CHAPTER IV

RESULTS AND DISCUSSIONS

1. Physical properties of gelatin solutions and gelatin films

As mentioned before, gelatin is a material of choice for hard gelatin industries; therefore, it is necessary to study physical properties of gelatin solution and gelatin film which is used as a control for starch substituted gelatin solutions and films.

1.1 Properties of gelatin solution

In this experiment, the concentration of gelatin was chosen at 33% w/w. This concentration is widely used in the hard gelatin capsule industries, also was recommended by Jones (1987: 68-79) within the range of 30-40% w/w. Table 4.1 showed physical properties of gelatin solution. It was found that the solution of gelatin was a slightly brown clear gel, the viscosity of gelatin solution at 50 ± 2°C was about 1457.86 mPa.s.

Table 4.1 Properties of gelatin solution

Solution properties	Result
Concentration (w/w)	33 %
Appearance of solution	Clear gel and slightly brown
Viscosity at 50 ± 2°C (mPa.s)	1457.86

In this thesis, only two batches with the same source of gelatin were used in order to control the variation between the different manufactures and manufacturing process. Several sources of gelatins were brought for preliminary study. Finally, gelatin from Gelita® has been chosen for this study and it also has been used in the industries. It was observed that the colors of gelatin solutions are different depending on the source of materials.

1.2 Properties of gelatin films.

Properties of obtained gelatin film were presented in table 4.2 Gelatin solution could be used to prepare gelatin film by casting method using TLC spreader with 0.75 mm. Film thicknesses of three samples were evaluated with a digital micrometer and found the average to be 0.110 ± 0.005 mm. for 30 point-measurements. The thickness was reduced to be about 0.1 mm. because of the evaporation of water from the films. After 2-hour drying, cast gelatin films were kept in the same controlled conditions as drying which are 30°C, 50%RH. Finished gelatin film was clear and flexible with no cracking and moisture content of finished gelatin film was in the range of 14.16 ± 0.10%, within the normal range of hard gelatin capsule shells (12-16%).

Table 4.2 Properties of obtained gelatin films

Film properties	Values
Appearance	Clear and Flexible
Thickness (mm.)	0.110 ± 0.005
Mechanical properties	
-Maximum stress ($N/mm.^2$)	86.149 ± 3.839
-Extension at break (mm.)	2.537 ± 0.276
Moisture content (%)	14.16 ± 0.01

Measurements of mechanical properties were done as described in chapter III. Averages of maximum stress value and extension at break for gelatin films were 86.149 ± 3.839 N/mm^2 and 2.537 ± 0.276 mm., respectively.

Overall properties of gelatin films were considered comparatively to commercial hard gelatin capsules in terms of its appearance, thickness and % moisture content. Base on these data (table 4.2), our gelatin has been used as a representative of commercial gelatin film which also used as a comparative control to starch-gelatin films.

2. Starch-gelatin film preparations

2.1 Properties of starch-gelatin solutions

Eight starches were chosen to represent 3 groups of starches: 1) native starches (rice starch, glutinous rice starch and tapioca starch), 2) pregelatinized starched (Eragel® and Alpha starch®) and 3) modified starches (Elastigel 1000J®, Elastigel 2000C® and Elastigel 3000M®). Most of starch-gelatin solutions were colloid solutions with small starch particles (invisible sized) dispersed over the gelatin solution. However, at high concentrations of some starches, the precipitations of starch particles such as glutinous rice starch and tapioca starch was found at 15% w/w concentration and white floccules were seen and settled down later on.

Higher concentrations of most starch substitutes showed an increase in viscosities. As shown in table 4.3, the viscosity of starch-gelatin solutions were increased after gradually increasing the percentage of substituted starch in gelatin solution.

Table 4.3 The viscosity and physical appearance of substituted starch in gelatin solution (starch-gelatin solution)

Starch types	% starch substitution	Solution viscosity (mPa.s)	Physical appearance
Rice	5	1601.76	Colloid solution
	10*	1931.45	Colloid solution
	15	1839.03	Small particle of starch in the solution
	20	2202.59	Small particle of starch in the solution
	25	2251.89	Small particle of starch in the solution
	30	2657.78	Two layers separation
Eragel®	5	1539.75	Colloid solution
	10	1677.96	Colloid solution
	15	1737.53	Colloid solution
	20	1898.55	Colloid solution
	25*	2022.50	Colloid solution, hard to remove air bubbles
	30	2633.86	Hard to remove air bubbles
	35	2964.35	Hard to remove air bubbles
Glutinous	5	1462.26	Colloid solution
	10*	1600.74	Colloid solution
	15	1802.22	White floccules and settle down later
	20	1980.36	White floccules and settle down later
	25	2077.45	White floccules and settle down later
Tapioca	5	1532.01	Colloid solution
	10*	1536.81	Colloid solution
	15	1835.39	White floccules and settle down later
	20	1753.63	White floccules and settle down later
Alpha starch®	5	1491.58	Colloid solution
	10*	1381.71	Colloid solution
	15	1654.85	White floccules and settle down later
	20	>6000.00	White floccules and settle down later

Table 4.3 The viscosity and physical appearance of substituted starch in gelatin solution (starch-gelatin solution) (cont.)

Starch types	% starch substitution	Solution viscosity (mPa.s)	Physical appearance of solution
Elastigel 3000M®	5	1671.83	Colloid solution
	10	1762.61	Colloid solution
	15	1837.74	Colloid solution
	20*	2049.35	Colloid solution, hard to remove air bubbles
	25	2254.96	Hard to remove air bubbles
	30	2534.90	Hard to remove air bubbles
Elastigel 2000C®	5	1448.52	Colloid solution
	10	1362.62	Colloid solution
	15	1518.28	Colloid solution
	20	1512.05	Colloid solution
	25	1394.47	Colloid solution
	30	1441.54	Colloid solution
	35*	1463.06	Colloid solution, hard to remove air bubbles
	40	1586.65	Hard to remove air bubbles
	45	1711.08	Hard to remove air bubbles
Elastigel 1000J®	5	1424.12	Colloid solution
	10	1829.00	Colloid solution with the most white turbidity
	15*	2839.56	Colloid solution, hard to remove air bubbles
	20	2905.05	Hard to remove air bubbles
	25	3548.51	Hard to remove air bubbles
Pure gelatin	0	1457.86	Clear gel and slightly brown

* represented the maximum of starch substitution with homogenous solution and without air bubbles.

The difficulty for air bubble removal was one of criterias to select the appropriate solutions.

It is interesting that the viscosity of Alpha starch increased dramatically when the concentration has been changed from 15% to be 20%. It was also observed in 20% of Elastigel 1000J® substituted and 30% of Eragel® substituted that air bubbles were hardly removed even using sonicator for a long time to get rid of air bubbles. Thus, formulations with severe air bubbles were eliminated for further study due to the difficulties in preparing solution and casting smooth film.

As mentioned before, pure gelatin solution were used as a comparator to substituted starch selection due to its excellent properties for hard capsules.

Therefore, the maximum percentage of substituted starch were selected by considering samples that showed value quite similar to gelatin solution. However, the maximum substituted starch in gelatin solution had to be considered with the appearance of the films after casting.

2.2 Properties of starch-gelatin film

After casting and film drying, all starch-gelatin films were not clear (slightly turbid), as compared with pure gelatin film. For rice starch at 5-10% substituted, it was little rough but could provide a homogeneous film. Until 15% or more substituted, it had a small particle of starch in film with rough surface. Starch-gelatin solution at 15% substitution did not give a homogenous film eventhough solution was stirred before casting. Eragel® produced rougher films when compared with gelatin film and modified starch films. Glutinous rice starch did not give a homogenous film where some small particles of starch appeared in the film texture. These particles were easily seen at 10% substitutions or more. Tapioca and Alpha starch® provided homogenous films at 5% substitution but at 10% or more substitutions it showed clear small particles inside the films. Elastigel 2000C® and Elastigel 3000M® at any substitutions gave homogenous films but not very clear as compared to gelatin films. Elastigel 1000J® gave homogenous films at 20% and lower substitutions where at more than 20% substitutions showed some starch particles in the films.

High percent substitutions of all starches resulted in more viscous solutions and easily to trap air bubbles, which affect the film textures.

In the previous section, average maximum stress for gelatin film was 86.149 ± 3.839 N/mm^2 and gelatin film is able to form a hard gelatin capsule by dipping method. By substituting gelatin with starches, it was found to reduce the maximum stress of films. However, the preliminary studies showed that reducing in maximum stress to some level, starch-gelatin solution can still be used to produce good hard gelatin capsules. Moisture content for all formulations fell within the standard range of 12-16%. The maximum stress, extension at break, and the moisture content were showed in the figure 4.1, 4.2 and 4.3 respectively.

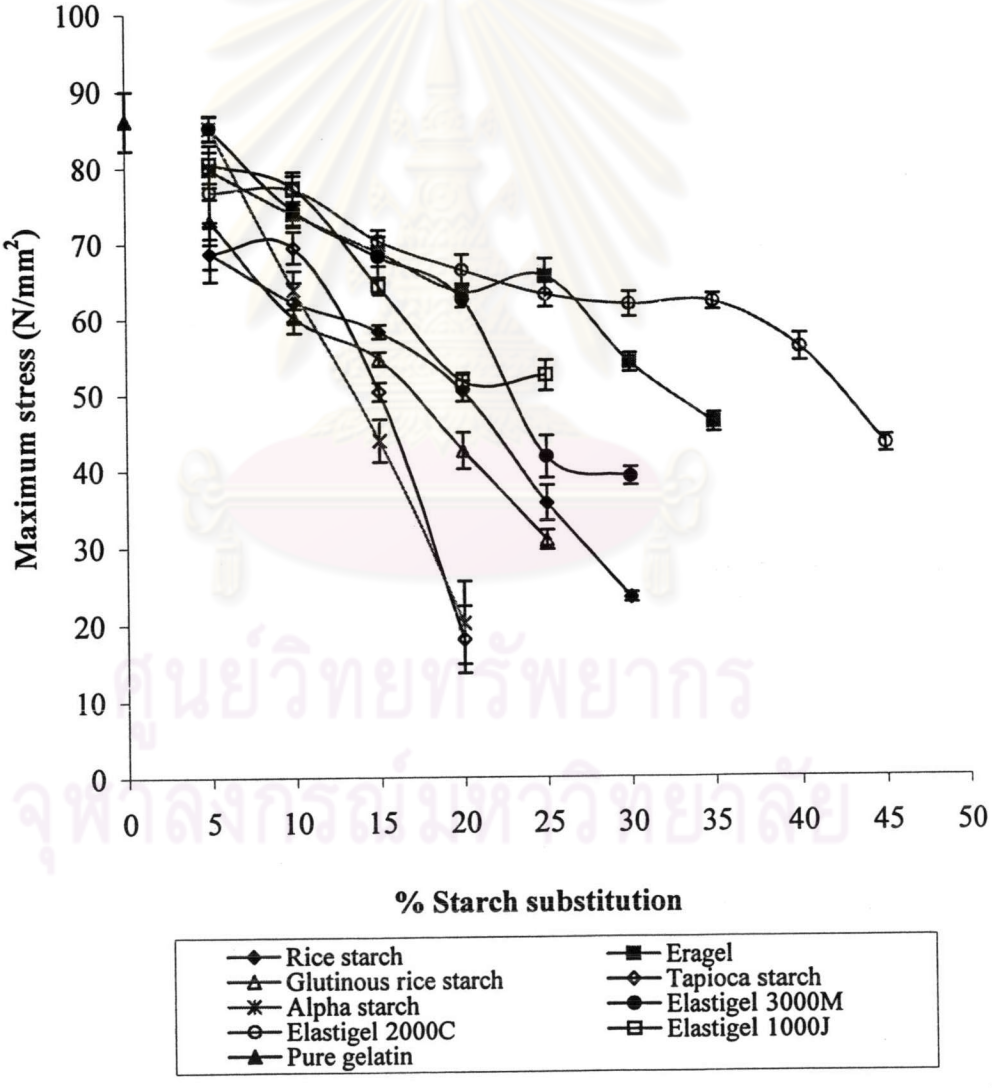


Figure 4.1 The maximum stress of starch-gelatin films

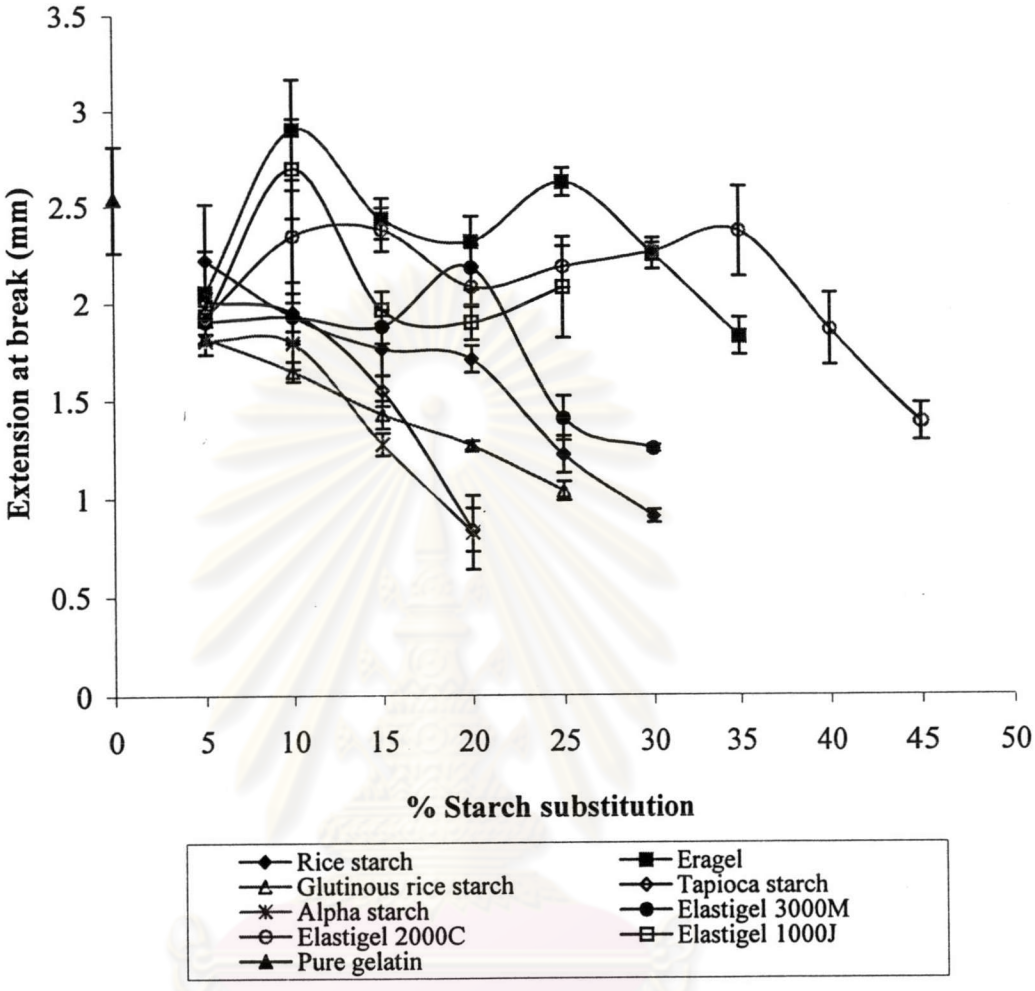


Figure 4.2 The extension at break of starch-gelatin films

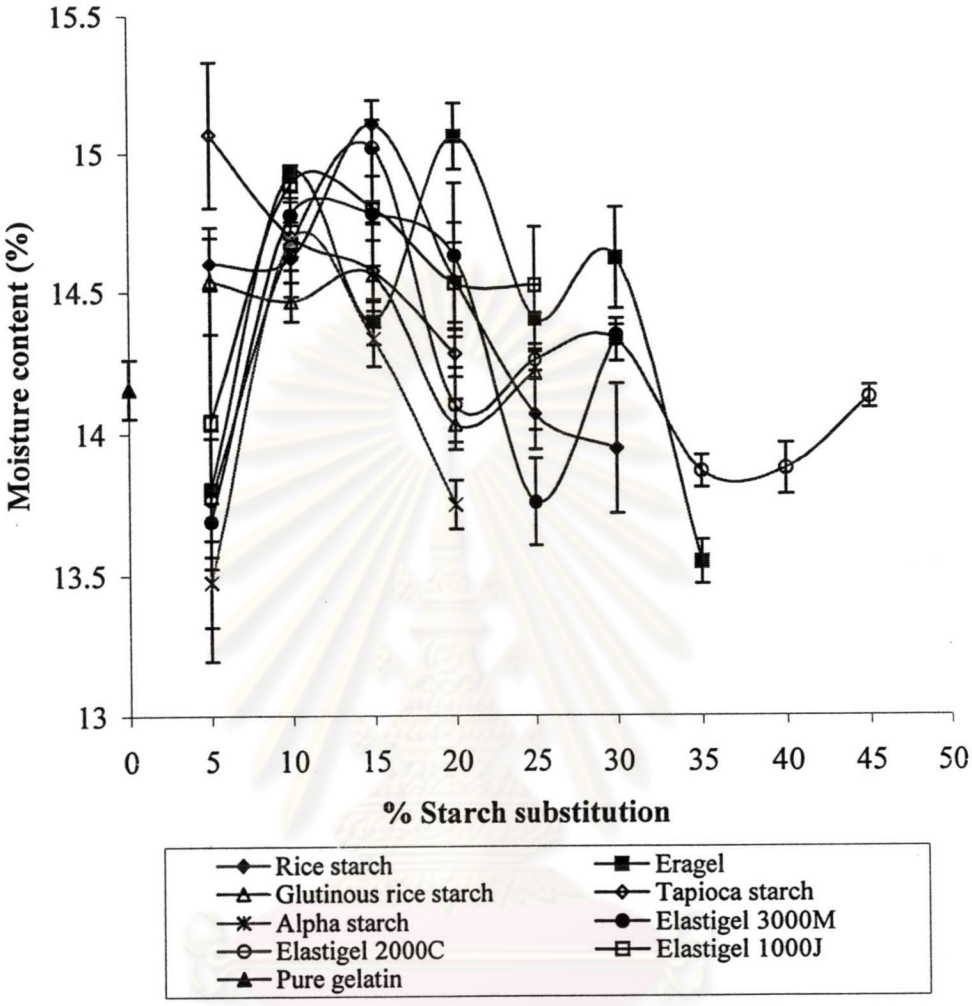


Figure 4.3 The moisture content of starch-gelatin films

The maximum percentage of starch substitution in gelatin solution were determined by comparing values with pure gelatin properties.

Not only maximum stress, extension at break and the percentage of moisture content were used to determine appropriate starch-gelatin films, but also the viscosity of starch-gelatin solutions.

Thus, 35% substitution with Elastigel 2000C®, 25% substitution with Eragel® and 20% substitution with Elastigel 3000M®formulations were selected for further study because these three formulations gave maximum percentage of starch substitution in gelatin and homogenous solution. The viscosity of 35% substitution with Elastigel 2000C® was similar to pure gelatin 33% and air bubbles could be removed from the solution. 25% substitution with Eragel® and 20% substitution with Elastigel 3000M® had the viscosity higher than 33% pure gelatin. In this viscosity, air bubbles could be removed easily whereas it is hard the remove air bubbles at higher viscosity. The appearance of Elastigel 2000C® and 3000M® gave homogenous films while some of starch films showed starch particles scattering in the films. Eragel® film gave the same appearance of film but rougher than Elastigel 2000C® and 3000M. As compared to other starches, the mechanical properties of these three formulations gave higher maximum stress (about 60 N/mm^2), extension at break nearly similar to the gelatin film. Results showed that other starches at 20% substitution, the maximum stress was dropped to about 20-50 N/mm^2 and extension at break below 2 mm which gave more weak and brittle film.

3. Effect of plasticizers on starch-gelatin solutions and films

From previous experiment, three formulations were selected which are 35% substitution with Elastigel 2000C®, 25% substitution with Eragel® and 20% substitution with Elastigel 3000M® respectively. In this study, two plasticizers such as glycerine and sorbitol were chosen to study the effect of plasticizers on gelatin and starch-gelatin solutions and films. Various concentrations of sorbitol within the range of 1-10% and glycerine within the range of 1-5 % w/w were gradually added.

3.1 The effects of plasticizers on gelatin and starch-gelatin solutions by determination of viscosity.

Table 4.4 Viscosity determination of gelatin solution.

Concentrations of plasticizers (w/w)	Viscosity (mPa.s)	
	Sorbitol	Glycerine
0	1457.86	1457.86
0.1	1411.67	1423.54
0.5	1533.34	1541.35
1	1447.41	1705.92

By increasing the concentration of both plasticizers, the viscosity of solution with glycerine was increased while sorbitol within the range of 0-1% showed no effect on the viscosity of solution (table 4.4).

Table 4.5 Viscosity determination of starch-gelatin solution.

Concentration of plasticizers (w/w)	Elastigel 2000C® Viscosity (mPa.s)		Eragel® Viscosity (mPa.s)		Elastigel 3000M® Viscosity (mPa.s)	
	Sorbitol	Glycerin	Sorbitol	Glycerin	Sorbitol	Glycerin
0	1463.06	1463.06	2022.50	2022.50	2049.35	2049.35
1	1390.95	1389.17	2329.20	2325.42	2382.28	2124.08
2	1429.81	1441.68	2467.95	2394.37	2442.70	2139.02
3	1642.62	1797.99	2720.51	2344.89	2439.90	2220.11
4	1695.30	1753.40	2672.31	2387.57	2448.08	2218.51
5	1764.30	1749.63	3116.21	3182.18	2543.26	2214.77
6	1883.22	-	2862.54	-	2419.76	-
7	2082.34	-	3223.39	-	2671.16	-
10	2172.14	-	3600.70	-	3258.92	-

- Elastigel 2000C® = 35% substitution with Elastigel 2000C®
- Eragel® = 25% substitution with Eragel®
- Elastigel 3000M® = 20% substitution with Elastigel 3000M®

From table 4.5, it was indicated that the viscosity of starch-gelatin solutions were increased by increasing the concentration of both plasticizers. It can be explained that the plasticizer molecules were trapped inside the entangled polymer or network between

starch-gelatin, starch-starch or gelatin-gelatin in solution. Normally, sorbitol or glycerine are likely to adsorb water to their molecules. Thus, more water in the solution tends to be trapped inside the network as increased the amount of plasticizers, resulting in higher viscosity.

3.2 The effects of plasticizers on gelatin and starch-gelatin films.

Generally, 0.1-1% w/w of plasticizers were used in hard capsule manufacturing. Therefore, 0.1-1% w/w of plasticizers were selected to evaluate the effects of plasticizers on gelatin films.

Table 4.6 The mechanical properties and moisture content of gelatin containing plasticizers films

Concentration of plasticizers (w/w)	Maximum stress (N/mm^2) ± SD.					
	Sorbitol			Glycerine		
0	86.149	±	3.839	86.149	±	3.839
0.1	79.398	±	1.858	74.685	±	1.188
0.5	79.723	±	1.370	78.137	±	1.020
1	79.180	±	0.514	80.611	±	3.328
Concentration of plasticizers (w/w)	Extension at break (mm)					
	Sorbitol			Glycerine		
0	2.537	±	0.276	2.537	±	0.276
0.1	2.559	±	0.096	2.415	±	0.137
0.5	2.575	±	0.067	2.276	±	0.067
1	2.4140	±	0.078	2.348	±	0.032
Concentration of plasticizers (w/w)	Moisture content (%)					
	Sorbitol			Glycerine		
0	14.53	±	0.16	14.53	±	0.16
0.1	14.93	±	0.07	14.78	±	0.18
0.5	14.32	±	0.11	13.49	±	0.25
1	14.20	±	0.10	13.43	±	0.06

There were slightly decreased in maximum stress while there were no differences in extension at break and moisture content for all gelatin films with plasticizers (table 4.6). However, Jones recommended that the amount of plasticizer for hard gelatin capsules should not exceed 5% by weight (Jones, 1987: 49-60).

After adding starches in gelatin solution, properties of starch-gelatin film showed less maximum stress, less extension at break as compared to gelatin film. Starch-gelatin film tends to be less hard and brittle. Thus, the properties of starch-gelatin films should be enhanced by adding plasticizer to make films softer. Varied concentration such as 0-10% w/w of sorbitol and 0-5% w/w of glycerine were used for this study.

Figure 4.4 and 4.5 showed that the maximum stress were decreased and extension at break were increased by increasing the concentration of sorbitol or glycerine. This study confirmed that plasticizers should not be added more than 5% by weight (Jones, 1987: 49-60). The moisture content of formulations added sorbitol were almost within the range of 12-16% while with added 3-4% glycerin were lower than the standard range (as shown in figure 4.6).

Arvanitoyannis et al. (1998b) were studied the effect of glycerine on hydroxypropyl starch-gelatin blends at high glycerine content, the same kind of results were found. The flexibility of film increase can be explained by the assumption of the gel theory (Sears, and Darby, 1982: 35-77).

There were so many points of attachment along the chain of starch-gelatin films. The plasticizer would break the attachment or mask the center of force. These effects could reduce the rigidity of the films which gave the films more flexible. However, there were some interesting points for substituted Elastigel 2000C® film. It was found that the extension at break has been decreased between 1-5% of sorbitol and 1-2% of glycerine. This effect of plasticizer is called "antiplasticization" which occurs with many polymers at low content of plasticizer. Antiplasticization could be explained that plasticizer molecules may be almost totally immobilized by attachment between plasticizer molecules and polymer by various forces including hydrogen bonding. This tends to restrict the freedom of small portions of the polymer molecule side chains and segments (Sears, and Darby, 1982: 35-77).

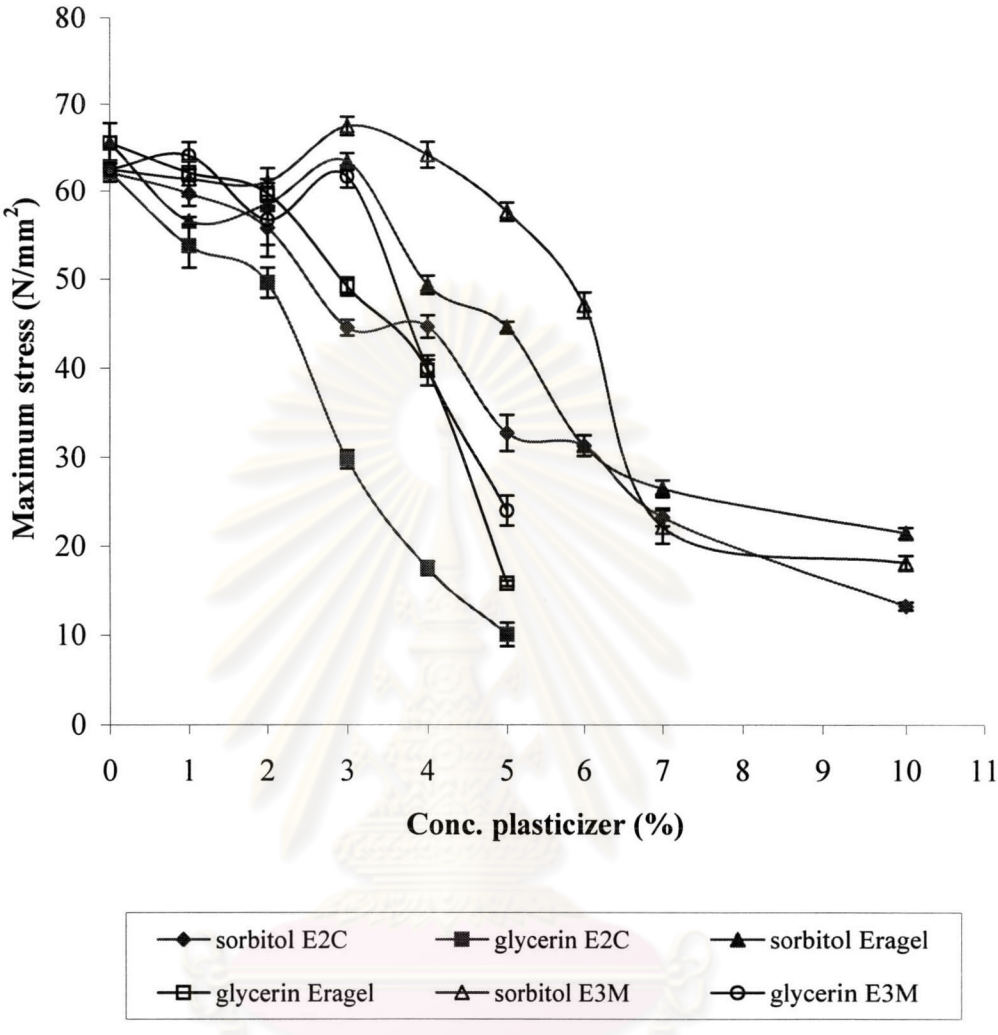


Figure 4.4 The maximum stress of starch-gelatin film containing plasticizers

Note: E2C = 35% substitution with Elastigel 2000C®

Eragel = 25% substitution with Eragel®

E3M = 20% substitution with Elastigel 3000M®

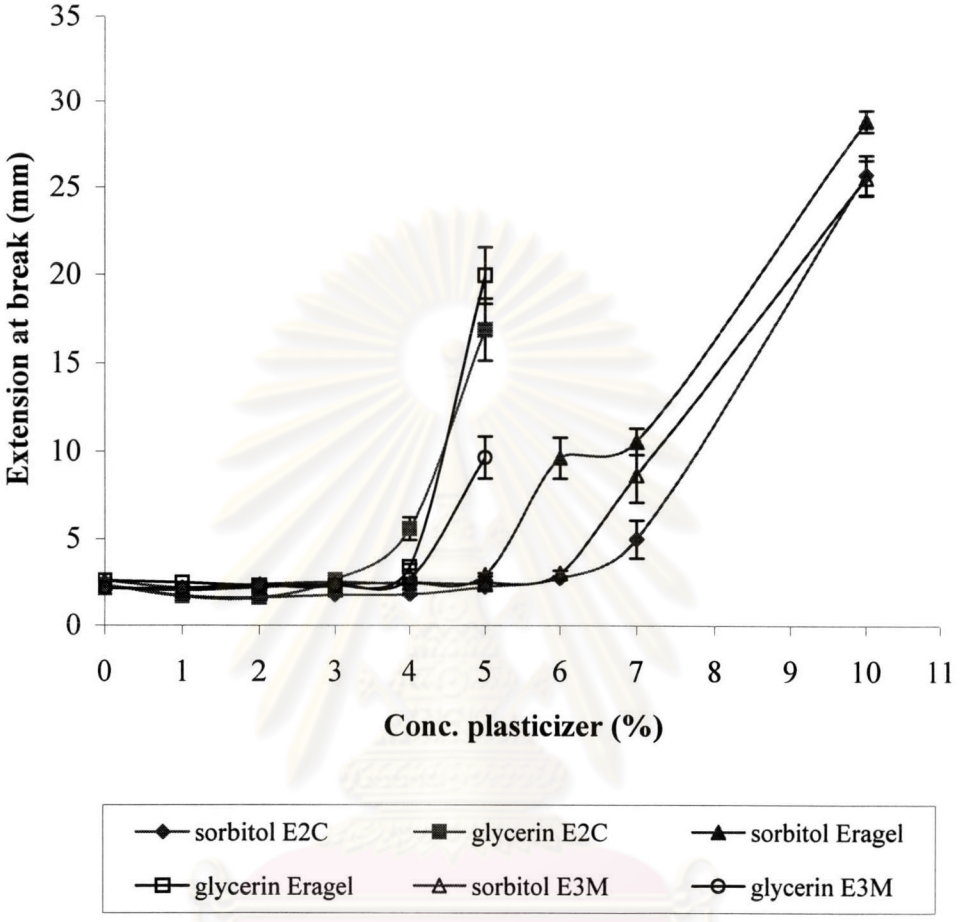


Figure 4.5 The extension at break of starch-gelatin film containing plasticizers

Note: E2C = 35% substitution with Elastigel 2000C®

Eragel = 25% substitution with Eragel®

E3M = 20% substitution with Elastigel 3000M®

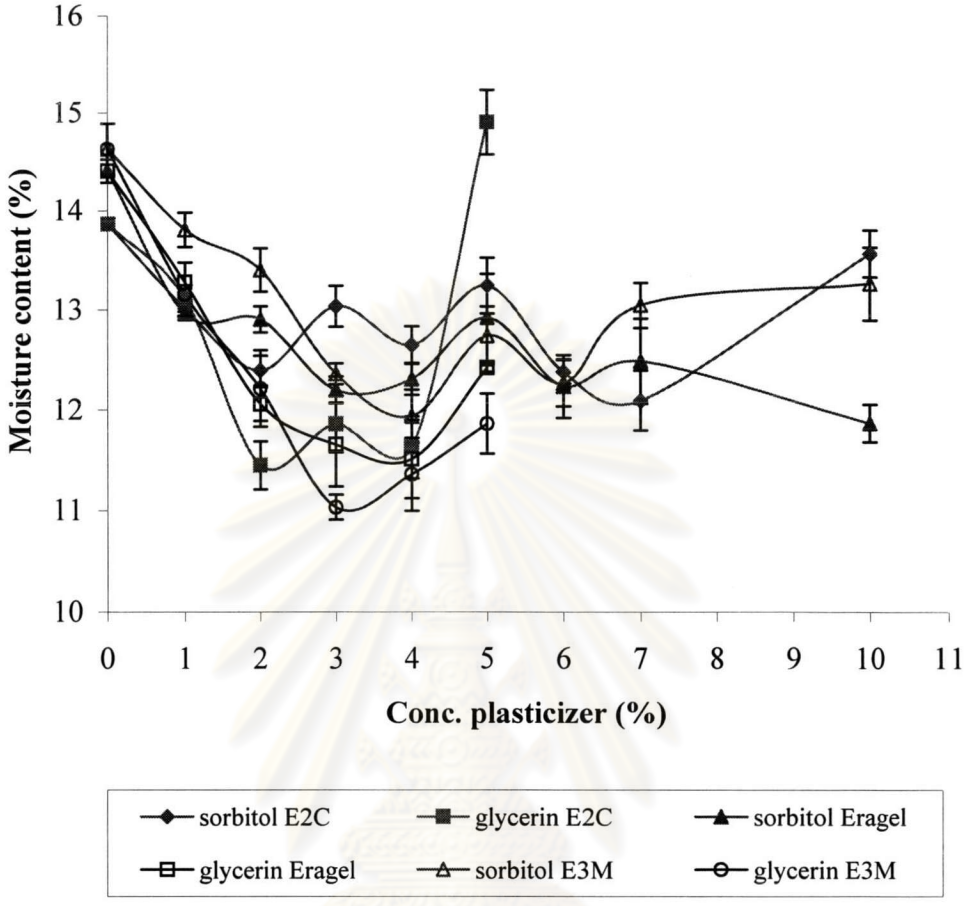


Figure 4.6 The moisture content of starch-gelatin film containing plasticizers

Note: E2C = 35% substitution with Elastigel 2000C®

Eragel = 25% substitution with Eragel®

E3M = 20% substitution with Elastigel 3000M®

Table 4.7 The appropriate plasticizers for starch-gelatin films

Type of substituted starch	% plasticizer	
	sorbitol	glycerine
35% substitution with Elastigel 2000C®	0%	0%
25% substitution with Eragel®	0-4%	0-3%
20% substitution with Elastigel 3000M®	0-5%	0-4%

It was also observed that glycerine showed more effects on starch-gelatin films than sorbitol as compared at the same concentration. The appearance of films and mechanical properties of 35% Elastigel 2000C®–gelatin films showed slightly difference as compared to pure gelatin film. While Eragel®–gelatin with 0-4% sorbitol and 0-3% glycerine also gave slightly difference to pure gelatin film. For substituted Elastigel 3000M®, 0-5% of sorbitol and 0-4% of glycerine were suitable concentrations as the film were similar to pure gelatin films.

Table 4.7 displayed suitable percentages of plasticizers for 3 substituted starch-gelatin films. Even starch-gelatin film without plasticizers showed no difference as compared with gelatin film but plasticizers were recommended to be added in the formulation so as to reduce the brittleness in visible appearance except substituted Elastigel 2000C® without of sorbitol and glycerine were recommended for 35% substituted Elastigel 2000C®–gelatin film.

In addition, not only mechanical properties of films were considered but also the stability of films because deformation and contraction of films may occur during long term storage. Therefore, next study would be the effects of plasticizers on the stabilities of films.

4. Stability testing of gelatin and starch-gelatin films

All films were kept at 40°C, 75% RH and evaluated after 1, 2, 4, 8 and 12 weeks.

4.1 Stability testing of gelatin film

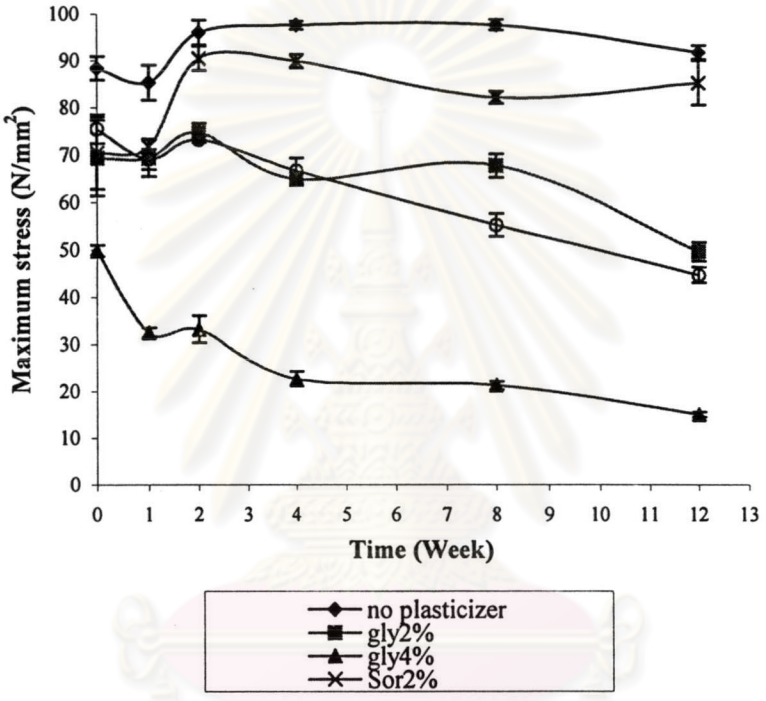


Figure 4.7 The maximum stress of gelatin containing plasticizer films at 40°C, 75% RH

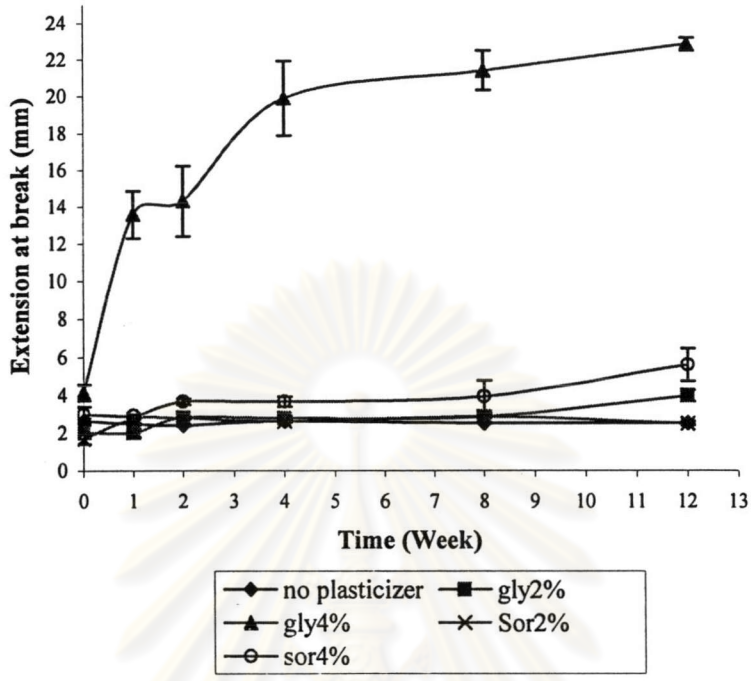


Figure 4.8 The extension at break of gelatin containing plasticizer films at 40°C, 75% RH

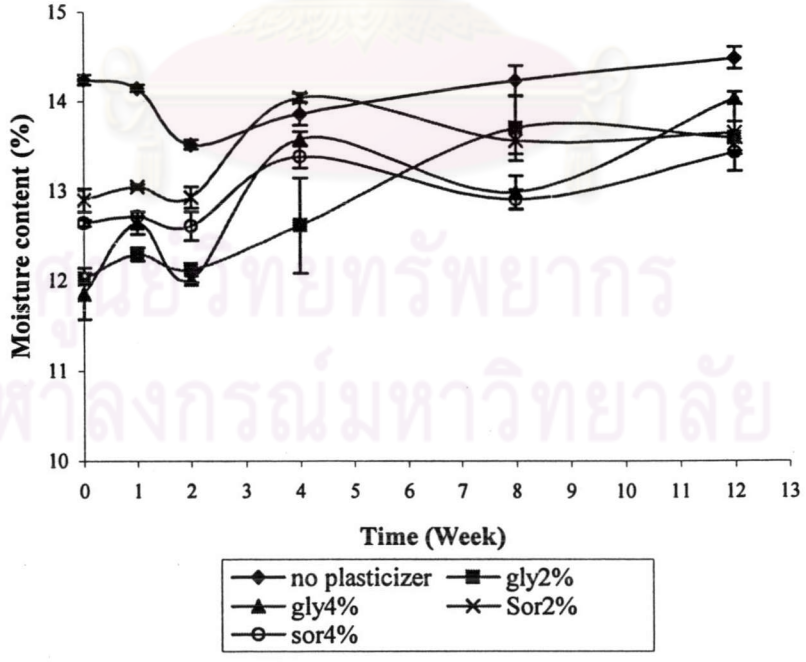


Figure 4.9 The moisture content of gelatin containing plasticizer films at 40°C, 75% RH

Figure 4.7 showed mechanical properties of gelatin film stored at 40°C, 75% RH. Without plasticizer, the maximum stress increased from 88.404 ± 2.553 N/mm^2 to 96.007 ± 2.637 N/mm^2 after two weeks and slightly reduced at after 12 weeks which was 91.739 ± 1.509 N/mm^2. However, the maximum stress was increased after 12 weeks because it may absorb water sufficiently to reform and give greater strength of crystallite while the extension at break and moisture content were unchanged (Jones, 1987: 31-48). For 2% sorbitol, the maximum stress slightly increased from 70.371 ± 7.563 N/mm^2 to 85.261 ± 4.727 N/mm^2 after 12 weeks where the extension at break and moisture content were increased from the initial storage. Sorbitol may not be enough to stabilize the amorphous form of gelatin film; therefore, the maximum stress increased after the storage in stability chamber. In case of the extension at break and moisture content, high moisture content (75% RH) may be absorbed in films and cause the higher extension at break. For 4% sorbitol, 2%, and 4% glycerin formulations, the maximum stress was decreased after the storage conditions. For example, the maximum stress of gelatin with 4% sorbitol was significantly decreased after 8 weeks; also 2% and 4% glycerin were markedly decreased after 12 and 4 weeks respectively. The extensions at break and moisture contents for the 4% sorbitol and 2% and 4% glycerin formulations were also increased as shown in figure 4.8 and 4.9 respectively.

4.2 Study stability of starch-gelatin film

4.2.1 Stability of 35% substitution with Elastigel 2000C® containing plasticizer film

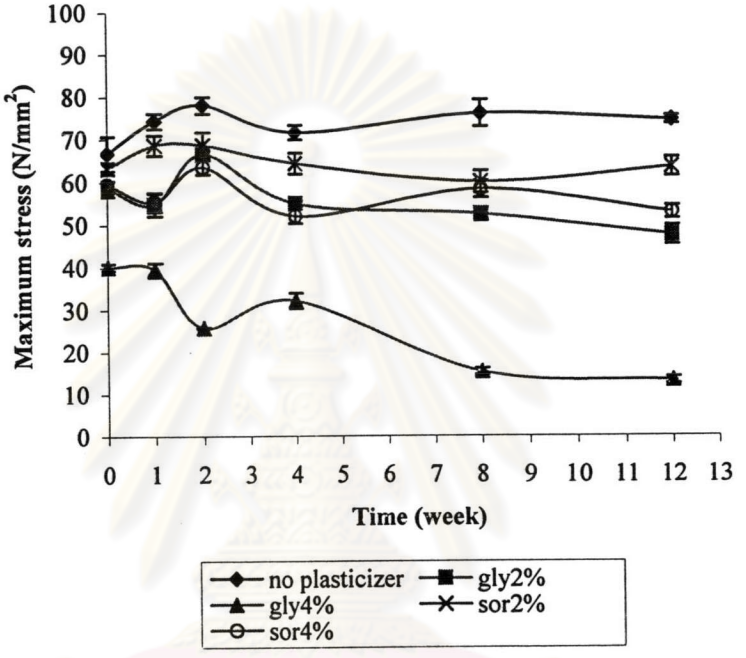


Figure 4.10 The maximum stress of 35% substitution with Elastigel 2000C® containing plasticizer film at 40°C, 75% RH

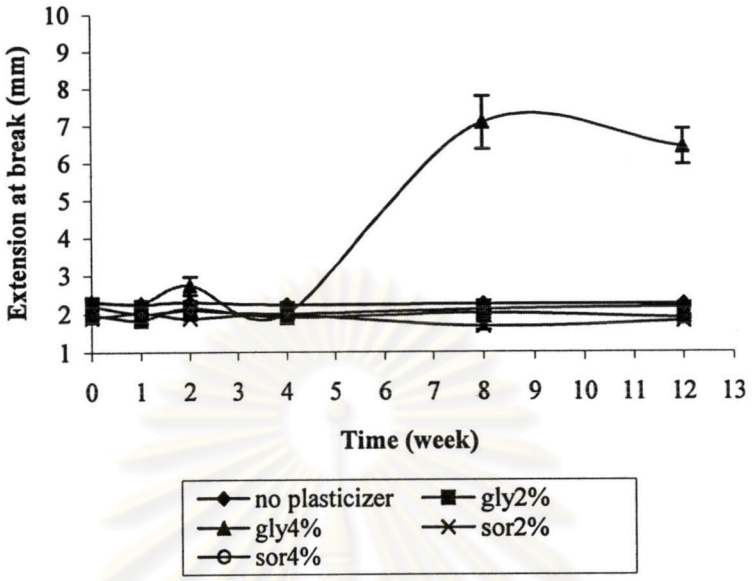


Figure 4.11 The extension at break of 35% substitution with Elastigel 2000C® containing plasticizer film at 40°C, 75% RH

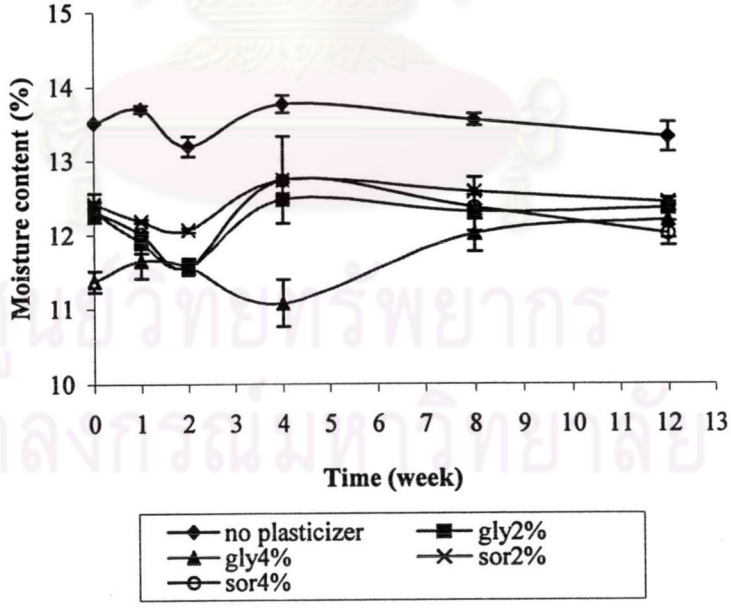


Figure 4.12 The moisture content of 35% substitution with Elastigel 2000C® containing plasticizer film at 40°C, 75% RH

From figure 4.10, 4.11 and 4.12 they were observed that the maximum stress of 35% substituted Elastigel 2000C® without plasticizer were slightly increased from 66.753 ± 4.030 N/mm^2 to 74.368 ± 0.956 N/mm^2 after 12 weeks of storage while the extension at break and moisture content were unchanged. For 2% and 4% sorbitol, the maximum stress, extension at break, and moisture content showed very slightly difference after 12 weeks. For 2% glycerin, it gave the same result after 12 weeks. It is interesting for 4% glycerin which the maximum stress were significantly decreased after 8 weeks while the extension at break were extensively increased after 8 weeks and moisture content were unchanged.

It was observed that Elastigel 2000C® with sorbitol or glycerin showed the maximum stresses lower than without plasticizer while the extension at break showed no difference except after 8 weeks for 4% glycerin. The moisture content of Elastigel 2000C® with plasticizer were lower than the film without plasticizer. Especially, films containing 2% and 4% glycerin showed that the moisture content were lower than the acceptance criteria (12-16%) of standard capsules.

4.2.2 stability of 25% substitution with Eragel® containing plasticizer film

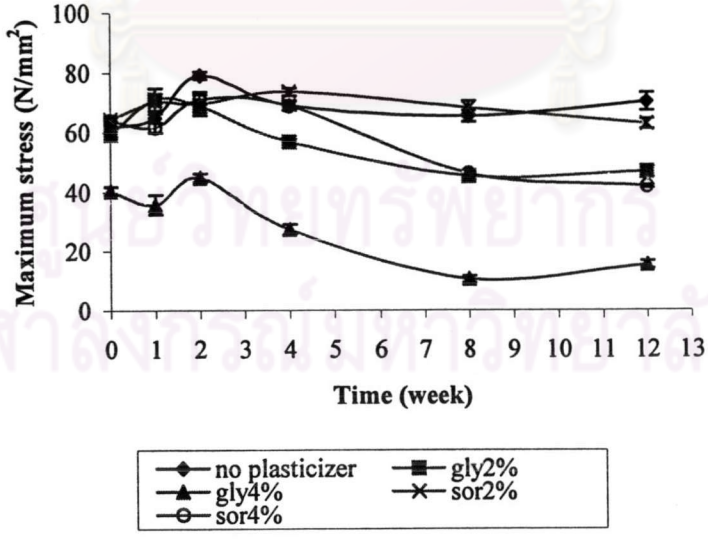


Figure 4.13 The maximum stress of 25% substitution with Eragel® containing plasticizer film at 40°C, 75% RH

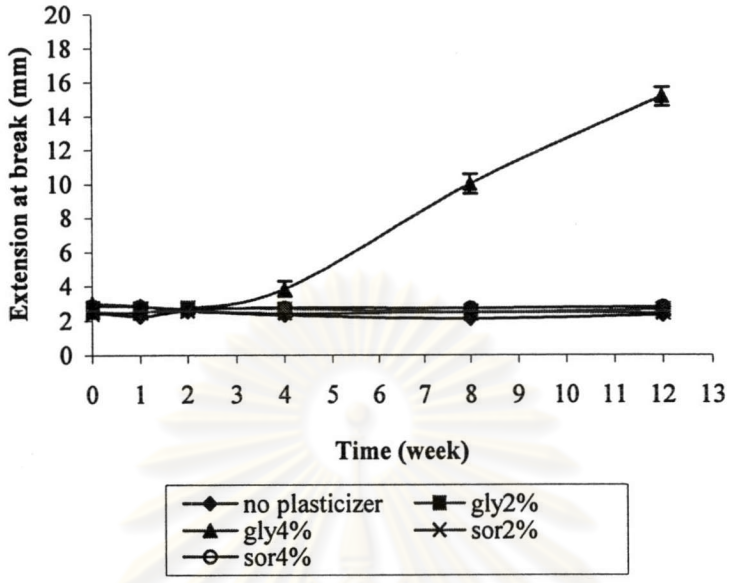


Figure 4.14 The extension at break of 25% substitution with Eragel® containing plasticizer film at 40°C, 75% RH

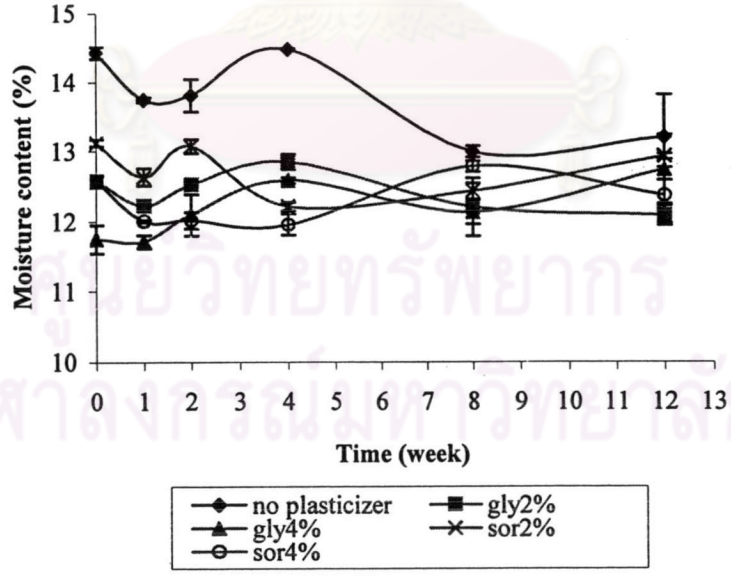


Figure 4.15 The moisture content of 25% substitution with Eragel® containing plasticizer film at 40°C, 75% RH

From figure 4.13, it was illustrated that the maximum stress of 25% substituted Eragel® without plasticizer were increased after 12 weeks. For 2% of sorbitol, the maximum stress had increased in 4 weeks but the maximum stress was dropped dramatically after 12 weeks. For 4% sorbitol, 2% and 4% glycerin, the maximum stresses were decreased significantly after 4 weeks storage. Figure 4.14 showed the extensions at break without plasticizer and with 2%, 4% sorbitol and 2% glycerin were unchanged while the extension at break of 4% glycerin was significantly increased after 8 weeks. The moisture content were similar to Elastigel 2000C® (figure 4.15).

It is interesting that 4% sorbitol, 2% and 4% glycerin with 25% substituted Eragel films after 8 weeks were unstable as the maximum stress had been dropped significantly.

4.2.3 stability of 20% substitution with Elastigel 3000M® containing plasticizer film

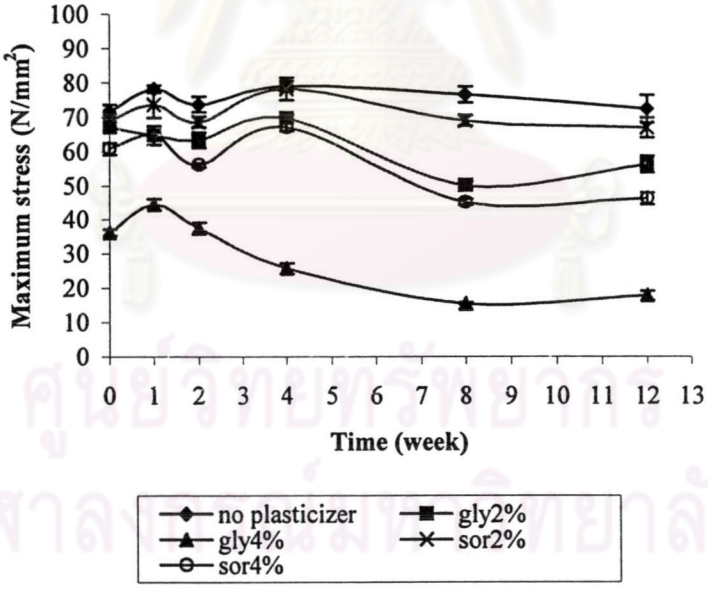


Figure 4.16 The maximum stress of 20% substitution with Elastigel 3000M® containing plasticizer film at 40°C, 75% RH

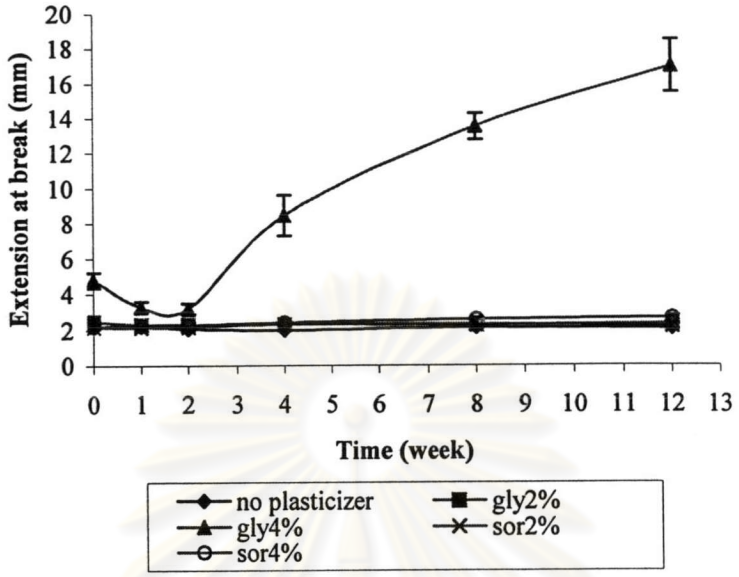


Figure 4.17 The extension at break of 20% substitution with Elastigel 3000M® containing plasticizer film at 40°C, 75% RH

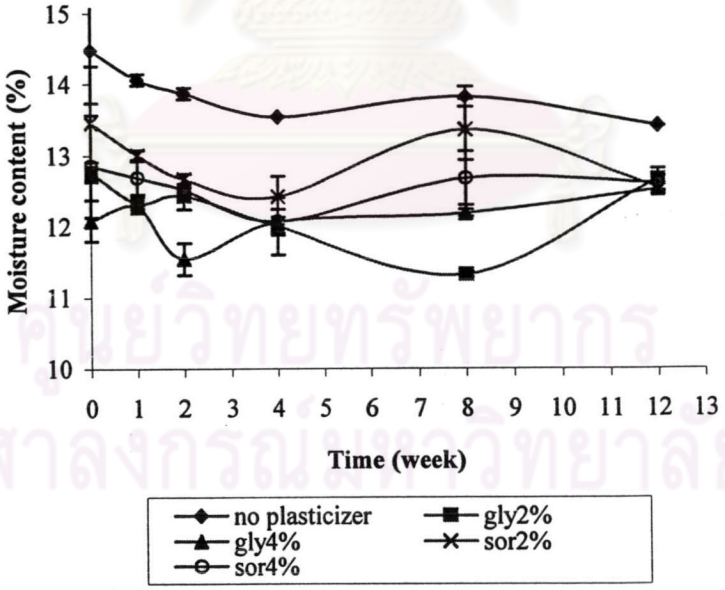


Figure 4.18 The extension at break of 20% substitution with Elastigel 3000M® containing plasticizer film at 40°C, 75% RH

From figure 4.16, it was exhibited that the maximum stress of 20% substituted Elastigel 3000M® without plasticizer and with 2% sorbitol were unchanged while 4% sorbitol, 2% and 4% glycerin showed the maximum stress decreased after 12 weeks. The extensions at break as shown in figure 4.17. For 20% substituted Elastigel 3000M® without plasticizer, with 2% sorbitol and 2% glycerin were unchanged while with 4% sorbitol and with 4% glycerin were increased similar to previous result, moisture content were unchanged (figure 4.18). It was observed that 4% glycerin showed more effects in the maximum stress and extension at break than sorbitol and lower concentration as shown in figure 4.16.

Table 4.8 Summary of formulations which fall in the selection criteria

Type of substituted starch	% plasticizer	
	sorbitol	glycerin
35% substitution with Elastigel 2000C®	0%	0%
25% substitution with Eragel®	0%-4%	0%-2%
20% substitution with Elastigel 3000M®	0%-4%	0%-2%

Table 4.8 was summerised to show the appropriate percentage of plasticizer which gave excellent and stable films for each substituted starches. 0% of plasticizer was used for 35% substitution with Elastigel 2000C® because the moisture content and extension at break were similar to gelatin film and the maximum stress was higher than films with plasticizer. Results showed that 4% glycerin produced sticky film with lower maximum stress and higher extension at break; therefore, 0-4% of sorbitol and 0-2% of glycerin were selected for 25% substitution with Eragel® and 20% substitution with Elastigel 3000M® because it showed similar results within this range.

It can be concluded that the film stability could be affected by plasticizers, therefore, the amount of plasticizer added in solution should be concerned.

5. Starch-gelatin hard shell capsules by dipping method

5.1 Hard gelatin capsules

In this study, the production of hard gelatin capsule shell was done by dipping method and was prepared from 33% w/w gelatin solution. The physical properties of finished hard gelatin capsule shell were tested. From table 4.9, the weight and thickness of hard gelatin capsules obtained from dipping method were compared with the commercial hard gelatin capsule. The variation weight and thickness of hard gelatin capsule from dipping method was higher than commercial gelatin capsules because the machine were in lab scale and human control. While commercial gelatin capsules were produced from automatic machine. It was found that there were no difference between our gelatin capsules and commercial capsules. The moisture content of commercial gelatin capsules and our capsules were in the standard range of 12-16%. This confirmed that the process of dipping and drying could be used and gave no difference between lab scale machine and automatic machine.

5.2 Preparations of starch-gelatin capsules without plasticizer

From previous section, three starches were selected to study starch-gelatin in hard capsule forms by dipping method. After dipping and drying, starch-gelatin capsules without plasticizers were formed. The results showed that the weight and thickness of cap and body for Elastigel 2000C®-gelatin capsules, Eragel®-gelatin capsules and Elastigel 3000M®-gelatin capsules were in the standard range which is 77 ± 6 mg. (TIS 913-2545).

The moisture content of Elastigel 2000C®-gelatin, Eragel®-gelatin and Elastigel 3000M®-gelatin capsules were 12.26, 11.88 and 13.40% respectively. It was seen that Elastigel 2000C® and Elastigel 3000M® capsules were in the standard range while Eragel®-gelatin capsules was below the range (12-16%).

Table 4.9 Weight and thickness of hard capsule shell without plasticizers

Material	Weight (mg)		Thickness (mm)	
	Cap	Body	Cap	Body
Commercial capsule	30.629 ± 0.807	42.627 ± 1.053	0.122 ± 0.005	0.102 ± 0.005
Gelatin dipping	30.143 ± 2.085	45.203 ± 2.924	0.129 ± 0.016	0.106 ± 0.013
Elastigel 2000C*	28.101 ± 2.234	40.599 ± 1.946	0.111 ± 0.017	0.103 ± 0.015
Eragel**	30.140 ± 3.009	42.700 ± 2.996	0.124 ± 0.015	0.101 ± 0.010
Elastigel 3000M***	32.946 ± 2.153	48.938 ± 5.127	0.134 ± 0.019	0.115 ± 0.018

*35% substitution with Elastigel 2000C®

**25% substitution with Eragel®

***20% substitution with Elastigel 3000M®

5.3 Starch-gelatin capsule shells with plasticizers

Not more than 5% plasticizer was usually used in the preparation of hard gelatin capsule. According to the results from previous sections, the plasticizers were found to be useful in some of substituted starch. This section will be concentrated on the plasticizer effects on the properties of three starch substitutes hard capsule shells. The concentration of sorbitol and glycerin were varied within 1-3%. The results were compared with commercial hard gelatin capsules as shown in table 4.10 and 4.11

Due to the lack of weight and thickness specification for gelatin capsules, in-house specification was created for starch-gelatin capsules determination. The specification done by was measuring the weight and thickness of commercial gelatin capsules for 10 capsules. The weight and thickness of in-house specification was found to be 30.629±0.807 mg, 0.122±0.005 mm and 42.627±1.053 mg, 0.102±0.005 mm for caps and bodies respectively.

5.3.1 35% substituted Elastigel 2000C®-gelatin capsules with plasticizers

From table 4.16 and 4.17, the weight of Elastigel 2000C®-gelatin capsules with and without sorbitol and glycerin was not different from commercial capsules and also in the standard range (TIS 913-2545).

The weight of all formulations fell in in-house specification except the weight of 3% sorbitol formulation were over the specification. The thickness of all Elastigel 2000C®-gelatin capsules was also not different from commercial capsules and within the range.

5.3.2 25% substituted Eragel®-gelatin capsules with plasticizer

From table 4.10 and 4.11, the weight of Eragel®-gelatin capsules with and without sorbitol and glycerin was not different from commercial capsules and also in the standard range. For the moisture content of Eragel®-gelatin, all formulations were about 10.64-11.96% which are lower than standard range (12-16%) except 1% sorbitol formulation was about 12.32% which was in the range (TIS 913-2545).

Table 4.10 showed that the weight of Eragel® without plasticizer, 1% and 2% sorbitol and 1% glycerin were within in-house specification while 3% sorbitol, 2% glycerin and 3% glycerin were above the specification. It was concluded that the thickness of formulation with sorbitol were in the range whereas the thickness of formulations with glycerin were in the range only 1% and 2% (table 4.11).

Although the weight, the thickness and the moisture content of Eragel®-gelatin capsules with sorbitol was in the range but the textures were found to be too brittle and difficult for stripping as compared to Eragel®-gelatin with glycerin. Thus, Eragel®-gelatin with 1% glycerin was chosen for further study.

5.3.3 20% substituted Elastigel 3000M®-gelatin capsules with plasticizers

From table 4.10 and 4.11, weight of Elastigel 3000M®-gelatin capsules with and without sorbitol and glycerin were not different from commercial capsules and also in the standard range (TIS 913-2545). Eventhough all formulations

were in the standard range but none of them passed in-house specification in terms of weight and thickness. The moisture content of Elastigel 3000M®-gelatin capsules without plasticizer and 1-2% of sorbitol were in the range of 12-16% while with 3% sorbitol and 1-3% glycerin were lower than the standard range.

However, the difficulties in stripping and the brittleness were used to consider the appropriate formulation for further study. Finally, Elastigel 3000M®-gelatin capsules with 2% glycerin were selected.

Belows are the selected starch-gelatin formulation for hard capsules.

1) Starch-gelatin (Elastigel 2000C®) no plasticizer.
2) Starch-gelatin (Eragel®) with glycerin 1%
3) Starch-gelatin (Elastigel 3000M®) with glycerin 2%

Table 4.10 The weight of starch-gelatin capsule at vary concentration of sorbitol and glycerin

Weight of caps (mg)

Materials	No plasticizer	Sorbitol			Glycerine		
		1%	2%	3%	1%	2%	3%
Elastigel 2000C®*	28.101 ± 2.234	28.673 ± 1.255	28.705 ± 2.487	32.014 ± 1.759	27.911 ± 3.157	29.522 ± 0.974	29.731 ± 1.585
Eragel®**	30.143 ± 3.009	29.515 ± 3.353	30.418 ± 1.701	31.285 ± 1.042	30.943 ± 3.076	32.271 ± 2.246	35.787 ± 3.082
Elastigel 3000M®***	34.276 ± 2.261	30.958 ± 1.476	33.564 ± 3.069	35.351 ± 4.397	33.099 ± 1.433	36.065 ± 2.500	38.382 ± 4.677

Weight of bodies (mg)

Materials	No plasticizer	Sorbitol			Glycerine		
		1%	2%	3%	1%	2%	3%
Elastigel 2000C®*	40.599 ± 1.946	42.602 ± 3.394	39.377 ± 2.330	46.981 ± 3.189	45.36 ± 4.178	45.589 ± 3.701	49.161 ± 6.164
Eragel®**	42.700 ± 2.996	43.411 ± 1.251	44.222 ± 2.378	48.257 ± 4.259	45.24 ± 2.757	49.174 ± 4.846	51.318 ± 3.328
Elastigel 3000M®***	48.935 ± 5.127	47.695 ± 2.124	53.168 ± 3.407	51.027 ± 4.748	50.637 ± 4.615	51.505 ± 3.036	48.826 ± 3.388

*35% substitution with Elastigel 2000C®

**25% substitution with Eragel®

***20% substitution with Elastigel 3000M®

Table 4.11 The thickness of starch-gelatin capsule wall at vary concentration of sorbitol and glycerin

Thickness of cap (mm)

Material	No plasticizer	Sorbitol			Glycerine		
		1%	2%	3%	1%	2%	3%
Elastigel 2000C®*	0.111 ± 0.017	0.117 ± 0.014	0.12 ± 0.026	0.128 ± 0.016	0.114 ± 0.017	0.12 ± 0.012	0.119 ± 0.011
Eragel®**	0.124 ± 0.015	0.125 ± 0.024	0.138 ± 0.019	0.129 ± 0.014	0.131 ± 0.014	0.133 ± 0.015	0.156 ± 0.017
Elastigel 3000M®***	0.134 ± 0.019	0.130 ± 0.013	0.133 ± 0.019	0.139 ± 0.021	0.139 ± 0.013	0.145 ± 0.022	0.152 ± 0.027

Thickness of Body (mm)

Material	No plasticizer	Sorbitol			Glycerine		
		1%	2%	3%	1%	2%	3%
Elastigel 2000C®*	0.103 ± 0.015	0.108 ± 0.015	0.093 ± 0.011	0.122 ± 0.018	0.118 ± 0.016	0.104 ± 0.015	0.109 ± 0.016
Eragel®**	0.101 ± 0.010	0.104 ± 0.006	0.101 ± 0.007	0.113 ± 0.022	0.116 ± 0.01	0.117 ± 0.016	0.122 ± 0.010
Elastigel 3000M®***	0.115 ± 0.018	0.114 ± 0.013	0.134 ± 0.02	0.132 ± 0.018	0.12 ± 0.014	0.124 ± 0.017	0.127 ± 0.029

*35% substitution with Elastigel 2000C®

**25% substitution with Eragel®

***20% substitution with Elastigel 3000M®

6. The effect of process aids-sodium lauryl sulfate (SLS)

From previous section, to select the three formulations were chosen as follows

1. 35% substituted with Elastigel 2000C®
2. 25% substituted with Eragel® and glycerin 1% w/w
3. 20% substituted with Elastigel 3000M® and glycerin 2% w/w

For the table 4.12 the viscosity of substituted Elastigel 2000C® and substitute Elastigel 3000M® in each formulation was increased as increasing the amount of SLS, on the other hand, the viscosity of Eragel®-gelatin solutions were decreased.

Table 4.12 Viscosity of starch-gelatin solution with varied concentration of SLS

Material	Viscosity (mPa.s)
35% substituted Elastigel 2000C®	1302.30
35% substituted Elastigel 2000C® + 0.1% SLS	1236.02
35% substituted Elastigel 2000C® + 1% SLS	1656.89
25% substituted Eragel ® + 1% glycerin	2242.82
25% substituted Eragel ® + 0.1% SLS + 1% glycerin	1985.95
25% substituted Eragel ® + 1% SLS + 1% glycerin	2020.81
20% substituted Elastigel 3000M ® + 2% glycerin	2053.22
20% substituted Elastigel 3000M ® + 0.1% SLS + 2% glycerin	2058.06
20% substituted Elastigel 3000M® + 1% SLS + 2% glycerin	2278.08

After adding SLS at 0.1% and 1%, weight and thickness of different were used to compare to capsules were used to compare to capsules without SLS. It was observed that weight of capsules were difficult to differentiate the effect of SLS on starch-gelatin capsules but the consistence of wall thickness was used to determine. Not only the

consistence of wall thickness was used but also viscosity, gloss appearance and difficulties in manufacturing were considered. For Elastigel 2000C®, capsules with 0.1% SLS were suggested because it enhanced the gloss of films from 39.53 to be 62.36 GU as shown in table 4.13. Table 4.14 showed that the weight and thickness of capsule bodies slightly decreased and viscosity was not changed. For Eragel® (table 4.15), capsules with 0.1% were recommended because of the consistency of wall thickness (no difference between wall and top thickness).

It was interesting that the viscosity were unchanged after adding SLS into Elastigel 3000M®-gelatin solution. SLS produced bubbles which created problems for capsule manufacturing especially the smoothness of films and the gloss of film were decreased from 80.72 to be 63.97 GU therefore, Elastigel 3000M®-gelatin capsules without SLS was selected for further study (table 4.16).

Table 4.13 Gloss starch-gelatin films at varied concentration of sodium lauryl sulfate (SLS)

Concentration (%)	35% Elastigel 2000C (GU)*	25% Eragel (GU)*	20% Elastigel 3000M (GU)*
No SLS	39.53 ± 1.15	24.37 ± 0.3	80.72 ± 0.70
SLS 0.1%	62.36 ± 1.06	21.61 ± 0.19	63.97 ± 1.11
SLS 1%	18.01 ± 0.26	13.04 ± 0.07	14.56 ± 0.21

*GU = gloss units

Table 4.14 Weight and thickness of 35% substituted with Elastigel 2000C® with vary concentration SLS

Material	No plasticizer		
	No SLS	SLS 0.1%	SLS 1%
Weight of cap in added SLS (mg)	25.186 ± 1.062	23.717 ± 1.904	28.895 ± 1.569
Thickness wall of cap added SLS (mm)	0.107 ± 0.012	0.099 ± 0.009	0.118 ± 0.011
Thickness top wall of cap added SLS (mm)	0.121 ± 0.023	0.122 ± 0.019	0.145 ± 0.015
Weight of body added SLS (mg)	37.724 ± 2.040	33.722 ± 0.938	36.86 ± 1.052
Thickness wall of body added SLS (mm)	0.099 ± 0.012	0.083 ± 0.005	0.095 ± 0.011
Thickness top wall of body added SLS (mm)	0.097 ± 0.010	0.102 ± 0.007	0.109 ± 0.010

Table 4.15 Weight and thickness of 25% substituted with Eragel® and glycerin 1% w/w with vary concentration SLS

Material	Glycerine 1%		
	No SLS	SLS 0.1%	SLS 1%
Weight of cap in added SLS (mg)	35.567 ± 1.914	31.881 ± 1.303	32.497 ± 1.139
Thickness wall of cap added SLS (mm)	0.150 ± 0.017	0.137 ± 0.017	0.140 ± 0.018
Thickness top wall of cap added SLS (mm)	0.180 ± 0.025	0.135 ± 0.016	0.181 ± 0.031
Weight of body added SLS (mg)	51.898 ± 3.395	47.601 ± 2.921	47.435 ± 1.883
Thickness wall of body added SLS (mm)	0.121 ± 0.016	0.121 ± 0.017	0.127 ± 0.010
Thickness top wall of body added SLS (mm)	0.188 ± 0.012	0.135 ± 0.013	0.169 ± 0.022

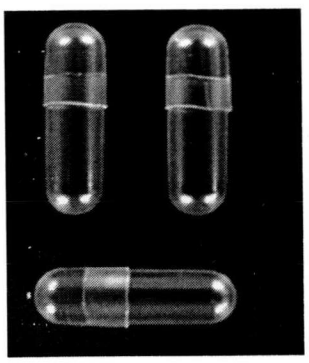
Table 4.16 Weight and thickness of 20% substituted with Elastigel 3000M® and glycerin 2% w/w with vary concentration SLS

Material	Glycerine 2%		
	No SLS	SLS 0.1%	SLS 1%
Weight of cap in added SLS (mg)	34.021 ± 1.069	33.191 ± 1.029	35.035 ± 1.046
Thickness wall of cap added SLS (mm)	0.143 ± 0.014	0.138 ± 0.013	0.143 ± 0.011
Thickness top wall of cap added SLS (mm)	0.165 ± 0.012	0.172 ± 0.017	0.192 ± 0.021
Weight of body added SLS (mg)	52.55 ± 1.842	50.162 ± 1.629	53.308 ± 1.556
Thickness wall of body added SLS (mm)	0.134 ± 0.012	0.126 ± 0.017	0.133 ± 0.007
Thickness top wall of body added SLS (mm)	0.170 ± 0.013	0.166 ± 0.017	0.192 ± 0.038

Final three formulations of hard capsule shells were selected for study as belows.

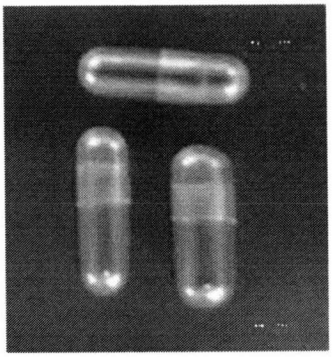
1. 35% substituted with Elastigel 2000C® and SLS 0.1%
2. 25% substituted with Eragel®, glycerin 1% w/w and SLS 0.1%
3. 20% substituted with Elastigel 3000M®and glycerin 2% w/w

The shape and size of capsules were similar to commercial gelatin capsule but the appearance showed the turbidity of capsules containing starches as compared to commercial gelatin capsules, which were clear (as shown in the figure 4.19).



35% substituted with Elastigel 2000C® and SLS 0.1%

25% substituted with Eragel®, glycerin 1% w/w and SLS 0.1%



20% substituted with Elastigel 3000M® and glycerin 2% w/w

Commercial gelatin capsule

Figure 4.19 Final three formulations of hard capsule shells compare with commercial gelatin capsule

7. Disintegration test

From previous section, Elastigel 2000C®+0.1% SLS, Eragel®+1% glycerin+0.1% SLS and Elastigel 3000M®+2% glycerin were selected for disintegration and dissolution studies and were compared with dipping gelatin capsules and gelatin capsules.

Usually, the disintegration test refers to filled capsules but some pharmacopoeias also include a test for empty capsules such as Japanese Pharmacopoeia. The limit of disintegration time in Japanese Pharmacopoeia was 10 minutes while TIS was 15 minutes.

The disintegration time for commercial gelatin capsules, gelatin dipping method, Elastigel 2000C®-gelatin capsules, Eragel®-gelatin capsules and Elastigel 3000M®-gelatin capsules were 3.13, 4.18, 4.65, 6.21 and 8.01 minutes, respectively.

Table 4.17 indicated that disintegration time for all of starch-gelatin capsules including prepared gelatin capsules were within 15 minutes which met TIS requirement.

Table 4.17 Disintegration time of gelatin and starch-gelatin formulations

Types of capsule	Time (min)±SD.
Commercial gelatin capsule	3.13 ± 0.48
Gelatin dipping method	4.18 ± 1.19
Elastigel 2000C-gelatin capsules	4.65 ± 1.51
Eragel-gelatin capsules	6.21 ± 1.46
Elastigel 3000M-gelatin	8.01 ± 1.37

8. Dissolution test

The amount of dicloxacillin dissolved at each sampling time was calculated using the calibration curve between the known concentrations of dicloxacillin and UV absorbance at the maximum wavelength of 274 nm. as referred in Appendix A. The dissolution of dicloxacillin filling in the commercial gelatin capsules, prepared gelatin capsules, and starch-gelatin capsules (Elastigel 2000C®-gelatin capsules, Eragel®-gelatin capsules and Elastigel 3000M®-gelatin capsules) were presented in table 4.18.

USP XXV for dicloxacillin capsules stated that none of six capsules should dissolve less than 75% labeled amount of dicloxacillin within 30 minutes. From figure 4.20, it was shown that all of different hard capsule shells containing dicloxacillin were in USP XXV standard with no significant difference in dissolution profile. Moreover, dicloxacillin in all types of capsules could dissolve completely within 10 minutes. This can be concluded that all of starch-gelatin capsules can be used as well as gelatin capsules.

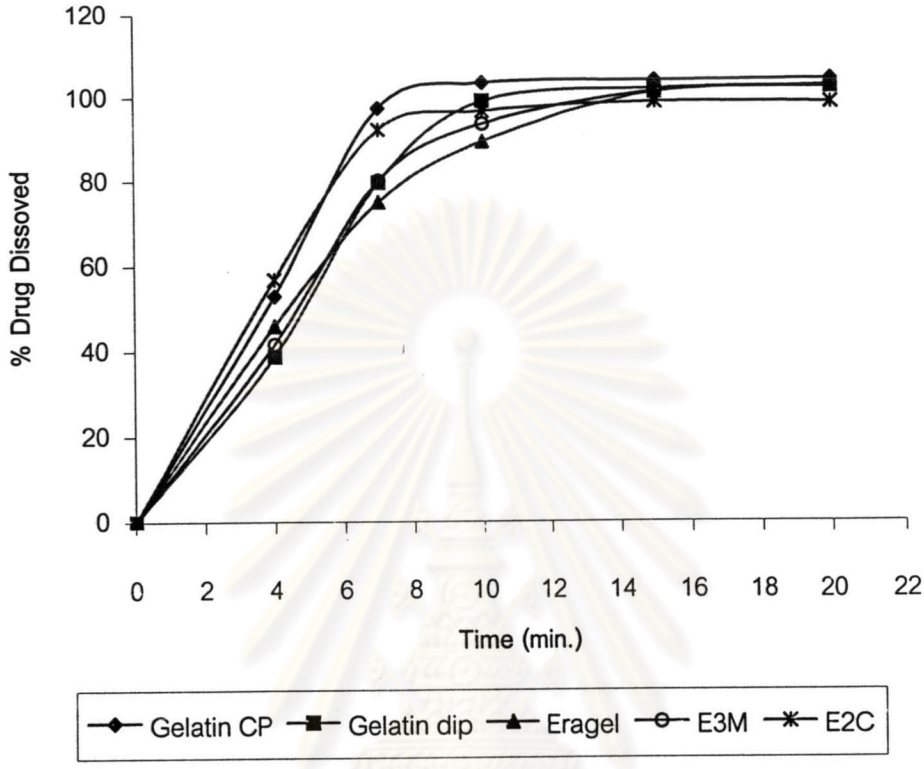


Figure 4.20 The mean dissolution profiles of five types hard capsule shells. Dicloxacillin 250 mg/capsule was used as a model drug. Values are mean of 6 units. Error bars were omitted for clarity

Note: Eragel = 25% substituted with Eragel®, glycerin 1% w/w and SLS 0.1%

E3M = 20% substituted with Elastigel 3000M ®and glycerin 2% w/w

E2C = 35% substituted with Elastigel 2000C® and SLS 0.1%

Table 4.18 Dissolution data of 250 mg dicloxacillin capsule of each type of hard capsule shell

Commercial gelatin capsule

Time (min)	T=4	T=7	T=10	T=15	T=20	T=30	T=45	T=60	T=90
	54.70	102.33	104.13	104.46	104.79	105.11	105.68	105.76	106.08
	52.48	102.07	103.87	104.20	104.28	105.09	105.41	105.74	106.30
	47.06	97.36	104.31	104.64	104.72	105.04	105.37	105.93	106.26
	52.73	90.74	102.33	104.13	104.45	105.76	106.58	107.40	107.24
	58.40	93.97	102.38	102.45	102.52	102.83	102.90	103.45	104.25
	52.24	97.88	103.11	103.18	103.75	104.31	104.39	104.95	105.76
Average	52.93	97.39	103.36	103.84	104.08	104.69	105.05	105.54	105.98
SD.	3.69	4.53	0.88	0.85	0.85	1.02	1.27	1.30	0.98
%CV.	6.98	4.65	0.85	0.82	0.82	0.97	1.21	1.23	0.94

Gelatin dipping

Time (min)	T=4	T=7	T=10	T=15	T=20	T=30	T=45	T=60	T=90
	37.49	76.77	98.77	101.95	102.41	102.82	103.31	105.05	106.01
	38.16	80.60	99.88	101.93	102.32	102.71	103.26	104.68	105.52
	35.79	76.30	93.65	102.50	102.47	102.81	103.00	104.32	105.01
	44.05	83.12	102.64	101.97	102.50	103.04	102.56	104.20	104.24
	38.80	77.99	100.29	101.87	102.21	103.02	102.69	104.25	103.83
	38.01	82.67	98.88	101.08	102.34	101.94	101.78	103.88	103.58
Average	38.72	79.57	99.02	101.88	102.38	102.72	102.77	104.40	104.70
SD.	2.80	2.98	2.98	0.46	0.11	0.40	0.57	0.41	0.97
%CV.	7.24	3.74	3.01	0.45	0.11	0.40	0.58	0.42	0.97

Table 4.18 Dissolution data of 250 mg dicloxacillin capsule of each type of hard capsule shell (cont.)

Elastigel 2000C® + 0.1% SLS

Time (min)	T=4	T=7	T=10	T=15	T=20	T=30	T=45	T=60	T=90
	54.38	91.93	97.07	98.49	97.09	98.03	97.21	97.76	97.74
	49.13	90.17	97.77	98.26	98.70	98.65	98.47	98.63	98.49
	59.16	93.53	96.17	99.17	98.87	98.67	98.19	98.30	98.56
	65.15	95.42	97.47	98.92	99.26	99.61	99.95	98.76	99.46
	56.38	94.85	98.43	98.75	98.65	98.08	98.39	97.96	98.16
	55.66	87.47	93.28	98.53	98.70	97.88	97.92	97.68	97.94
Average	56.64	92.23	96.70	98.69	98.55	98.49	98.36	98.18	98.39
SD.	5.32	3.02	1.84	0.33	0.75	0.64	0.90	0.45	0.61
%CV.	9.39	3.28	1.90	0.33	0.76	0.63	0.91	0.45	0.60

Eragel® + 1% glycerin + 0.1% SLS

Time (min)	T=4	T=7	T=10	T=15	T=20	T=30	T=45	T=60	T=90
	46.66	70.44	86.85	101.68	102.61	103.09	103.33	103.10	103.78
	53.17	79.08	85.16	100.84	102.45	102.96	102.91	102.60	102.86
	42.45	71.55	82.65	101.10	101.82	102.92	102.37	102.36	102.86
	48.41	69.37	89.47	100.98	102.35	102.39	103.12	103.14	102.73
	36.06	82.36	98.03	100.96	101.93	102.54	102.08	102.22	102.74
	47.95	76.83	93.90	101.17	102.22	101.49	101.28	101.48	101.56
Average	45.78	74.94	89.34	101.12	102.23	102.57	102.52	102.48	102.75
SD.	5.87	5.27	5.74	0.30	0.30	0.59	0.76	0.62	0.71
%CV.	12.83	7.03	6.42	0.29	0.30	0.62	0.79	0.64	0.73

Table 4.18 Dissolution data of 250 mg dicloxacillin capsule of each type of hard capsule shell (cont.)

Elastigel 3000M® + 2% glycerin

Time (min)	T=4	T=7	T=10	T=15	T=20	T=30	T=45	T=60	T=90
	40.82	95.70	100.03	101.66	103.38	102.66	103.66	105.50	106.14
	41.76	79.63	95.92	102.94	102.69	103.69	104.48	105.04	105.26
	38.82	73.97	93.34	102.50	104.05	103.17	104.10	104.09	105.17
	43.88	76.83	82.14	97.97	102.21	102.79	104.59	104.58	105.00
	45.26	82.26	98.10	102.24	102.19	104.96	103.12	103.67	104.28
	39.22	72.20	91.48	99.50	101.63	103.76	102.92	102.84	104.30
Average	41.63	80.10	93.50	101.14	102.69	103.51	103.81	104.29	105.03
SD.	2.55	8.47	6.37	1.96	0.89	0.84	0.70	0.96	0.69
%CV.	6.13	10.58	6.81	1.94	0.86	0.83	0.71	0.91	0.64

9. The stability of starch-gelatin capsule shells

In Thailand, the average temperature is about 30-40 °C with high humidity. Therefore, 30°C and 40°C at 75% RH were used to represent the storage condition for the tropical country. The low density polyethylene (LDPE) bag is commonly used for packing capsules in hard capsule industries. Thus, exposed capsules and inside the bag were used.

From previous section, three formulations were selected for stability study as belows

1. 35% substituted with Elastigel 2000C® and SLS 0.1%
2. 25% substituted with Eragel®, glycerin 1% w/w and SLS 0.1%
3. 20% substituted with Elastigel 3000M® and glycerin 2% w/w

After 3 months exposed to 30°C and 40°C, 75% RH with and without bags, it was found that weight and thickness could not be used for stability determination due to up and down values (table 4.21-4.26). However, it was observed that the moisture content in all formulations were increased after 1 and 3 months storage (table 4.27).

It was also found that disintegration time were increased after storage at 30°C and 40°C, 75%RH with and without bags. It was interesting that disintegration time was in the standard range (10-15 minutes) if capsules were stored at 30°C 75%RH inside the bag for 3 months. It can be recommend that starch capsules including gelatin should be kept below 30°C, 75%RH (table 4.20).

Moreover, Elastigel 2000C® and gelatin gave similar results, i.e. their disintegration times were still in the standard range even capsules were kept outside the bag at 30°C, 75%RH. This showed the resistance to temperature and humidity of these materials.

The cost of three formulations were calculated as shown in table 4.19

Table 4.19 Cost comparison between gelatin 100% and starch-gelatin capsules*

Material	100% gelatin		35% Elastigel 2000C®		25% Eragel®		20% Elastigel 3000M®	
	280 bahts/kg		110 bahts/kg		60 bahts/kg		105 bahts/kg	
	Quantity (kg)	Cost (baht)	Quantity (kg)	Cost (baht)	Quantity (kg)	Cost (baht)	Quantity (kg)	Cost (baht)
Starch	-	-	1,750	192,500	1,250	75,000	1,000	105,000
Gelatin	5,000	1,400,000	3,250	910,000	3,750	1,050,000	4,000	1,120,000
Total				1,102,500		1,125,000		1,225,000
Save cost				**297,500**		**275,000**		**175,000**

*Calculation upon 5,000 kg of gelatin batches production

After substituted with 35% Elastigel 2000C®, 25% Eragel® and 20% Elastigel 3000M®, it was shown that this study can reduce the production cost. Calculation upon 5,000 kg batches production, table 4.19 illustrated that the production cost for 35% Elastigel 2000C®, 25% Eragel® and 20% Elastigel 3000M® substitution can be reduced to be 297,500 bahts, 275,000 bahts and 175,000 bahts respectively.

Table 4.20 Disintegration time at 30°C, 75% RH and 40°C, 75% RH

Type****	T=0* (min) ± SD	30°C				40°C			
		No bag**		In bag***		No bag**		In bag***	
		T=1* (min) ± SD	T=2* (min) ± SD	T=1* (min) ± SD	T=2* (min) ± SD	T=1* (min) ± SD	T=2* (min) ± SD	T=1* (min) ± SD	T=2* (min) ± SD
Gelatin CP	3.13 ± 0.48	2.70 ± 0.55	2.93 ± 0.90	2.48 ± 0.53	3.76 ± 1.54	3.89 ± 1.24	5.66 ± 3.95	3.69 ± 0.63	4.43 ± 2.50
Gelatin dip	4.18 ± 1.19	5.88 ± 2.85	6.12 ± 1.35	3.59 ± 1.54	6.16 ± 0.71	6.38 ± 2.15	26.3 ± 4.99	8.59 ± 4.08	11.00 ± 4.75
Elastigel 2000C®	4.65 ± 1.51	5.73 ± 2.14	6.65 ± 0.97	4.45 ± 0.74	5.66 ± 1.53	8.97 ± 5.37	15.00 ± 9.22	5.71 ± 0.47	13.9 ± 7.65
Eragel®	6.21 ± 1.46	7.14 ± 2.91	10.3 ± 3.00	5.53 ± 1.46	6.69 ± 3.13	15.5 ± 8.84	25.70 ± 5.25	10.10 ± 2.87	11.4 ± 2.80
Elastigel 3000M®	8.01 ± 1.37	9.13 ± 2.40	9.60 ± 3.03	7.28 ± 1.03	8.90 ± 1.48	13.3 ± 5.16	30.60 ± 8.50	11.4 ± 3.71	9.98 ± 1.83

*T=0: initial time/ T=1: at the first month/ T=2: at the third month

** No bag = without bag (contact air)

***In bag = in low density polyethylene (LDPE) bag

****Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

Table 4.21 The cap weight of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mg)			In bag 30°C (mg)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	30.902 ± 1.192	31.607 ± 1.297	31.539 ± 1.264	30.598 ± 1.17	31.097 ± 1.103	31.609 ± 1.216
Gelatin dip	30.935 ± 1.317	31.945 ± 1.362	32.087 ± 1.348	31.601 ± 1.624	32.807 ± 1.691	32.65 ± 1.794
Elastigel 2000C®	24.247 ± 1.096	24.931 ± 1.137	24.907 ± 1.01	24.223 ± 0.667	25.324 ± 0.743	24.816 ± 0.695
Eragel®	32.205 ± 1.193	33.674 ± 1.332	33.323 ± 1.309	31.3 ± 1.305	32.617 ± 1.363	32.141 ± 1.336
Elastigel 3000M®	34.881 ± 1.713	36.095 ± 1.853	36.036 ± 1.864	34.532 ± 1.953	36.525 ± 2.133	35.982 ± 1.989
	No bag 40°C (mg)			In bag 40°C (mg)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	30.496 ± 0.626	32.16 ± 0.975	30.985 ± 0.615	30.227 ± 0.818	30.767 ± 0.821	30.962 ± 0.788
Gelatin dip	31.499 ± 1.704	32.49 ± 1.784	32.113 ± 1.775	30.078 ± 1.36	31.031 ± 1.28	30.645 ± 1.296
Elastigel 2000C®	24.209 ± 0.58	24.906 ± 0.61	25.06 ± 0.626	24.13 ± 0.811	24.739 ± 0.648	24.469 ± 0.793
Eragel®	32.703 ± 1.043	33.738 ± 1.098	33.077 ± 1.285	31.284 ± 1.248	32.221 ± 1.287	31.999 ± 1.344
Elastigel 3000M®	36.165 ± 2.059	37.169 ± 2.143	36.522 ± 2.122	35.419 ± 1.971	37.633 ± 2.125	36.012 ± 2.345

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

Table 4.22 The body weight of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mg)			In bag 30°C (mg)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	45.45 ± 1.219	46.523 ± 1.293	46.571 ± 1.214	45.186 ± 1.332	46.462 ± 1.518	46.48 ± 1.28
Gelatin dip	44.626 ± 1.81	45.995 ± 1.823	46.105 ± 1.805	44.28 ± 1.462	45.928 ± 1.544	45.405 ± 1.585
Elastigel 2000C®	39.293 ± 0.966	40.427 ± 0.981	40.381 ± 1.238	39.555 ± 0.91	41.099 ± 0.983	40.694 ± 1.025
Eragel®	48.427 ± 1.475	50.607 ± 1.565	50.21 ± 1.686	48.69 ± 1.482	50.905 ± 1.461	50.065 ± 1.691
Elastigel 3000M®	54.146 ± 1.25	56.292 ± 1.278	55.74 ± 2.119	55.3 ± 1.423	58.247 ± 1.546	57.96 ± 1.493
	No bag 40°C (mg)			In bag 40°C (mg)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	45.089 ± 1.417	46.902 ± 1.727	45.899 ± 1.343	45.057 ± 1.792	46.1 ± 1.846	46.22 ± 1.981
Gelatin dip	44.732 ± 1.585	46.239 ± 1.845	45.935 ± 1.843	43.827 ± 1.298	45.26 ± 1.373	44.65 ± 1.513
Elastigel 2000C®	38.777 ± 1.097	40.049 ± 1.11	40.103 ± 1.144	38.847 ± 1.309	40.098 ± 1.405	39.519 ± 1.371
Eragel®	48.394 ± 1.598	49.958 ± 1.685	49.388 ± 1.659	49.063 ± 1.095	50.576 ± 1.158	50.568 ± 1.17
Elastigel 3000M®	53.849 ± 1.585	55.543 ± 1.667	54.356 ± 1.776	55.531 ± 1.952	58.717 ± 1.921	56.584 ± 1.843

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

Table 4.23 The cap thickness wall of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mm)			In bag 30°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.122 ± 0.006	0.12 ± 0.008	0.122 ± 0.007	0.122 ± 0.006	0.121 ± 0.007	0.122 ± 0.006
Gelatin dip	0.128 ± 0.019	0.128 ± 0.017	0.13 ± 0.018	0.125 ± 0.017	0.128 ± 0.016	0.126 ± 0.016
Elastigel 2000C®	0.099 ± 0.008	0.101 ± 0.01	0.104 ± 0.009	0.1 ± 0.009	0.106 ± 0.011	0.107 ± 0.099
Eragel®	0.138 ± 0.01	0.138 ± 0.014	0.142 ± 0.012	0.135 ± 0.011	0.142 ± 0.012	0.14 ± 0.011
Elastigel 3000M®	0.152 ± 0.013	0.162 ± 0.015	0.162 ± 0.016	0.152 ± 0.011	0.158 ± 0.014	0.161 ± 0.013
	No bag 40°C (mm)			In bag 40°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.122 ± 0.006	0.132 ± 0.009	0.139 ± 0.008	0.122 ± 0.006	0.134 ± 0.009	0.132 ± 0.009
Gelatin dip	0.123 ± 0.018	0.135 ± 0.019	0.129 ± 0.02	0.121 ± 0.013	0.133 ± 0.021	0.131 ± 0.018
Elastigel 2000C®	0.103 ± 0.006	0.107 ± 0.007	0.101 ± 0.012	0.098 ± 0.006	0.104 ± 0.011	0.104 ± 0.008
Eragel®	0.140 ± 0.014	0.152 ± 0.015	0.148 ± 0.013	0.135 ± 0.010	0.144 ± 0.013	0.143 ± 0.014
Elastigel 3000M®	0.156 ± 0.014	0.176 ± 0.016	0.173 ± 0.017	0.154 ± 0.012	0.171 ± 0.013	0.172 ± 0.012

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

Table 4.24 The body thickness wall of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mm)			In bag 30°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.105 ± 0.004	0.108 ± 0.007	0.106 ± 0.004	0.105 ± 0.005	0.107 ± 0.005	0.106 ± 0.004
Gelatin dip	0.105 ± 0.012	0.106 ± 0.013	0.107 ± 0.012	0.105 ± 0.008	0.103 ± 0.016	0.107 ± 0.008
Elastigel 2000C®	0.093 ± 0.007	0.093 ± 0.006	0.096 ± 0.008	0.095 ± 0.007	0.098 ± 0.007	0.098 ± 0.007
Eragel®	0.119 ± 0.01	0.124 ± 0.012	0.12 ± 0.023	0.12 ± 0.013	0.118 ± 0.023	0.122 ± 0.012
Elastigel 3000M®	0.129 ± 0.01	0.138 ± 0.011	0.138 ± 0.01	0.137 ± 0.012	0.145 ± 0.013	0.145 ± 0.013
	No bag 40°C (mm)			In bag 40°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.105 ± 0.005	0.113 ± 0.005	0.118 ± 0.006	0.106 ± 0.005	0.118 ± 0.01	0.116 ± 0.008
Gelatin dip	0.106 ± 0.011	0.115 ± 0.012	0.119 ± 0.014	0.106 ± 0.012	0.11 ± 0.022	0.115 ± 0.012
Elastigel 2000C®	0.095 ± 0.006	0.1 ± 0.007	0.101 ± 0.005	0.093 ± 0.008	0.1 ± 0.009	0.1 ± 0.009
Eragel®	0.115 ± 0.009	0.126 ± 0.011	0.125 ± 0.008	0.118 ± 0.009	0.13 ± 0.014	0.13 ± 0.012
Elastigel 3000M®	0.128 ± 0.009	0.144 ± 0.011	0.143 ± 0.011	0.132 ± 0.01	0.146 ± 0.01	0.15 ± 0.012

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

Table 4.25 The cap thickness top wall of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mm)			In bag 30°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.131 ± 0.017	0.134 ± 0.018	0.133 ± 0.017	0.131 ± 0.013	0.134 ± 0.013	0.135 ± 0.013
Gelatin dip	0.114 ± 0.014	0.115 ± 0.015	0.117 ± 0.016	0.122 ± 0.014	0.124 ± 0.014	0.124 ± 0.015
Elastigel 2000C®	0.07 ± 0.007	0.071 ± 0.006	0.072 ± 0.006	0.068 ± 0.004	0.071 ± 0.005	0.068 ± 0.005
Eragel®	0.093 ± 0.014	0.094 ± 0.005	0.097 ± 0.006	0.095 ± 0.005	0.098 ± 0.005	0.101 ± 0.006
Elastigel 3000M®	0.105 ± 0.008	0.113 ± 0.009	0.113 ± 0.008	0.102 ± 0.007	0.108 ± 0.012	0.113 ± 0.016
	No bag 40°C (mm)			In bag 40°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.132 ± 0.01	0.146 ± 0.011	0.148 ± 0.012	0.124 ± 0.011	NA	NA
Gelatin dip	0.11 ± 0.022	0.132* ± 0.034	0.134* ± 0.028	0.117 ± 0.009	NA	NA
Elastigel 2000C®	0.068 ± 0.006	0.074 ± 0.008	0.074 ± 0.007	0.068 ± 0.004	NA	NA
Eragel®	0.095 ± 0.009	0.104 ± 0.008	0.102 ± 0.008	0.098 ± 0.008	0.104 ± 0.009	0.107 ± 0.011
Elastigel 3000M®	0.111 ± 0.008	0.124* ± 0.01	0.124* ± 0.01	0.104 ± 0.008	NA	NA

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

NA = Not available (capsule deformation)

Table 4.26 The body thickness top wall of hard capsule shell which storage at 30 and 40°C, 75% RH

material	No bag 30°C (mm)			In bag 30°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.128 ± 0.010	0.131 ± 0.011	0.131 ± 0.01	0.134 ± 0.008	0.138 ± 0.009	0.137 ± 0.009
Gelatin dip	0.110 ± 0.022	0.112 ± 0.025	0.123 ± 0.031	0.103 ± 0.012	0.105 ± 0.013	0.105 ± 0.012
Elastigel 2000C®	0.079 ± 0.009	0.083 ± 0.010	0.082 ± 0.011	0.078 ± 0.006	0.079 ± 0.006	0.08 ± 0.006
Eragel®	0.093 ± 0.014	0.094 ± 0.017	0.095 ± 0.018	0.096 ± 0.004	0.1 ± 0.006	0.100 ± 0.007
Elastigel 3000M®	0.109 ± 0.009	0.113 ± 0.009	0.116 ± 0.010	0.102 ± 0.012	0.109 ± 0.011	0.114 ± 0.014
	No bag 40°C (mm)			In bag 40°C (mm)		
	T=0	T=1	T=2	T=0	T=1	T=2
Gelatin CP	0.132 ± 0.009	0.144 ± 0.008	0.145 ± 0.009	0.126 ± 0.008	NA	NA
Gelatin dip	0.114 ± 0.016	0.123 ± 0.017	0.117 ± 0.016	0.101 ± 0.014	0.110 ± 0.014	NA
Elastigel 2000C®	0.076 ± 0.003	0.08 ± 0.005	0.081 ± 0.005	0.077 ± 0.005	NA	NA
Eragel®	0.094 ± 0.006	0.101 ± 0.007	0.101 ± 0.006	0.098 ± 0.006	0.106 ± 0.008	NA
Elastigel 3000M®	0.108 ± 0.009	0.12 ± 0.009	0.119 ± 0.009	0.109 ± 0.01	NA	NA

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month

NA = Not available (capsule deformation)

Table 4.27 The moisture content of hard capsule shell at 30 and 40°C, 75% RH

Moisture content (%)		no bag 30°C		in bag 30°C		no bag 40°C		in bag 40°C	
	T=0	T=1	T=2	T=1	T=2	T=1	T=2	T=1	T=2
Gelatin CP	13.24	14.67	15.05	14.96	15.55	13.93	15.26	14.24	16.19
Gelatin Dip	13.12	15.19	15.56	14.77	15.84	14.50	15.48	14.78	16.08
Elastigel 2000C®	12.19	14.40	14.50	14.23	14.60	13.77	14.16	13.83	14.91
Eragel®	11.51	14.28	14.94	13.91	14.95	14.70	15.29	13.88	16.05
Elastigel 3000M®	10.63	13.69	15.09	14.50	15.64	13.70	15.56	13.76	16.71

*No bag = no packaging (contact air condition), In bag = Packing in LDPE bag

**Gelatin CP=Commercial gelatin capsule, Gelatin dip=pure gelatin 33%, Elastigel 2000C®, Eragel®, and Elastigel 3000M® were formulation described in determination stability film and capsule in final formulation.

***T=0: initial time, T=1: at 1st month, T=2: at 3rd month