) were loaded with glabridin by the solvent evaporation method. Means, defined amounts of ethanolic glabridin solutions (ratio 9:1) were added to respective silica particles followed by controlled ethanol evaporation at 150 mbar and 40 °C for at least one hour. The so obtained loaded silica particles were further dried for 12 h under vacuum to obtain the final glabridin smartPearls. Amorphous state of loaded glabridin was confirmed by dynamic scanning calorimetry (DSC), showing the absence of crystallinity peaks in respective thermograms. Localization of glabridin in the different sized pores was verified by nitrogen ad- and desorption, relating the BET surface, pore volume and pore size. Difference of theoretical and real loading was investigated by high pressure liquid chromatography (HPLC). For storage stability investigations, all measurements were repeated after one week and one month.

HPLC showed that both theoretical and real loading of 36% are congruent with each other, proving that the solvent evaporation method is gentle and even suitable for loading chemically highly sensitive actives e.g. glabridin. However, DSC thermograms revealed that not all silica were suitable for the production of glabridin smartPearls. Silica with pore sizes of 3 and 17 nm had crystallinity peaks, indicating the presence of a non-amorphous glabridin fraction. In contrast, silica with pore sizes of 6 and 10 nm were indeed able to form crystalline free smartPearls and

stabilize this state for 1 month up to now. Therefore, it can be concluded, that the successful loading is much affected by the ratio of pore size to molecule size and should be considered beforehand to select the most suitable silica. Nitrogen ad- and desorption revealed that the pores of the smartPearls were evenly filled from bottom to top, having a concave shape. Due to the nano-sized pores the surface area of glabridin is increased. Following the Noyes Whitney equation, an increased saturation solubility as well as dissolution velocity can be assumed. Further, the strongly curved surface of the concave shaped interface will lead to an increased dissolution pressure according to the Kelvin equation. Altogether, a supersaturated state of glabridin will be reached, finally increasing the dermal bioavailability.

Summarizing, the solvent evaporation method is suitable for smartPearls production even for the chemically labile active glabridin. A high loading of 36% can be achieved in one loading step. Silica for loading should be selected carefully beforehand in dependence of the pore size and the to be loaded active. Further investigations will follow to confirm the long-term storage stability of amorphous state as well as the resulting increased saturation solubility and dermal bioavailability of glabridin smartPearls.

References

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