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EFFECT OF WATER-INSOLUBLE POWDER ADDITION ON PHYSICAL PROPERTIES OF GELATIN GEL

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ABSTRACT

Water-insoluble powder is often dispersed in shells of commercial soft capsules for various reasons, but little reports have been published about the effect of powder addition on the physical properties of the gelatin gel. Glass powder, titanium oxide, calcium carbonate and γ-orizanol were used as model of powder. Changes of Young modulus obtained from the tensile test showed that any powder addition to the gelatin sheet made the gelatin sheet hard not by the surface effect of powder but by the volumetric effect of it. In this test, any powders had no effect on the tensile strength of the gelatin sheet because there was little interaction between each powder and the gelatin gel in the break point. The limiting strain was

decreased a little up to the specific amount of each powder and then beyond the specific amount that decreased steeply in the case of glass powder and γ-orizanol. There might be a suitable range of the amount of powder for the gelatin sheet to keep the plastic flow similar to the gelatin sheet containing no powder. In this work, it was shown that the physical properties of the gelatin shell would be regulated by powder addition to the gelatin sheet.

INTRODUCTION

Soft capsules are unique pharmaceutical forms to make the oily drugs such as liquid, suspension and semisolids, the solid formulation by sealed them in the shell of gelatin. Since soft capsules have the protective barrier against external conditions such as oxidation[1], moisture[2] and light[3], these forms are optimum for the stability of active ingredients. In addition, these forms are known to have several pharmaceutical benefits ; optimum bioavailability[4,5], enhancement of absorption of slightly soluble drugs[6] and higher accuracy of single dosages[5]. At the view point of marketing benefits, these forms offer high commercial performance[7] because their appearance will be designed **freely** to have excellent color or shape.

In general the shells of soft capsules are mainly prepared with gelatin and plasticizer and occasionally contain water-insoluble materials such as titanium oxide or calcium carbonate for various purposes. Titanium oxide is dispersed in the shells of soft capsules as light-resistant reagent for the photosensitive drugs [2]. Calcium carbonate reacts with (gastric) acid with the evaluation of carbon dioxide. Utilizing this phenomena, calcium carbonate is added in the shells to reduce the integration time of administered capsules in stomach. If materials added in the shells have relatively small solubility in water, these materials would crystallize under the dryness of the shell.

It is assumed that such powder added in gelatin shell has several effects on the various physical properties of soft capsules. The shells of soft capsules play a role of container for oily drugs[5] so that the physical strength of the shell is very important. But, the effect of powder addition on the physical properties of gelatin gel has not been studied enough now. So the purpose of this work is to clarify the effect of powder addition on the properties of gelatin sheet.

MATERIALS AND METHODS

Materials and Preparations

The basic composition of the gelatin sheet was as follows ; alkali-processed gelatin (Nippi Gelatin INC., Japan), concentrated glycerin (40 parts by weight per hundred of gelatin by weight ; Nihon Yushi Co.,Ltd., Japan) as plasticizer, ethyl p-hydroxybenzonate (0.3 parts; Midori Chemical Co., Ltd., Japan) and n-propyl p-hydroxybenzonate (0.1 parts; Midori Chemical Co., Ltd., Japan) as preservatives. All components were dissolved in 140 parts of water by weight per 100 parts gelatin by weight, maintained at 70 ℃ for 2 hr with occasionally stirring. Under heating condition the solution was degassed by centrifugation, and subsequently was spread over a glass plate (200mm×200mm). Finally the sheet was cooled slowly to room temperature. Parts of the gelatin sheet were used as samples of thermal analysis without drying. The residual parts of the gelatin sheet were dried enough and confirmed that the weight loss after 2hr heating at 105℃ was 3.0 wt%. Then these were employed as samples of mechanical test. Spherical glass powder (Toshinriko Co., Ltd., Japan) was finally chosen as a model of powder because the glass powder had the regular shapes (i.e. sphere) and were sieved to classify into several different particle size with narrow distribution in size range.

Each of glass powders following average diameters (50, 75.5, 110, 214μm) was used to investigate the effect of particle size. Each particle of 40 parts by weight per hundred parts of gelatin by weight was added to the above gelatin solution. Titanium oxide (Chitan Industry Co., Ltd., Japan) and calcium carbonate (Kanto Chemical Co., INC., Japan) were chosen as the examples of inorganic powder. γ-Orizanol (Tsuno Finechemicals Co., Ltd, Japan) was chosen as the example of organic drug powder and was insoluble in water. The effect of the amount of powder was investigated using the glass powder (average diameters of 50 μm) and these powders in following range ; glass powder, from 10 parts to 80 parts ; titanium oxide, from 5 parts to 20 parts ; calcium carbonate, from 10 parts to 40 parts ; γ-orizanol, from 10 parts to 25 parts by weight /100 parts gelatin by weight. The sheets containing titanium oxide or calcium carbonate were prepared in the same manner as the glass powder. On the other hand, γ-orizanol was dispersed enough in concentrated glycerin by using high speed and high shear batch mixer (TK Homo-mixer,Tokushu kika Co., Ltd., Japan), then the dispersed fluid was completely mixed with the gelatin solution.

Tensile Test

Mechanical properties of each gelatin sheet were determined using tensile tester (STROGRAPH M-50, Toyou Seiki Co., Ltd, Japan) operated at a cross-head speed of 50mm/min.. Dumb-bell shaped specimens of the gelatin sheet prepared above were cut from with 10mm wide, 15mm long in central portion. Young modulus of each specimen was determined by the variation of extended length y as a function of applied stress P [8,9]. Namely, the ratio P/y is corresponded to the slope of the initial linearity before yield stress on the strain-stress curve. The specimen finally reached the break point, being loaded continuously beyond the yield stress. The limiting strain and the tensile strength were obtained from the break point because for soft capsules the break of the shells is the worst state.

Thermal Analysis

Thermal analysis was carried out by the thermal analyzer system (Mac Science Co., Ltd, Japan). The melting points of gelatin sheets were determined by using differential scanning calorimeter under closed condition. Samples were heated at the rate of 10 degree/min from 0℃ to 65℃ and endothermic peaks were observed with melting of the gelatin gel. The softening points of gelatin sheets were determined by using the thermal mechanical analyzer. The penetration mode (10g of load) was applied to this measurement with heating from room temperature to 65 ℃ at the rate of 10 degree/min.

RESULTS AND DISCUSSION

Effect of Glass Particle Size

The shells of soft capsules play the role of the container for drugs. Therefore, the physical strength of the shells is one of very important factors for soft capsules. Figure 1 shows the variation of Young modulus and tensile strength of the gelatin sheet with various particle size of glass powder. Young modulus of the control gelatin sheet (the symbol of particle size zero shows the basic gelatin sheet containing no glass powder) was 3.48×10^3 N/m. Young moduli of the gelatin sheets with any glass powders was higher than that of the control gelatin sheet. Young modulus of the gelatin sheet represents the hardness of gelatin shells. Hence, powder addition to the gelatin shell will make the gelatin shells harder than the shells containing no powder. In the field of polymer material science, similar phenomena was reported in the case of filler addition to rubber or resin and was applied to modify their characteristics[9]. The reinforce of polymer was considered to depend on either the total volume of the filler in the polymer or the total surface area of it[10]. Young moduli were

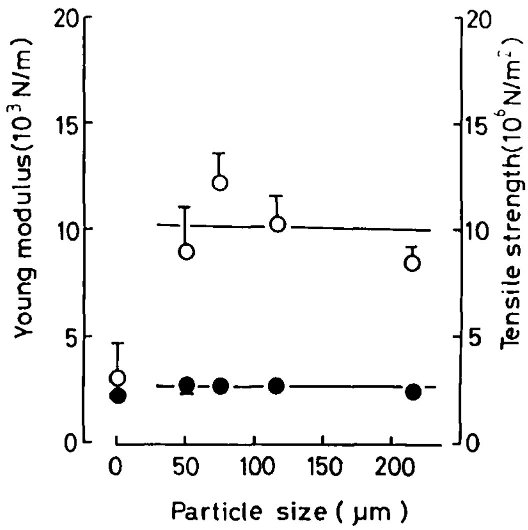

FIGURE 1

Young modulus and tensile strength of gelatin sheets with various glass particle size ; ○ — Young modulus ; ● — tensile strength. Mean (S.D.,n=6-18).

independent of the particle size in the range from 50 μm to 214 μm with constant values (10×10^3 N/m). Particle size is inversely proportional to the surface area. Therefore this result shows that the hardness of the gelatin sheet did not depend on the surface area of added glass powder.

The tensile strength of the control was 2.56×10^6 N/m^2. In this range of particle size the tensile strength did not almost vary as compared with the value of control. The tensile strength of the gelatin sheet was not affected by both the surface area of the powder and the volume of it. The tensile strength was related to the resistant strength to the break.

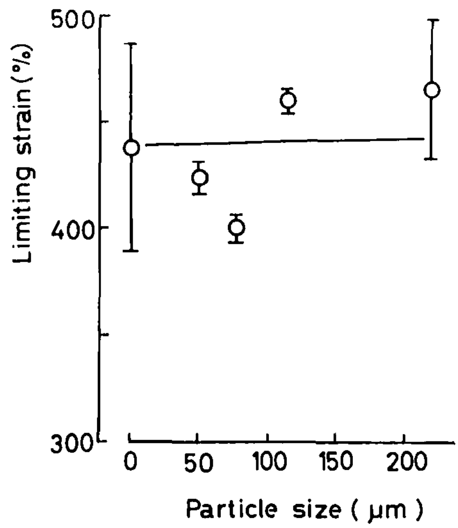

FIGURE 2

Limiting strain of gelatin sheets with various glass particle size. Mean (S.D., n=3-18).

Therefore, powder addition will have no affect on the break of the soft capsule shell.

Figure 2 shows the variation of limiting strain of the gelatin sheet with various particle size of glass powder. The limiting strain, which indicated flexibility of the gelatin sheet, of the control was 425% and was constant with the increase of the particle size.

Figure 3 shows the variation of the melting point and the softening point of the gelatin sheet without drying with the variation of the particle size of glass powder. The change of the melting point or the softening point is expected to indicate the interaction between the gelatin gel and the glass

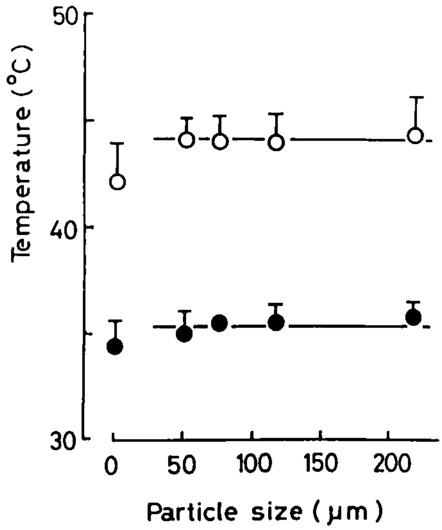

FIGURE 3

Melting point and softening point of gelatin sheets with various glass particle size ; ○ – melting point ; ● – softening point. Mean (S.D., n=9-20).

powder. The melting points of the gelatin sheet containing glass powder were independent of the particle size and were almost as same as the melting point of the control (34.2 ℃). This shows that the structure of the gelatin gel was not changed by the powder addition. However, by the addition of glass powder, softening points of the gelatin sheets (44℃) were higher than that of the control (42 ℃) and didn't vary with the variation of the particle size. After all, the powder addition made the gelatin sheet hard physically without change of the structure of the gelatin gel. This was similar to the results in Fig.1. Also, these results of thermal analysis would closely relate to the sealing temperature in production of soft capsules. Because, in manufacturing the sealing of soft capsules is achieved by both heating of the gelatin sheets by the injection segment and the mechanical pressure on the die roll in rotary die roll process. The high temperature for sealing is not proposal for the production because it is likely to cause the deformation of soft capsules. Above results in Fig.3 suggest that it may be more difficult for soft capsules to seal the shells containing powder than containing no powder.

The powder addition to the gelatin sheet made both Young modulus and the softening point increase. These results suggest that the powder addition strengthened the structure of gelatin gel physically, while that in production it might be difficult to make sealing.

Effect of Amount of Glass Particle

Figure 4 shows the variation of both Young modulus and tensile strength of the gelatin sheet with increasing the amount of 50μm diameters of glass powder. Young modulus was increased linearly with the amount of glass powder in ration of 1.26×10^3 N/m to 10g powder / 100 g gelatin. The increase of the amount of powder leads to the increase of both the total occupied volume and the total surface area of glass powder in the gelatin sheet. Since physical properties of the gelatin sheet were not related to the surface area as shown in Fig.1, the added powder had the volumetric effect on Young modulus of the gelatin sheet within the yield stress. On the other hand, the tensile strength was constant within the

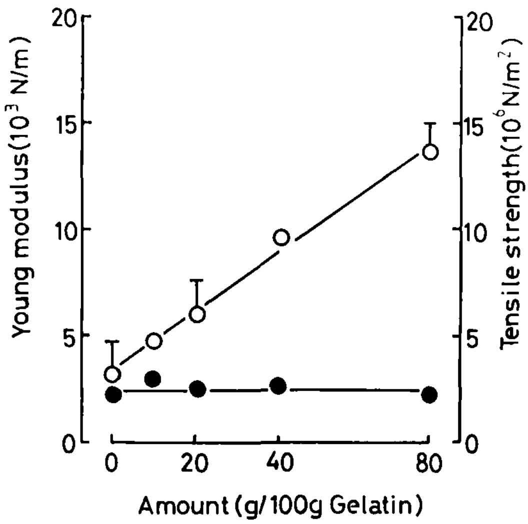

FIGURE 4

Young modulus and tensile strength of gelatin sheets with various amount of 50 μm diameter glass particles ; ○ — Young modulus ; ● — tensile strength. Mean(S.D.,n=3-18).

amount of 80g powder / 100g gelatin. From the results in both Fig.1 and Fig.4, there was no interaction between glass powder and the gelatin gel in the limiting conditions.

Figure 5 shows the variation of limiting strain with the increase of the amount of powder. The limiting strain of the gelatin sheet was slightly decreased up to the addition of about 40 g powder / 100 g gelatin. But that decreased remarkably in the higher ratio of powder against gelatin and went up to 324% in 80g powder / 100g gelatin. The gelatin gel will enable to behave the plastic flow enough even with powder addition of below 40 g powder / 100g gelatin. But the further

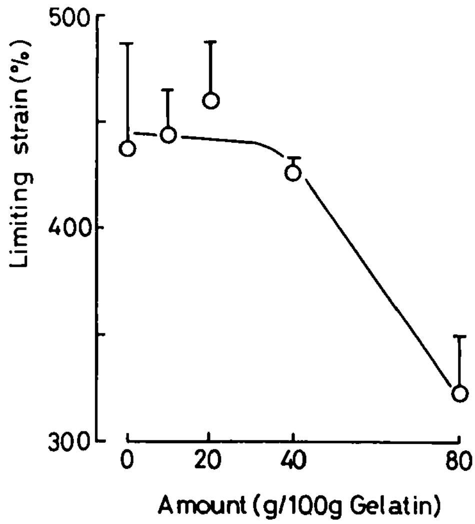

FIGURE 5

Limiting strain of gelatin sheets with various amount of 50 µm diameter glass particles. Mean (S.D., n=3-18).

amount of powder may prevent from the plastic flow of the gelatin gel because of the destroy of the gelatin gel matrix by the powder. There is the suitable range for the powder addition to the gelatin sheet to keep the plastic flow of the gelatin gel.

The melting point was constant within the amount of glass powder up to the addition of 80g powder / 100g gelatin. On the other hand, the softening point increased with the increase of the amount of glass powder and went up to 44.5℃ in 80g powder / 100g gelatin from 42℃ (control sheet). This suggests that the amount of glass powder did not alter the structure of the gelatin gel, while that the the more the amount of powder were, the stronger the gel structure were and the higher the sealing temperature might be in production.

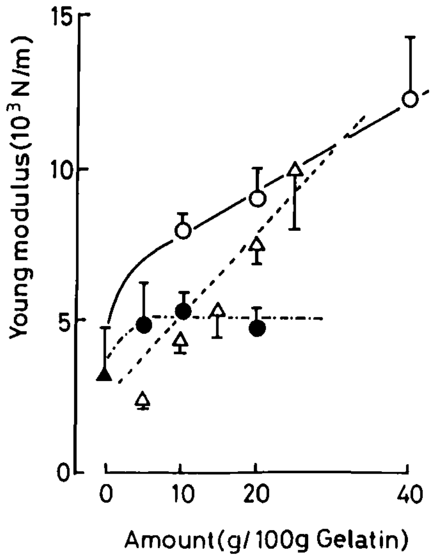

FIGURE 6

Young modulus of gelatin sheets with various amount of powder ; ○ — Calcium carbonate ; ● — Titanium oxide ; △ — γ-orizanol. Mean (S.D., n=3-18).

Effect of Different Kinds of Powder Addition

Figure 6 shows the variation of Young modulus with the variation of the amount of powder. In the case of either calcium carbonate or γ-orizanol addition, Young moduli increased linearly with the increase of the amount of powder, as well as in the case of glass powder addition. On the other hand, in the case of titanium oxide addition, Young modulus was slightly higher than the value of the control and was constant at 5×10^3 N/m up to 20g powder / 100g gelatin. Kellaway et al. had reported a similar tendency that titanium oxide had

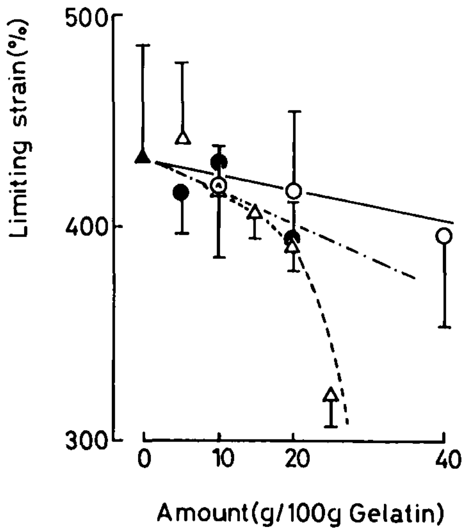

FIGURE 7

Limiting strain of gelatin sheets with various amount of powder ; ○ — Calcium carbonate ; ● — Titanium oxide ; △ — γ-orizanol. Mean (S.D.,n=3-18).

negligible effect on the mechanical properties of gelatin films such as Young modulus and the tensile strength[11]. These different tendencies between titanium oxide and the other powders were probably due to the difference in the occupied volume of each powder. In the case of glass powder described as above, the powder in the gelatin sheet didn't have the surface effect but the volumetric effect on the gelatin sheet. The particle size of titanium oxide is below 1μm diameter and the specific gravity is the largest among the powders. Therefore, the occupied volume of titanium oxide in the gelatin sheet was so very small that the volumetric effect might not be almost appeared in this experimental range.

The tensile strength of the gelatin sheet containing any powder varied little with the amount of powder. When the sheet was torn momentarily in the limiting stage, there might be little interaction between powder and the gelatin gel. It appeared that the mechanical properties of the gelatin sheet were not changed by powder addition in the break points.

Figure 7 shows the variation of limiting strain with the amount of powder. In the case of titanium oxide addition the limiting strain decreased a little with the increase of amount of powder. In the case of calcium carbonate addition, the limiting strain decreased slightly. On the other hand, in the case of γ-orizanol, the limiting strain decreased by the same ratio as the case of titanium oxide up to 20 g powder/ 100g gelatin and did extremely by 25g of the powder addition. There might be a suitable range for powder addition to keep the plastic flow for the gelatin gel, in the case of γ-orizanol and glass powder (Fig.5).

The variation of the melting point and the softening point with increased amount of powder showed the similar tendency as shown in the case of glass powder.

In this work, the powder addition to the gelatin gel made it hard physically by the volumetric effect. While the powder addition had no effect on the mechanical properties of the gelatin sheets in the break points. Utilizing this result, the physical properties of the gelatin shell might be regulated by the powder addition to the gelatin gel.

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