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Degradation of Properties and Loss of Nutrients in Gelatin Soft Capsules the Manufacturing Process

Jin Kyoung Lee*

Department of Polymer Science and Engineering, Inha University, Incheon 22212, Korea

Abstract Gelatin soft capsules, manufactured by the press through package(PTP) process, are widely used in the production of multivitamin dietary supplements and other health functional foods. Gelatin capsules can prevent light and air from having a direct contact with the contents in the capsule, and the nutrients inside the capsules are preserved without any loss. In the present study, on the basis of the results on the safety of gelatin capsules. The parameters investigated included degradation of the capsules before their shelf life, capsule deformation, and changes in specific nutrients. Moisture and heat in the production and storage environments of the capsules caused the gelatin to swell and attach some of the inorganic salts in the vitamin contents. Nutritional component analysis showed that B1, B5, B9, and B12 contents were decreased, while mineral elemental analysis shown calcium, chloride, and zinc compound were found to be infused into the gelatin of the capsule shell.

Keywords Gelatin soft capsule (GSC), Press through package (PTP), Water and heat degradation, Water-soluble vitamin B group, Non-destructive X-ray analysis

Introduction

Multi-vitamin supplements, considered functional health foods, are typically packaged in soft gelatin capsule shells. The process for manufacturing gelatin soft capsules (GSC) that contain supplements involves formulating gelatin sheets, placing a mould above and below the two gelatin sheets in two rotating die stamping rollers, filling the sheets with medication, and compressing the sheets into the desired shape capsule. These soft capsules are subjected to an appropriate drying process and are packaged using press through packaging (PTP) blister process. For the part to be careful during the manufacturing process, it was recorded in Fig. 1[1]. The gelatin soft capsule PTP packaging structure and shape was presented in Fig. 2(a), 2(b). Gelatin shell protects the active ingredients in the capsule from light, oxygen, moisture, and temperature changes, thus reducing nutrient loss and increasing the shelf life. Active ingredients in solid or liquid form are packaged in capsules to prevent oxidation from exposure to air and minimize volatility and degradation. The thickness of the capsule shell can vary from several nm to 1 μm. The capsule contents could be in the form of liquid suspensions, viscous materials, powders, or granules. Capsules can be categorized as hard and soft capsules.

Soft capsules are formed by increasing the plasticity of the original ingredients using diluting agents and plasticizers such as gelatin or glycerin and by adding colorants and preservatives[2]. Capsules processed in this manner are widely used because they mask bitter tastes and unpleasant odors, prevent irritation from the contents, and reduce unwanted changes to the contents by preventing direct exposure to light and air, thus minimizing nutrient loss until the expiration date[1,2]. Since gelatin is sensitive to moisture and heat, exposure to moisture or heat during processing may transform the capsules, degrade the quality of the contents, and change the color appearance.

Therefore, the manufacturing and formulation environments as well as the storage environment after manufacturing should be maintained at optimal levels of temperature and moisture.

The objective of this study was to examine the changes in GSC exposed to moisture and heat, using non-destructive X-ray analysis, scanning electron microscopy (SEM) visualization of the capsule micro structure, and mineral composition analysis. The results showed that the inorganic salts in the nutrient formulations are transferred to the gelatin capsule shell. There was a consider able loss of some of the water-soluble B group vitamins, as indicated by HPLC analysis of the composition.

†Corresponding Author : Jin Kyoung Lee
Department of Polymer Science and Engineering, Inha University, Incheon 22212, Korea
Tel : +82-32-860-8641, Fax : +82-32-865-5178
E-mail : i_jklee@naver.com

material preparation ↓	20−26℃, RH 40−50%↓
gelatin melting and solution formulated − water − plasticizer − color − other additives(opacifier) ↓	20−26℃, RH 40−50%↓ Kept at gelatin solution temp 57~60℃
gelatin sheet and encapsulation process (encapsule machine) ↓	18~24℃, RH 30−40%↓ encapsulation contents at 35~37℃
capsule shape fixing and Drying process (tumbler dry machine) ↓	18~24℃, RH 30−40%↓ cooling drum 13−14℃
capsule air drying process ↓	30~35℃, RH 15−25%↓
PTP blister process (PTP process)	20~24℃, RH 40−60%↓ film preheating(upper)120−140℃ pocket forming(under)120−140℃ aluminum and film adhesion 140−160℃ PTP case cutting 90−110℃
↓ storage ↓	20~30℃, RH 50−70%↓

Fig. 1. Making GSC manufacturing process and step notice[1].

Materials and Methods

Gelatin soft capsule (GSC) and contents

GSC samples from normal production one lot runs were used as controls. Omega-3 capsules that had expired 2 years earlier (undamaged) and capsules from two defective lots, which contained soluble and highly concentrated vitamin B and C supplements, were used as experimental samples. Gelatin raw materials used in the GSC shell was used as the reference sample. Capsule shell raw materials were gelatin (grade 200B, lot no. 1406212, Geltech Co., Ltd. Busan, Korea), titanium oxide (high-purity food grade, lot no. 13070853175, Huntsman), glycerin (purity 98%, R98F, lot no. 100117A, Ulsan LG Household & Health Care). Colorant is food yellow no. 5 and food blue no. 1 these were provided by the related to the company with this event.

GSC manufacturing process condition and notices

Gelatin is sensitive to water, a soft capsule manufacturing process, the moisture content is produced by blending different for every season. The amount of plasticizer to be added to different formulations are classified into hard capsule and soft capsule according to the application. Particularly sensitive to humidity and heat, attention defined during the manufacturing process of the step stage by temperature and humidity. The making GSC manufacturing process and step notice shown Fig. 1.

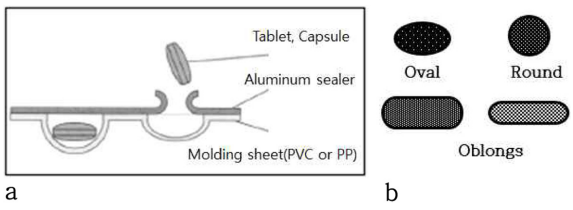


Fig. 2. Photographs of PTP blister pack structure and capsule shape. (a)PTP blister structure[3] (b) type of soft gelatin soft capsule.

Thermal analysis

Thermal analysis is a group of techniques that study the changes in properties of materials with temperature. Changes in the mass and stability as a function of temperature are measured by thermogravimetric analysis (TGA, NETZSCH TG

209 F3) by raising the temperature from room temperature to 600°C at a rate of 10°C /min. And determined phenomena causing changes in heat/temperature of substance to Differential scanning calorimetry (DSC, NETZSCH DSC 404F1). The temperature range over which Tg was analyzed condition of -70°C to 200°C during elevated the 10°C/min. Normal and damaged capsules devoid of their contents were subjected sample to DSC and TGA analysis.

Non-destructive X-ray scanning

A three-dimensional computed tomography (CT) scanning method was employed using a non-destructive X-ray Inspection System (X-eye SF160 FCT, SEC Co., Ltd., Gyeonggi-do, Korea) to visualize the interior of the gelatin soft capsule without destroying or damaging the contents. Images of normal and defective samples were acquired without sample destruction.

Sample preparation for component analysis by high performance liquid chromatography (HPLC)

Samples were prepared according to the manufacturer's instructions. A minimum of 20 capsules were cut, and the contents were pooled and mixed well. Approximately 1 g of this sample was added to 30 mL of dilute water in a 100-mL beaker and dissolved by heating at 70°C, followed with shaking extraction by sonication for approximately 30 min. Further, the contents were transferred to a 50-mL brown flask. The process was repeated using a suitable amount of dilute water until the oil layer became transparent. The resulting filtrates were mixed and cooled to room temperature. The volume was made up to 50 mL with dilute water. This solution was filtered using a 0.45 μm membrane-filter and used as the HPLC test sample[4-6].

HPLC nutritional component analysis standard and reagent

Vitamin B1, nicotinamide and vitamin B6 were analyzed as previously described. Vitamin C, vitamin B2, vitamin B5, vitamin B 12, and folic acid were analyzed according to health functional food standards and test specifications[5,6]. Standard reagents used for component analysis were thiamine hydro chloride ($C_{12}H_{17}CIN_4OS{\cdot}HCl$, 68-26-8), pyridoxine hydrochloride($C_8H_{11}NO_3{\cdot}HCl$, 58-56-0), nicotinamide ($C_6H_6N_2O$ 98-92-0), riboflavin ($C_{17}H_20N_4O_6$, 83-85-5), D-pantothenic acid hemicalcium salt ($HOCH_2\ C(CH_3)_2\ CH(OH)CONHCH_2\ CH_2CO_2{\cdot}1/2Ca$, 137-08-6), folic acid ($C_{19}H_{19}N_7O_6$, 59-30-3),

Table 1. HPLC Analytical Instrumental Condition

Model	Item	Column, Mobile phase	Analytical condition
Agilent 1120	Vitamin B1, B3, B6	1. YMC-Pack ODS-AM (4.6×250 mm) 2. A: 5 mM sodium hexansulfonate / 0.1% Acetic acid [70] B: 5 mM sodium hexansulfonate / 0.1% Acetic acid (35) methanol (65) [30]	- Inject Vol: 10 μL, - column: 40°C - UVD: 270 nm - Flow rate: 1.0 mL/min
	B2	1. YMC-Pack ODS-AM (4.6×250 mm) 2. methanol : 10 mM NaH_2PO_4 (pH 5.5) = 25:75	- Inject Vol:10 μL, - column: ambient - FLD: exit: 445 nm, detect: 530 nm - Flow rate: 600 μL/min
	B5	1. YMC-Pack ODS-AM (4.6×250 mm) 2. NaH_2PO_4 (pH 2.1): ACN 30 mL	- Inject Vol: 10 μL, - column: 40°C - UVD: 200 nm - Flow rate: 1.0 mL/min
	B9	1. Eclipse XDB-C18 (4.6×250 mm) 2. A: 5 mM Tetrabutylammonium bromide / 10 mM Phosphate buffer (pH 7.2) B: Acetonitrile (A 85% : B 15%)	- Inject Vol: 10 μL, - column: 40°C - UVD: 270 nm - Flow rate: 1.0 mL/min
	C	1. YMC-Pack ODS-AM (4.6×250 mm) 2. A: 0.05 M KH_2PO_4 / B: Acetonitrile (A: 95 : B: 5)	- Inject Vol:10 μL, - column: 40°C - UVD: 254 nm - Flow rate: 0.7 mL/min
Shimadzu LC	B12	1. Pre-ACE 5C8-300 (4.6×150 mm, 5 μm) Con-YMC PackProC18 (4.6×50 mm, 3 μm) Anal-ACE 3 C18 AR (4.6×100 mm, 5 μm) 2. A: 5 mM KH_2PO_4 / B: Methanol (A: 80, B: 20)	- Inject Vol: 500 μL, - column: 40°C - DAD :540 nm - Flow rate :Pre - 067 mL/min Anal - 0.3 mL/min

cyanocobalamine ($C_{68}H_{88}CoN_{14}O_{14}P$, 68-19-9), L-ascoric acid ($C_6H_80_6$ 50-81-7). Vitamin standards are purchased from Sigma-Aldrich Co., LLC. (St. Louis, Mo, USA). Sample preparation reagent were sodium hexansulfonate, acetic acid, tetrabutyl ammonium bromide were wako Pure Chemical Industries, Ltd. (Osaka, Japan). Methanol, acetonitrile were HPLC grade Merck & Co., Inc. (White-house station, NJ, USA). And general reagent are purchased from Daejung chemicals and metals Co., LTD. (Siheung, Korea) potassium dihydrogen phosphate (KH_2PO_4, 7778-77-0), sodium dihydrogen phosphate (NaH_2PO_4, 7558-80-7), sodium hydroxide (NaOH, 1310-73-2) disodium hydrogen phosphate (Na_2HPO_4, 7558-79-4). These analytical instrumental conditions are shown in Table 1.

GSC morphology and mineral composition analysis

The surface, interior, and lateral morphologies of the capsules, as well as the mineral component analysis of each portion of the capsule were performed using a field emission scanning electron microscope (FE-SEM/EBSD S-4300SE, Hitachi, Tokyo, Japan). For morphological analysis of the gelatin surface and the interior region, samples were prepared as described here. The capsules were cut and the contents were removed. A capsule fragment was fixed onto the carbon tape of the SEM adaptor and coated with gold using a sputtering coater.

Only skin of the gelatin capsule to remove the contents of treated in the furnace, were carried out inorganic materials component analysis of the ashes residue. Compared analysis samples are standard reference, normal and defective gelatin capsules shell.

The residues were obtained by ashes the samples at 550°C for 4 h and at 700°C for 6 h. The mineral composition and images of each sample fragment were analyzed.

Results and Discussion

GSC damaged by moisture and heat

Exposure to moisture and heat during the GSC manufacturing process may lead to various negative changes before the expiration dates. These include: a) thermal damage in the capsule interior during the PTP packaging process, b) sweating of the capsule convex surface and easy bursting even with slight application of pressure, c) bursting within the PTP packaging, adhesion to the PTP surface and a sticky PTP exterior resulting from oil leakage, and d) thermal damage during the PTP packaging process, which causes capsule adhesion to the aluminum, discoloration, and softening. These conditions are shown in Fig. 3. Gelatin solution process and PTP blister process of heating during the PTP process can result in heat exposured shown Fig. 1.

Moisture- and heat-damaged samples of GSC used in the present study Fig. 3.(3) contained large quantities of water-soluble B group vitamins and vitamin C. Thermal damage during the PTP process is shown in Fig. 3.(1) and (4). The large quantities hydrophilic contents soften the gelatin on exposure to moisture and heat. Vitamin C was to lower (acidic) the pH of the contents and degrade the gelatin capsule, vitamin B inorganic salt complex materials was crystallized with contents and the combination, It promotes the degradation and transfer loss of nutrients by attached the capsule. Calcium salt of pantothenate, thiamine hydrochloride, and zinc oxide were difficult to work with as these powders would scatter and be easily adsorbed. Made standard contents of capsule furthermore, very hard crystals would form and become a separate layer from oil, which made them impossible to handle. The dissolution and crystallization of calcium, chloride, and zinc compounds in the raw materials used for formulating vitamin preparations, caused by the seepage of moisture, resulted in the phenomena shown in Fig. 3.(2). The images of the interior region are shown in Fig. 5.b) (5)-(8). This was caused by the migration of mineral crystals into the thermally damaged area as well as by adhesion, leading to the softening of the capsule shell and swelling.

Fig. 3. Moisture and heat damage to gelatin capsule photos.

According to Hiroki I.[7] faulty manufacturing of tablets often occurs from tablet breaking, not being filled, or being blocked due to the pocket size of PTP. As a solution to this problem, the diameter of the pocket hole can be made larger, thus reducing the defect rate. The pocket size affects both tablets and capsules. Some of the companies have overcome this problem by altering the size of the inside of the pocket, as shown in Table 2. note 1. There was enough room when the upper width, pocket height, and pocket inner depth were increased by 0.1 mm, 0.1 mm, and 0.2 mm, respectively. Table 2. note 2. Comparison analysis of PTP pockets and capsules of advance and target capsule PTP pockets. Results of compared to PTP porket size (Table 2. note4.) was damaged capsule PTP smaller than advanced capsule PTP porket size, because the damaged capsule height size was 0.95 cm greater than damaged capsule pocket size height 0.9 cm, it can be seen that exposured to heat in the PTP packaging process.

General analysis of degradation in damaged GSC

The time course of the problem point in the general analysis of the specified damaged sample gelatin capsules was con-

Table 2. Comparison Analysis of PTP Pockets and Capsules of Advance and Damaged

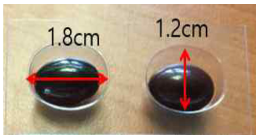
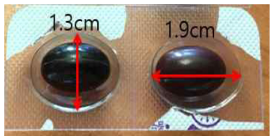
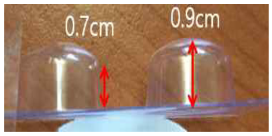
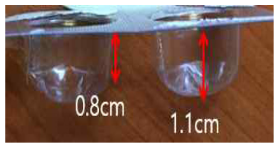
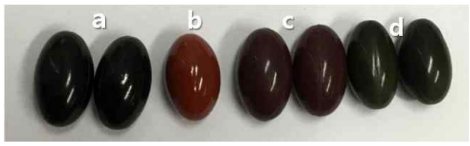
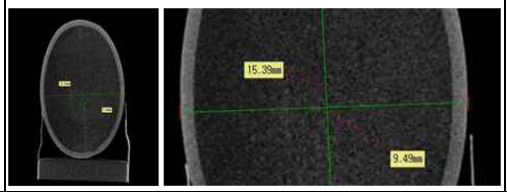
Part	Damaged capsule PTP porket		Reference advance capsule PTP porket	
(Note 1) PTP porket size (length, width)		length: 1.83 cm (seal), width: 1.27 cm (seal)		length: 1.92 cm (seal), width: 1.32 cm (seal)
(Note 2) PTP porket size (height)		height: 0.9 cm		height: 1.1 cm
PTP material	PVC		PVDC	
(Note 3) Capsule size			a), c), d) The damaged GSC 10 oval capsules - length :1.54 cm, width 0.95 cm → 1 mm larger b) Reference advanced capsule - length :1.4 cm, width 0.9 cm → 1 mm smaller	
(Note 4) Damaged capsule (Note 3, C type)			Damaged sample capsule size - length : 1.54 cm, width : 0.95 cm (capsule is too large)	

Table 3. Quality Analysis of Degradation GSC and Processes Condition

Item	Specification	Target GSC-1	Target GSC-2	Target GSC-3	Decision
Appearance	dark green capsule	surface is uneven and odd shape	surface is uneven and odd shape	surface is uneven and odd shape	unfit
Shell moisture	10% under	11.58%	12.32%	10.34%	unfit
Weight variation	500 mg±3% (485-515 mg)	493	512	491	fit
Disintegration	20 min under	16 min	14 min	10 min	fit
Acid value	soybean oil (standard) 0.0054	4.9	28.7	8.2	-
General bacteria	negative	negative	negative	negative	fit
Coliform group	-	negative	negative	negative	-
Gelatin solution	60°C under	73-75°C			unfit
Capsule contents	30±10°C	32-35°C			-
Capsule sheet thickness	0.75±0.02 mm	0.75 mm			fit
PTP preheating (upper)	120-130°C	121°C	150°C		unfit
PTP preheating (under)					
Aluminum cover sealing	140-160°C	151°C	180°C		unfit
Slitter	90-110°C	100°C	100°C		fit

firmed as a result of the general analysis. Shows in Table 3.

Thermal analysis of normal and damaged GSC

Temperature changes caused a change in the melting temperature (Tm), glass transition temperature (Tg), thermal indications, and crystallization of the normal and defective samples. Few studies have examined the effects of softening temperature, humidity, and contents of the gelatin capsules. Thermal analysis provides important data regarding the physical changes observed in the gelatin capsules, which may depend on external conditions and the internal contents[8]. TGA thermograms of the gelatin reference standard raw materials and

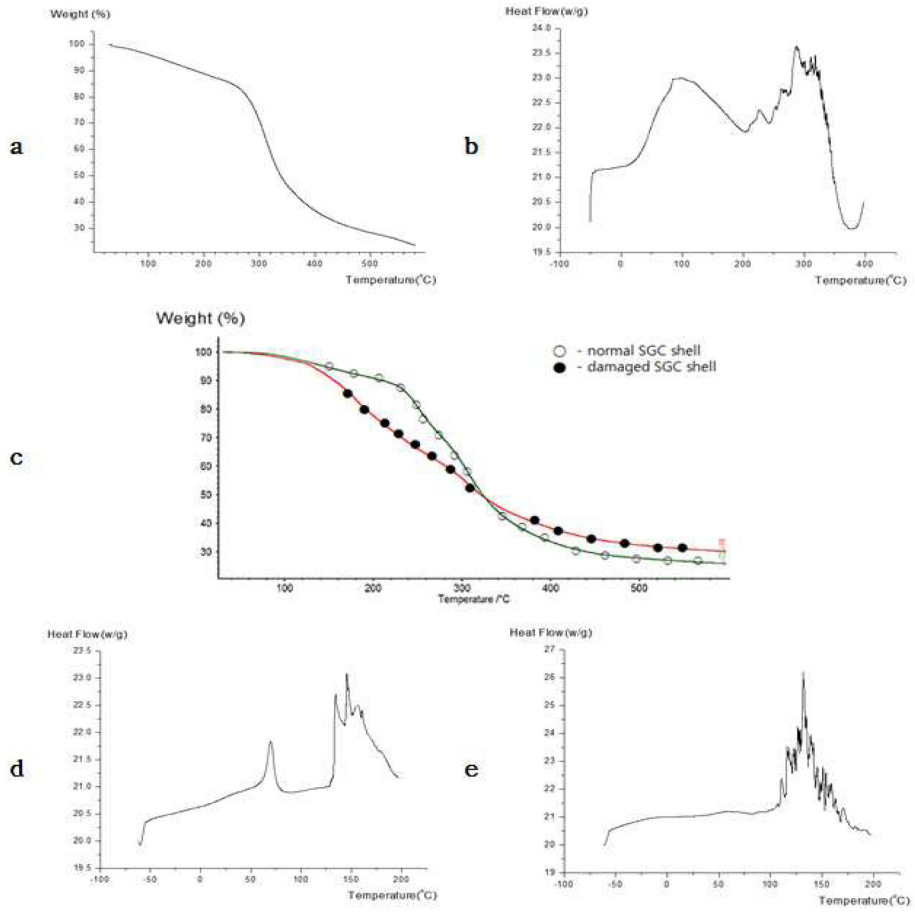


Fig. 4. Thermogram of comparison capsules: (a) gelatin standard referen ce TGA (b) gelatin standard reference DSC (c) gelatin capsule shell TGA (○ - normal GSC shell, ● - damaged GSC shell) (d) heat exposured normal GSC shell DSC (e) heat exposured damaged GSC shell DSC.

intact and damaged GSCs are shown in Fig. 4.(c).

These observations indicate that thermogravi metric changes in gelatin or in normal capsules included a decrease in the moisture content by 5% at 100 °C, and by 15% at 250 °C. Thermal strain curves of normal capsules and compared capsule samples containing omega-3 that had expired 2years earlier, were in accordance with those of gelatin in the reference standard Fig. 4.(a). The experimental good results with normal capsule lot sample and contents in omega-3 expired shelf life sample (non damaged capsule). In contrast, defective capsules began degrading at 120°C. In general, endothermic reactions cause melting, whereas exothermic reactions lead to crystallinity, curing, oxidation, and cross linking. DSC thermograms showed the thermal history, including melting, crystallinity, curing oxidation, and crosslinking.

The reference standard gelatin was unchanged according to DSC at 40-200°C; however, the capsules shown in Fig. 4.(b) revealed that Tg was 40°C, and a part of the thermal history was maintained up to 60-70°C. Curing and degradation began at 150°C, indicating that the thermal history was utilized during the manufacturing process. For Fig. 4. (d) exposed to heat was not damaged, Tg becomes high, but the curing temperature decreases seen. It was difficult to identify Tg and thermal history in defective capsules, as shown in Fig. 4.(e) These capsules began hardening at 100°C and showed degradation.

Nondestructive X-ray analysis of normal and damaged GSC

Internal images of the capsules from non-destructive X-ray analysis are shown in Fig. 5. Degradation or damage of the GSC renders it impossible to observe the inside of the capsule and impairs the analysis of film thickness, content packing, and capsule joint adhesion; however, satisfactory outcomes were obtained using an X-ray inspection system in this study. Images acquired without damaging the capsules are shown in Fig. 5.a) (1)-(4) for normal samples and Fig. 5.b) (5)-(8) for defective samples. The normal capsules in Fig. 5.a) (1) show

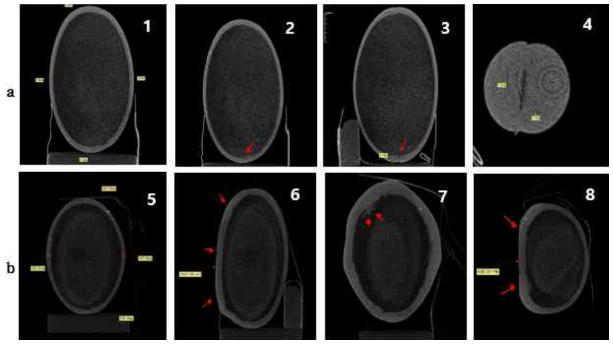


Fig. 5. Nondestructive X-ray CT scanning analysis. (a) reference normal gelatin soft capsule samples 1-4 (b) defective gelatin soft capsule samples 5-8.

that film thickness and its contents were evenly distributed. Fig. 5.a) (2), reveals air bubbles in the joint of the capsule tip, a film thickness gap between horizontal and vertical sides. Fig. 5.a) (3) shows that the capsule shell in 2 was 25% thinner than normal because of the loss caused by the disappearance of the air bubble in the capsule shell. The oval shape was slightly biased towards one end. Fig. 5.a) (4) shows that the upper joints were not smooth and it caused the phenomena observed in 5.a) (2) and 5.a) (3). Fig. 5.b) (5) shows defective capsules in which films were swollen because of moisture, resulting in an uneven distribution of contents and separation of the oil and contents layers. In addition, films in the damaged areas were more swollen than those in the intact areas. Fig. 5.b) (6) shows that the capsule shells were swollen and that the content particles adhered to the shells, resulting in an uneven distribution of contents and separation of the oil and contents layers.

In addition, films in the damaged areas were more swollen than those in the intact areas. Fig. 5.b) (6) shows that the capsule shells were swollen and that the content particles adhered to the shells, leading to large aggregate particles. Shells with particles were more swollen and content separation was observed because of density differences. Fig. 5.b) (7) and (8) show that dense contents were separated into 3 layers. High-density particles adhered to the damaged area and the absorbed moisture caused the swelling of the shell, leading to softening of the capsule shells. Under these conditions, there were significant losses of vitamin C, folic acid, cyanocobalamine, B group vitamins, including calcium salt of pantothenate, chloride salt of pyridoxine, and thiamin hydrochloride, which migrated to the gelatin capsule shell.

Surface morphologies of normal and damaged GSC

Fig. 6.a)-d) show the cross section according to the degree of damage morphologies of GSC as follows: a) cross section

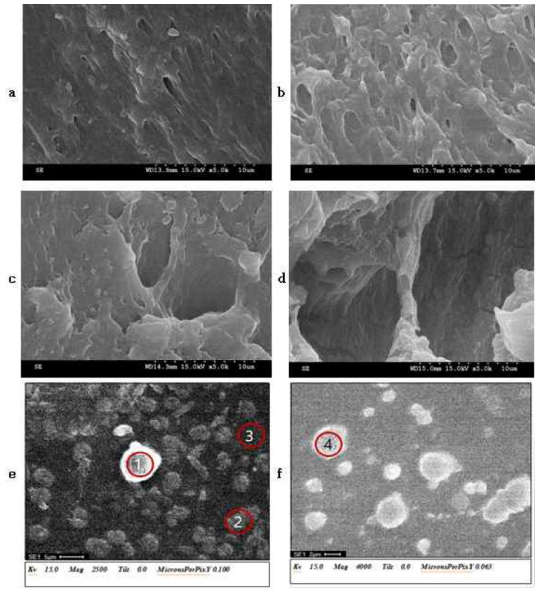


Fig. 6. GSC cross-section and surface morphologies. (a)-(d) shell cross-section, (e)-(f) shell inner surface section.

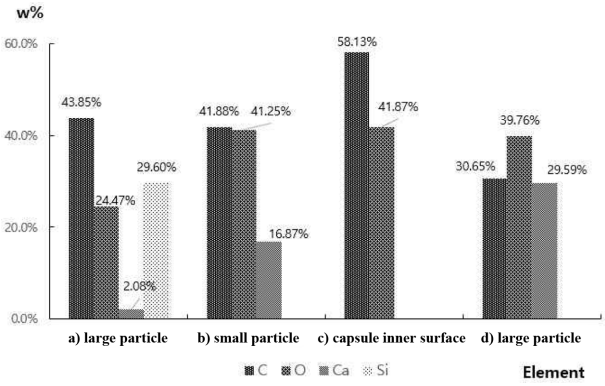


Fig. 7. Fig. 6.e) 1-4 GSC surface attach element composition. a) large particles of the capsule inside surface, b) small particles of the capsule inside surface, c) capsule inner surface, d) large particle of the capsule inside surface.

of a normal capsule; b) and c) increase in pore size depending on the degree of capsule damage; d) cracks, which may cause loss of contents. Fig. 6.e)-f) show the internal surfaces of GSC where the formation of crystallized particles was observed. Component analysis was performed for the adsorbates on the surfaces of the crystals inside the GSC. In Fig. 7. the atomic composition of the area Fig. 6.e)(3) included C and O, small particles in Fig. 6.e)(2) were composed of C, O, and Ca atoms, and large particles in Fig. 6.e)(1) were made up of C, O, Ca, and Si atoms. Another large particle Fig. 6.f)(4) were composed of C, O, and Ca atoms. Analysis of Si revealed that Si

originated from the raw gelatin reference standard material, which may have been formed by the adsorption and accumulation of particles over a long period of time. To confirm this, Table 4 shown the mineral composition of the ashes in the gelatin capsules was analyzed.

GSC shell was produced based on a standard recipe and used as a standard sample to be compared with damaged GSC shell. The samples analyzed included gelatin alone a), TiO_2 and colorant (yellow 5, blue 1) as inorganic compounds b), and GSC containing a) and b) generated as reference standard c), and damaged capsules two lot shown the d) and e). The inorganic components were analyzed by FB-SEM/EBSD following heat treatment in a Muffle furnace. Results of the analysis showed that the Table 4. a) gelatin itself, which is a main component of the GSC shell, consisted of 0.9% Ca and 33.79% Na, and the generated GSC shell reference sample (Table 4. c)) consisted of 18.28% Na, 2.84% Ca, and 1.57% K and no Cl. However, the two lots of the damaged GSC shell showed Table 4. d), e) 11.2% and 12.3% of Ca, 5.3% and 5.4% of Zn, and 8.7% and 7.5% of Cl, respectively, showing that they were adsorbed and transferred to the shell. Na, which dissolves relatively quickly, decreased to 8.2% and 7.7%, respectively. The results which are shown in Table 4 indicate that the zinc, calcium, and chloride components in damaged capsules were adsorbed and transferred onto the gelatin capsule shell surface.

Loss of B group vitamins via transfer to the gelatin capsule surface

It was previously reported that some soluble vitamins migrate to the gelatin layers and that the migration rate increased with increasing water solubility of vitamins[4,9]. Among the water soluble vitamins examined in this study, nicotinamide and pyridoxine hydrochloride showed the highest migration to the gelatin layer, whereas thiamin, riboflavin, and ascorbic acid showed limited migration[4]. As shown in Table 5 analysis of changes in the nutritional components during manufacturing process and product damage detected the presence of pantothenate content in calcium salts, pyridoxine and thiamine in chloride salts, and significant loss of folic acid and cyanocobalamin and vitamin C. These results were consistent with those for the mineral composition and nutritional components.

In contrast, loss of nicotinamide was small and its migration to the gelatin shell was difficult results previous study Oh, S.J et al.[4]

However, zinc and calcium salts as well as chloride salts in calcium pantothenate, thiamine hydrochloride migrated to the gelatin shell. And loss of nutrition nutrients was ascorbic acid, folic acid and cyanocobalamine.

To summarize, crystallinity and solubility changed the minerals bound to the raw materials of soluble vitamin compounds; particularly, the nutritional components, calcium, chloride, and zinc migrated to the gelatin capsule.

During the production of soft capsules, drugs can infiltrate the films by adsorption and cause discoloration, hardening and melting of the shell. In addition, highly hydrophilic drugs can migrate to the film after packaging and, if bound by a hydrophobic matrix, the elution rate or bioavailability of the nutrient can be reduced[10]. Melting of the contents results in capsule sweating, triggering the migration of surrounding vapors. Approximately 60% of the plasticizer in the capsule film migrates into the contents, and the amount of external moisture that enters is approximately equal to the loss within the shells, increasing the pressure in the shell and leading to migration and subsequent swelling. Once the internal pressure of the capsule decreases, the inflow of external moisture is promoted increasing pressure and volume[11].

The results show that moisture control is important during the formulation of the GSC and the press through packaging process can cause thermal damage.

Table 4. Elemental Composition Analysis of the Ashes of the GSC

a) making Gelatin alone standard (W%)		b) making inorganic reference (TiO_2, colorant)(W%)		c) making reference gelatin shell (W%)		d) damaged GSC shell-1 lot (W%)		e) damaged GSC shell-2 lot (W%)	
C	11.11%	C	7.54%	C	4.03%	C	1.50%	C	1.50%
O	47.67%	O	23.86%	O	48.55%	O	32.60%	O	34.10%
-	-	N	11.18%	-	-	-	-	-	-
Ti	-	Ti	51.12%	Ti	20.48%	Ti	26.20%	Ti	24.40%
Na	33.79%	Na	1.94%	Na	18.28%	Na	8.20%	Na	7.70%
-		-	-	-	-	Zn	5.30%	Zn	5.40%
Ca	0.90%	Ca	-	Ca	2.84%	Ca	11.20%	Ca	12.30%
-	-	Cl	0.18%	-	-	Cl	8.70%	Cl	7.50%
K	-	K	1.42%	K	1.57%	K	1.30%	K	2.10%
S	3.87%	S	1.75%	S	4.25%	S	3.80%	S	3.40%
Si	2.65%	Si	1.02%	Si	-	Si	1.20%	Si	1.60%

Table 5. Nutritional Component Analysis of GSC contents on Production Time and Degraded Finding Time

Component	Index	Content (%)	Production time[a] (%)			Degraded finding time[b] (%)			Decision
Vit C (ascorbic acid)	117 mg/1000 mg	15.6929	86	115	106	164	93	83	unfit
Vit B6 (pyridoxine hydrochloride)	22 mg/1000 mg	3.0588	136	101	115	141	117	124	fit
Vit B5 (calcium pantothenate)	14 mg/1000 mg	1.7647	169	146	133	22	12	17	unfit
Vit B3 (nicotinamide)	21 mg/1000 mg	2.3539	126	89	100	125	99	124	fit
Vit B2 (riboflavin)	18 mg/1000 mg	2.00	157	89	122	120	105	131	fit
Vit B1 (thiamine hydrochloride)	14 mg/1000 mg	2.1176	150	96	111	65	50	60	unfit
Vit B9 (folic acid)	400 μg/1000 mg	0.04	98	86	86	32	8	9	unfit
Vit B12 (cyanocobalamine)	16 μg/1000 mg	0.1882	123	89	89	36	2	8	unfit
Vit B7 (biotin)	65 mg/1000 mg	0.0082	111	105	95	-	-	-	

a) Production time: after manufactured self quality test point b) Degraded finding time: after one year elapsed (in shelf life).

Further, B1, B5, B9, and B12 contents were found to be decreased, while calcium, chloride, and zinc were found to migrate into the gelatin.

Additional factors that influence the stability of GSC include the nature of the shell components, contents filling ingredients, and the physical transfer of the components between shell and external environments. There are some studies that address these issues and it is important to give due consideration to these complexities while developing soft capsules[1,11].

Conclusion

Gelatin is sensitive to moisture and temperature changes. The temperature and relative humidity must be maintained at approximately 18-24°C and 30-40%, respectively, during the capsule manufacturing process[1,2,10]. Although the recommended temperature of gelatin solution is approximately 55-60°C, the capsules are exposed to heat as high as 73-78°C during the general manufacturing process. Thermal damage during PTP can be minimized by altering the pocket sizes of the metal moulds during the heat sealing step. The residual moisture level within the capsules must be controlled during the final drying step in capsule production, using appropriate drying method and equipment. Nutritional component analysis showed that B1, B5, B9, and B12 contents were decreased, while mineral elemental analysis shown calcium, chloride, and zinc were found to be infused into the gelatin of the capsule shell. Finally, warehouses that store drugs also need to have appropriate climate control systems in place.

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