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Pharmaceutical Microbiology 2018 -Study on physicochemical interaction between a variety of saccharide and nanoparticles during freeze-drying and normal drying- Seitaro Kamiya- Nagasaki International University

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There are many reports on the in vivo behavior study of nanoparticles administered to the systemic circulation. However, there are few reports on the preservation of nanoparticles. It is very difficult to maintain the nanoparticle suspension state for a long-term storage because it is thermodynamically unstable. Thus, maintaining a constant state in nanoparticles is an important major issue. A lyophilization method with the addition of saccharides has been utilirized to maintain their particle size of nanoparticles. Despite this method is very predominant, the physicochemical intereaction between nanoparticles and saccharides was not studied till now.

At the present study, trisaccharides, tetrasaccharides, or pentasaccharides were added to the nanoparticle suspensions, followed by rehydration of the samples, which had been either dried normally or freeze-dried. The particle size after rehydration at that time was then measured. In addition, each saccharide was measured using a powder X-ray diffractometer and differential scanning calorimetry (DSC) device. We studied the association between the nanoparticles aggregation and the crystal form of saccharides and their mechanisms by using the obtained results of the data of particle size, powder X-ray pattern, and DSC curves. The particle size of the nanoparticles was maintained when it was freeze-dried, while particle aggregation occurred when normal dried samples were used. In addition, crystallinity of each saccharide was not observed in the in the freeze-dried group but was in the normal dried group.

Since their early discovery by Bangham et al. in 1965,1 the advantages of liposomes as drug carriers have been quickly recognized and intensive research efforts have been made with the outcome of translating liposomal formulations into marketable products.2 One of the obstacles that has been limiting the availability of therapeutic products on the market, along to demonstration of efficacy, is attributed to the physical (leaking, fusion, aggregation) and chemical instability (hydrolysis and oxidation of the lipids) of liposomes on long-term storage, when formulated as aqueous dispersions.3 Freeze-drying represents an attractive way to overcome these stability issues and has been proved to increase the shelf-life of liposomes and preserve them in a more stable dry state. Nevertheless, the freeze-drying process can generate stress during the freezing and drying steps. Hence, one of the major challenges is to identify the optimum lyophilization conditions, to maintain certain desired characteristics of the final product: an appropriate cake appearance with a rapid reconstitution time, acceptable physico-chemical characteristics (unmodified particle size, narrow size distribution, and small percentage of leaked drug), and a low residual moisture content

membrane vesicles by sugars is associated with the ability of sugars to form a glassy matrix, which can prevent aggregation and mechanical stress from the crystallization of ice.11-13 The formulation of a freeze-dried product not only requires the consideration of a suitable carbohydrate as lyoprotectant but also the optimization of the lyoprotectant concentration and a careful consideration of the processing parameters, such as freezing conditions and

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primary and secondary drying protocol, to guarantee the quality of the final product.14 Liposomes loaded with prednisolone sodium phosphate (PLP) and coated with polyethylene glycol (PEG) were selected as a model for our study. PEGylation of the liposomes was applied to protect liposomes from recognition and rapid removal from the circulation by the mononuclear phagocyte system and to allow the liposomes to extravasate and accumulate in tumors, hence the terminology long-circulating liposomes (LCL-PLP).15,16 In-line vibrational spectroscopic techniques such as nearinfrared (NIR) and Raman spectroscopy have previously demonstrated to be able to provide valuable product information during the entire freeze-drying process.17-20 NIR spectroscopy technique offers the advantages of being fast, nondestructive, and noninvasive; does not require sample preparation18; and allows us to continuously monitor chemical and physical phenomena occurring during freeze drying, with the outcome of increasing process understanding and process knowledge.21 Previous studies from Christensen et al.22 and Porfire et al.23 demonstrated that it is possible to apply off-line NIR spectroscopy to determine the lipid content of liposomes, with a precision and accuracy as good as for HPLC and differential scanning calorimetry (DSC) methods. To our knowledge, the ability of NIR spectroscopy to predict critical changes in acyl chain packing of the liposome bilayers, by monitoring the specific bands for phospholipids, has not been yet investigated. Therefore, the aim of this study was to optimize the formulation of a freeze-dried liposomal product in terms of lyoprotectant type and concentration, to assure the desired characteristics of the final product. The choice of lyoprotectant type and concentration was based on analysis of the encapsulated drug percentage, assessment of size, and size distribution of the liposomes before and after freeze-drying, investigations of the carbohydrates' influence on liposomal stability through DSC and FTIR measurements and analysis of the cake morphology by means of scanning electron microscopy (SEM). Furthermore, we examined whether NIR spectroscopy combined with chemometry allows us to build a multivariate model that would enable us to obtain a better understanding the critical changes occurring in acyl chain packing of the liposome bilayers. Changes in acyl chain packing can reflect the damage caused during the process, being closely correlated with the lipid phase transition and aggregation/fusion of vesicles. Moreover, we investigated into the possibility to determine the end point of drying phases, which would allow optimization of the cycle parameters.

Injectable products are often the formulation of choice for new therapeutics; however, formulation in liquids often enhances degradation through hydrolysis. Thus, freeze-drying (lyophilization) is regularly used in pharmaceutical manufacture to reduce water activity. Here we examine its contribution to 'state of the art' and look at its future potential uses. A comprehensive search of patent databases was conducted to characterize the international patent landscape and trends in the use of freeze-drying. A total of 914 disclosures related to freeze-drying, lyophilization or drying of solid systems in pressures and temperatures equivalent to those of freeze-drying were considered over the period of 1992-2014. Current applications of sublimation technology were contrasted across two periods those with patents due to expire (1992-1993) and those currently filed. The number of freeze-drying technology patents has stabilized after initial activity across the biotechnology sector in 2011 and 2012. Alongside an increasing trend for patent submissions, freeze-drying submissions have slowed since 2002 and is indicative of a level of maturity.

Biography

Seitaro Kamiya has completed his PhD at the age of 27 years from University of Shizuoka and entered employment as assistant professor at a Faculty of Pharmaceutical Sciences Nagasaki

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