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Pharmaceutical formulation analysis of gelatin-based soft capsule film sheets using near-infrared spectroscopy

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ABSTRACT

In order to investigate the properties of gelatin film sheets for soft gelatin shell capsules, we compared gelatin and succinylated gelatin film sheets using dynamic vapor sorption (DVS), static near infrared (NIR), and dynamic NIR during tensile strength measurements. A steep increase in the amount of water vapor absorbed was observed with relative humidity > 70% for both gelatin and succinylated gelatin film sheets. From the static NIR measurement, it was considered that the −OH alcohol groups in glycerin were coordinated with gelatin or succinylated gelatin molecules by replacing H_2O in the gelatin or succinylated gelatin film sheets as the glycerin concentration increased. It was found that gelatin molecules showed a change in the molecular net structure before and after stress, but this phenomenon was not observed for the succinylated gelatin film sheets. The properties of gelatin simultaneously explained the flexibility and stronger resistance to contortion. In relation to these results, we considered that the gelatin molecules made a stronger net structure among gelatin-water-glycerin complexes because of the free ε-NH_2 groups compared with succinylated gelatin.

1. Introduction

Soft capsules are a commonly used dosage form [1–3]. Such soft capsules are prepared using two methods: rotary die and falling seamless droplet methods. The rotary die process is more effective for the mass production of soft capsules. A fundamental step in the rotary die process of producing soft capsules is to prepare a film sheet because the soft capsules are produced by superposing two film sheets while encapsulating a liquid or semi-solid fill. Thus, the quality of the finished soft capsules depends on the properties of the film sheet used. Because quality control of the film sheet is very important, the physical properties of gelatin sheets of shells have been investigated [4,5]. The aqueous solution of gelatin shows the sol-gel transition phenomena reversibly depending on the temperature. Although gelatin has good film-forming properties, there are 3 types of interaction between film sheets and content of soft capsules, interfacial chemical reaction, inward or outward components transfer through the interface. The typical interfacial chemical reaction is the condensation reaction of the amino groups of gelatin with an aldehyde of content. On the dosage form design, we should consider the quality of soft capsules will be maintained after product release. Gelatin-based film sheets for soft capsule shells are usually manufactured as a mixture of gelatin and plasticizer, plus various additives [6,7], and the representative plasticizer is glycerin. Bergo et al. [8] and Vanin et al. [9] reported that the plasticizers, especially glycerin, reduce the interactions between the adjacent gelatin chains in the gelatin films using the FTIR spectrum, XRD and tensile strength. Glycerin has useful effect on film forming properties such as high flexibility and toughness by reduction of adjacent gelatin-gelatin interaction, lowering the glass transition temperature and stabilizing the gel-state of films in accordance with the glycerin content.

In order to prepare the film sheet, gelatin is mixed with water and glycerin, then heated to about 70 °C while mixing gently to make a homogeneous solution [5]. When it is needed to prevent gelatin molecules from cross-linking because of chain reactions of aldehyde-containing fill [10–14], various additives or succinylated gelatin are mixed with the gelatin solution [10,15–18]. One characteristic feature of gelatin is subject to aging or reaction with content which contains aldehyde, cinnamic acid, peroxide or radicals. The phenomenon is caused by the formation of additional intermolecular bonds (cross-links) and is manifested by the loss of solubility which leads to the prolongation of the disintegration time of soft capsules. The formation of the chemical cross-links involves predominantly the ε-amino groups of lysine and

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hydroxylysine. In order to conquer the cross-links issue, succinylated gelatin was introduced by the blocking of free ε-amino groups using the anhydride of succinic acid. Succinylated gelatin was used alone or mixed to gelatin for the soft capsule film sheets.

Zaupa et al. [18] reported that collagen has a triple helix structure with weak and cooperative forces. However, gelatin chains are disrupted to random coil structure over the helix-to-coil transition temperature. Cooling of the gelatin solution results in physically cross-linked gels (film sheets formation) that possess partially re-associated collagen-like triple helices below the helix-to-coil transition temperature [12,18,19]. Istranova et al. [20] reported that the triple helix structure is retained in succinylated collagen using optical rotatory power. Therefore, it is thought that succinylated gelatin may retain the triple helix structure of initial (non-modified) gelatin.

As shown in above section, there are many reports regarding chemical studies for the gelatin as pure chemicals, but there are little studies regarding the production of soft gelatin type shell capsules using process analytical technology (PAT). The difference of gelatin and succinylated gelatin films from the view point of physical properties and molecular orientation are also not well studied. The aim of this work is to obtain the basic data for continuous production of soft gelatin type shell capsules based on the PAT control. We investigated the effect of glycerin contents on properties of gelatin and succinylated gelatin film sheets using dynamic vapor sorption (DVS), tensile strength, static near infrared (NIR), and dynamic NIR measurements during tensile strength tests in order to obtain insights into the structural changes occurring in gelatin capsules. NIR spectroscopy has a wide variety of applications for chemical, physical, and process analysis [21–28]. The NIR spectral range extends from 780 nm to 2500 nm (from 12800 cm^{-1} to 4000 cm^{-1}). NIR spectra are dominated by C—H, N—H, O—H, and S—H overtones and combinations of fundamental mid-infrared (MIR) vibrations [29]. Because absorptivity in the NIR range is low, radiation can penetrate up to several millimeters into materials, including solids. Suitable chemometric analysis may be required for the identification of absorption bands because of the broad and overlapped bands. NIR spectroscopy provides not only quantitative but also qualitative information involving molecular interactions such as with hydrogen bonds [30]. Generally, a number of hydrated water and functional groups including protons, such as hydroxyl and carboxyl groups, exist in pharmaceutical formulations. The interaction between these functional groups contributes to gelatin film sheet formation. Thus, it should be possible to predict the film properties and the effect of agents that inhibit the cross-linking of gelatin by monitoring the NIR spectral change in the molecular interaction. DVS is a gravimetric technique that measures how quickly and how much water vapor is absorbed by a sample. The change in mass is measured while varying the relative humidity (RH) surrounding the sample.

2. Materials and methods

2.1. Materials

Gelatin (porcine, bone/skin, alkali treated) and succinylated gelatin were provided by Nippi Incorporated (Tokyo, Japan). Reagent grade glycerin (NOF Corporation, Tokyo, Japan) was used as received. Purified water (Milli-Q, Gradient A-10, Millipore, Merck KGaA Darmstadt, Germany) was used to prepare a solution in all experiments.

2.2. Preparation of the gelatin and succinylated gelatin film sheets

Various amounts of glycerin (0, 6, 12, 18, 24, 30, or 36 g) were mixed with 60 g of gelatin or succinylated gelatin in a beaker, and 122 g of purified water was added. The mixture was heated in a water bath at 70 °C. The mixture was stirred with a spatula every 15 min for an hour. After the mixture melted completely, the resultant solution was further incubated for 4 h at 60 °C to remove air bubbles. After gently stirring the gelatin or succinylated gelatin solution, 15 g of the solution was poured into a glass petri dish of about 10 cm diameter as a liquid reservoir. The gelatin or succinylated gelatin film sheets were prepared on a glass petri dish by drying under air blown at 30 °C for 2 h and after reversing the film for additionally drying at 25 °C for 16 h. The water content of the film sheet was measured using an infrared moisture determination balance (Digital Thermometer FD-720, Kett Electric Laboratory, Tokyo, Japan) with a 1 g of sample after heating at 115 °C for 15 min. The concentrations of glycerin are presented as the W/W (%) ratio to gelatin or succinylated gelatin.

2.3. Measurement of dynamic vapor sorption

A 2 mg film sample was placed in a sample pan and after reaching equilibrium, water sorption/desorption data were collected using a DVS instrument (Surface Measurement Systems Ltd., London, UK) for gelatin-based film sheets containing 0–60% glycerin concentration at 25 °C with relative humidity (RH) 0–90%.

2.4. Measurement of near infrared

2.4.1. Near infrared (static near infrared)

Static NIR spectra of the gelatin-based film sheets containing 0–60% glycerin were collected using a NIR spectrometer (FT-NIR, MPA, Bruker

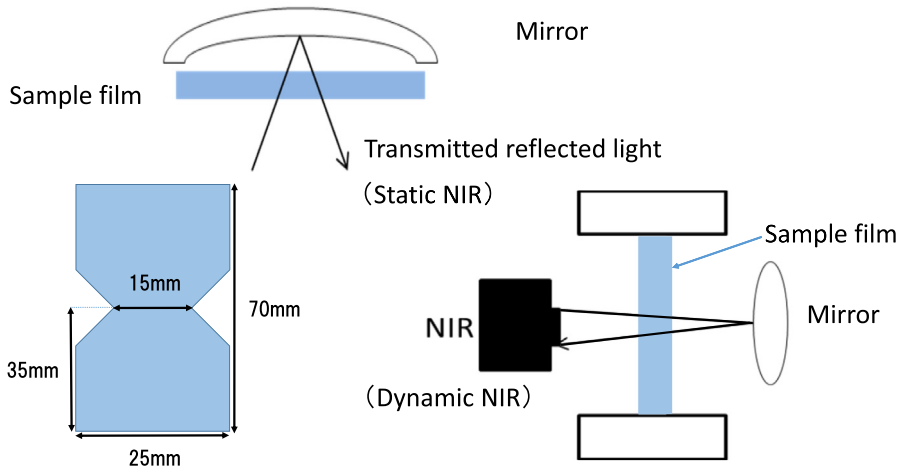

Fig. 1. Diagram of measurement by near-infrared spectroscopy of a film sheet sample: transmitted reflected light (static NIR) and NIR during dynamic stretching test (dynamic NIR).