Design of Nano-Sized Carrier for Delivery of Natural Compounds with Pharmacological Activity

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（薬理活性を有する天然化合物の薬物送達ナノキャリアの設計）

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論 文 内 容 の 要 旨

Natural compounds have a great potential for to cure or prevent a number of diseases, due to they have biological function as well as pharmacological activities in biomedicine. However, delivery of natural compounds into the target disease remains challenging. The aim of this work is to deliver natural compounds, such as protein and small molecular natural products using surfactant-based nano-carrier. For this purpose, phycocyanin (PC) and curcumin (Cur) were selected as model therapeutic agents, which are a naturally occurring protein and natural products, respectively. PC, a water-soluble protein-chromophore complex composed of hexameric $\alpha_6\beta_6$ subunits, has important biological functions in blue-green algae as well as pharmacological activities in biomedicine, such as anticancer, anti-inflammantory, and antidiabetic. In addition, Cur, a hydrophobic polyphenol compound, holds promising potential as an anticancer agent.

In Chapter 2, the mechanism of transcutaneous protein delivery using a solid-in-oil (S/O) nanodispersion method was investigated. PC, a protein-chromophore complex, as a model protein was chosen to evaluate how the proteinaceous macromolecules formulated in an oil phase might permeate the skin. The solid-in-oil (S/O) nanodispersion was prepared by coating PC with hydrophobic surfactants. The extent of S/O nanodispersion of PC was dependent on the type of surfactant, suggesting that the selection of a suitable surfactant is crucial for encapsulating a large protein having a subunit structure. By measuring the intrinsic fluorescence of PC, we found that S/O nanodispersion facilitated the accumulation of PC in the stratum corneum (SC) of Yucatan micropig skin. Furthermore, after crossing the SC layer, the fluorescent recovery of PC was evident, indicating the release of the biologically active form of PC from the SC into the deeper skin layer.

Based on the findings in Chapter 2, the conformational structure of proteins formulated in oil phase was influenced to their functional integrity after released from the formulation, thus in Chapter 3, a novel oil-based drug delivery system, namely gel-in-oil (G/O) nanodispersion, was proposed to stabilize proteins. G/O nanodispersion has a gel core oil-based system for protein delivery, which the trapping protein drugs in the gelatin-based hydrogel coated with a hydrophobic surfactant using

emulsion technology. PC was loaded in G/O nanodispersion as model protein, and was evaluated their functional integrity and skin permeability. A nano-sized range of particle with high entrapment efficiency of protein was achieved by G/O nanodispersion. Spectroscopic studies indicated that G/O nanodispersion might able to retain and protect an active form of PC. The gelatin concentration is a key factor for stabilizing the native structure of PC in G/O nanodispersion. *In vitro* skin permeation studies showed the enhanced permeability of protein delivery through the deep skin layer using G/O nanodispersion with a low concentration of surfactant.

In Chapter 4, the formulation of curcumin using a solid-in-water (S/W) nanodispersion technique to enhance water solubility and therapeutic activity of curcumin was studied. This new aqueous formulation comprises simple preparation protocols: emulsification and freeze-drying for encapsulating hydrophobic biomolecules with a hydrophilic surfactant, followed by redispersion of the resultant solid complexes in an aqueous solution. Pluronic F68 and F127 were used here for the encapsulation of curcumin. Enhanced aqueous solubility of curcumin was achieved by encapsulating curcumin with a hydrophilic surfactant using the S/W nanodispersion technique. The resultant nano-sized formulation had a narrow size distribution and high entrapment efficiency of curcumin. The highest loading capacity of curcumin in S/W nanodispersion was obtained with a weight ratio of curcumin to Pluronic of 1:10 for both surfactants. The release profile of the complexes was found to depend on the type of surfactant, suggesting that the selection of a proper surfactant is crucial for controlling curcumin delivery. The anticancer activity of the S/W formulation of curcumin was correlated with the drug release profiles and cellular uptake, which in turn was influenced by the hydrophobicity and chemical structure of the surfactant.

〔作成要領〕

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