Emulsion Type New Vehicle for Soft Gelatin Capsule Available for Preclinical and Clinical Trials: Effects of PEG 6000 and PVP K30 on Physicochemical Stability of New Vehicle

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To prevent temperature-dependent gel–sol transformation of an o/w emulsion type new vehicle system for a soft gelatin capsule, which may be available for both preclinical and clinical trials, the basic new vehicle formulation (PEG 400 : purified water : medium chain triglyceride : polyoxyethylene (20) cetylether=77 : 10 : 10 : 3) was modified by partially (1, 2 or 3%) replacing PEG 400 with PEG 6000 or PVP K30.

When 2 or 3% of PEG 400 was replaced with PEG 6000, temperature-dependent gel–sol transformation was prevented at temperatures below 40 °C, and the vehicle appeared to be stable during 8 weeks of storage at 4 to 40 °C; the particle size distribution remained unchanged. When 1% of PEG 400 was replaced with PEG 6000, gel–sol transformation was not prevented, though phase separation was not observed at sol state, and the particle size distribution was shifted to be in a larger particle size range after 2 weeks of storage.

When PEG 400 was partially (1, 2 or 3%) replaced with PVP K30, temperature-dependent gel–sol transformation was not prevented and, after 2 weeks of storage at 40 °C, the particle size distributions of the vehicles were shifted to be in a larger particle size range and the vehicles were separated into two layers.

These results suggested that a small amount of PEG 6000 plays an important role in preventing temperature-dependent gel–sol transformation of our developed vehicle system.

Key words soft gelatin capsule; PEG 400; polyoxyethylene (20) cetylether; PEG 6000; PVP K30; gel–sol transformation

A soft gelatin capsule generally encapsulates such drug formulations as water soluble non-aqueous solution, oil solution, or suspension. It has been well known that a soft gelatin capsule can improve the bioavailability of a drug[2—5)] by accelerating disintegration, dispersion and dissolution in the gastrointestinal tract, and can also improve the stability of a drug due to poor permeability to oxygen.[6)] A soft gelatin capsule has an advantage that the encapsulated solution can also be used in preclinical studies, minimizing potential dosage form-related discrepancies between clinical trials in human and preclinical studies in laboratory animals and, thereby, bridging between preclinical studies and clinical trials.

For oil-solved or hydrophobic drugs, self-emulsifying drug delivery systems[7—9)] and microemulsions[10,11)] have recently been developed to overcome the problems of poor and/or erratic absorption due to poor miscibility or dissolution in the aqueous environment in the gastrointestinal tract. However, these newly developed formulations requires a high surfactant content (approximately 30 to 60% of formulation), and it may lead to some disadvantages, for example, damage to Kupffer cells[12,13)] and unexpectedly enhanced absorption of a drug of simultaneous use.

In our preceding studies,[14,15)] an o/w emulsion type new vehicle for a soft gelatin capsule was developed using a low content (3%) of a surfactant (polyoxyethylene (20) cetylether (BC-20TX®)), polyethyleneglycol 400 (PEG 400) and purified water for the hydrophilic phase, and medium chain triglyceride (Miglyol 810®) for the hydrophobic phase. This new vehicle has thixotropic properties at room temperature (about 25 °C) and temperature-dependent gel–sol transforming properties at about 37 °C, and can be adequately dispersed in water. This new vehicle was suggested to be relatively stable, potentially allowing utilization in preclinical studies during the period of 1 d to 12 d after preparation.[15)] However, although this new vehicle is expected to improve the poor miscibility of hydrophobic drugs in the gastrointestinal tract by fine dispersion in water, the temperature-dependent gel–sol transforming property might be disadvantageous for an accelerated stability test at temperatures above 40 °C. With regard to gel formation, it was reported that surplus surfactant and the outer PEG 400 phase bound cross linking (hydrogen bonding with polyoxyethylene units) and formed a gel state[16,17)] and, therefore, it was considered that the temperature-dependent gel–sol transforming property may be prevented by tightening the cross linking by increasing viscosity. As an approach to prevent temperature-dependent gel–sol transformation, the use of an additional surfactant (polyoxyl 60 hydrogenated caster oil) was proposed in the development of a vehicle for a hard gelatin capsule.[18)] However, this requires a high content of a surfactant.

Therefore, in this study, polyethyleneglycol 6000 (PEG 6000) and polyvinylpyrrolidone K30 (PVP K30), both hydrophilic but surface inactive materials, were tested for their abilities to prevent temperature-dependent gel–sol transformation by examining the physicochemical properties of this new vehicle system during an 8-week stability test at 4 °C, at room temperature and at 40 °C as a preliminary study for clinical trials. PEG 6000 was selected as a typical compound of a high molecular polyethyleneglycol series that may be able to tighten cross linking (hydrogen bonding with polyoxyethylene units)[16,17)] between the surplus surfactant and PEG 400. PVP K30 was selected as an additive compound generally used to increase the viscosity of inner solutions of commercial soft gelatin capsule products (such as cold remedies, antitusives and antipyretics). PVP K30 can reportedly

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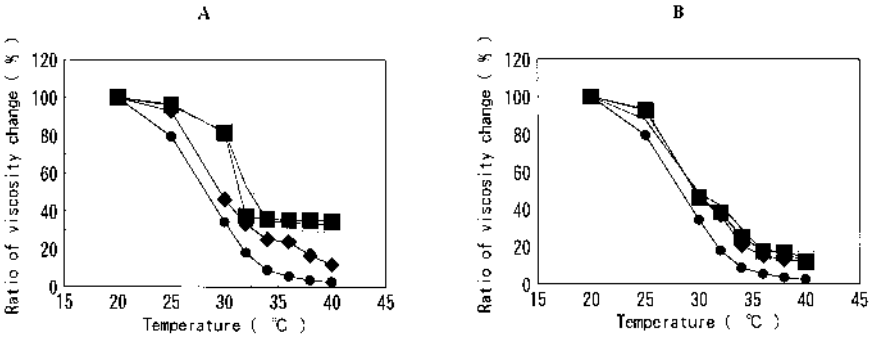

Fig. 1. Effect of the Partial Replacement of PEG 400 with PEG 6000 and PVP K30 on the Viscosity of the Newly Developed Vehicle

A: Effect of PEG 6000. Formula A (—◆—), formula B (—■—), formula C (—□—), basic formulation (—●—). B: Effect of PVP K30. Formula D (—◆—), formula E (—■—), formula F (—□—), basic formulation (—●—).

dissolve in PEG 400 at concentrations higher than 10% and increase the viscosity of PEG 400 solution.[19] The contents of PEG 6000 and PVP K30 varied from 1 to 3% against PEG 400, the contents of which are generally used to increase the viscosity of the inner solutions of soft gelatin capsules.

Experimental

Materials Polyethyleneglycol 400 (JP: PEG 400) and polyethyleneglycol 6000 (JP: PEG 6000) were purchased from NOF Corporation (Japan). Medium chain triglyceride (JPE: Miglyol 810®) was purchased from Hüls AG (Germany). Polyoxyethylene (20) cetylether (BC-20TX®) was purchased from Nikko Chemicals Co., Ltd. (Japan). Polyvinylpyrrolidone K30 (JP: PVP K30) was supplied from BASF Japan, Ltd. (Japan).

Methods Formulation: Six formulations, which are shown in Table 1, were investigated in terms of stability.

Preparation of Test Samples: A mechanical method using a high-pressure homogenizer[20,21] was selected as the preparation method in this study from several emulsion preparation methods,[20—25] because the mechanical force (caused by cavitation) may help prepare an emulsion more efficiently with less surfactant.

Materials were weighed in a stainless steel beaker, heated at about 60 °C in a water bath, mixed using a high-speed mixer (Cell-master® CM-100, SMT Co., Ltd., Japan, 15000 rpm, 10 min), and then homogenized using a high-pressure homogenizer (Microfluidizer® M-110, Mizuho Industrial Co., Ltd., Japan, 10000 psi and 5 treatments), as described in our preceding reports.[14,15]

Storage Conditions and Terms in Stability Study: Each test sample was poured into a 10 ml glass tube and, according to standard procedures for the evaluation of a new drug formulation, stored at 4 °C, at room temperature (25 °C) or at 40 °C for up to 8 weeks.

Evaluation of Physicochemical Properties of Test Samples: The physicochemical properties of the test samples were evaluated 1 d after preparation (Initial), when the particle size distribution was found to be temporarily stabilized in our preceding study,[15] and after 2, 4 and 8 weeks of storage by examining changes in the particle size distribution profile, parameters of the particle size distribution and appearance (phase separated or not).

The particle size distribution of the samples was measured using a laser diffraction particle size analyzer (SALD®-2000A, Shimadzu Corporation, Japan). Each sample was diluted about 3000 times with water for the measurement, since the measurement could not be made without this dilution.

The viscosity of a new vehicle was measured using a cone-and-plate viscometer (Visconic ED®, Standard cone: R=24 mm, ψ=1.34′, Tokimec Inc., Japan). Because the new vehicle had thixotropic property and the viscosity could not be evaluated by absolute viscosity, the viscosity was evaluated using the ratio of changes of the viscosity.

Results

Effects of PEG 6000 and PVP K30 on the Viscosity *versus* Temperature Profile of a New Vehicle System In our preceding studies,[14,15] we reported that our newly developed vehicle for a soft gelatin capsule has a thixotropic property at room temperature and temperature-dependent gel–sol transforming property at about 37 °C and that the gel state at lower temperatures was presumed to be maintained by cross linking (hydrogen bonding with polyoxyethylene units) of the surplus surfactant and the PEG 400 in the outer phase. A thixotropic property is advantageous for preclinical studies in laboratory animals, because the new vehicle supplied as a gel can be transformed to a sol by agitation for oral administration using gastric tubes. However, a temperature-dependent gel–sol transforming property might be disadvantageous for an accelerated stability test at temperatures above 40 °C, where the vehicle is in a sol state, because this type of vehicle would be less stable in the sol state than in the gel state. We therefore explored a method to prevent this by tightening the cross linking by increasing viscosity while maintaining the thixotropic property which is advantageous for preclinical application; we tested modified formulations prepared by partially replacing PEG 400 (1, 2 or 3%) of the basic formulation (PEG 400 : Water : Miglyol 810® : BC-20TX® = 77 : 10 : 10 : 3) with PEG 6000 or PVP K30.

As shown in Fig. 1-A, the ratio of the viscosity change in formulas B and C, which contain 2 and 3%, respectively, of PEG 6000, were constant at temperatures above 34 °C (up to 40 °C), and gel–sol transformation was not observed. However, the ratio of the viscosity change *versus* temperature profile of formula A, which contains 1% of PEG 6000 was similar to that of the basic formulation. Thus, it was found that more than 2% of PEG 6000 is required to reduce the temperature-dependent decrease in viscosity and successfully prevent gel–sol transformation.

In the case of PVP K30, there was no great difference in the ratio of the viscosity change versus temperature profile among all modified formulations (formulas D, E and F), and these profiles were similar to that of the basic formulation (Fig. 1-B). The viscosity decreased with an increase in temperatures from 20 to 40 °C, and gel–sol transformation was observed. Thus, it was found that PVP K30 cannot prevent the temperature-dependent decrease in viscosity and gel–sol transformation in this experimental condition.

Effect of PEG 6000 on the Stability of a New Vehicle In our preceding studies,[14,15] we found that the particle size distribution of the new vehicle ranged from 0.5 to 50 μm 1 d after preparation and did not change up to 12 d of storage at room temperature. It was considered that this new vehicle is relatively stable, potentially allowing utilization in preclinical studies during a period of 1 d to 12 d after preparation,[15] and

Table 1. Formulations of Test Samples (%)

	Formula A	Formula B	Formula C	Formula D	Formula E	Formula F
PEG 400	76.23	75.46	74.69	76.23	75.46	74.69
PEG 6000	0.77[a)]	1.54 [b)]	2.31[c)]	—	—	—
PVP K30	—	—	—	0.77[a)]	1.54 [b)]	2.31[c)]
Miglyol 810®	10.00	10.00	10.00	10.00	10.00	10.00
Purif. water	10.00	10.00	10.00	10.00	10.00	10.00
BC-20TX®	3.00	3.00	3.00	3.00	3.00	3.00

a) 1% of PEG 400 was replaced with the excipient, *b*) 2% of PEG 400 was replaced with the excipient, *c*) 3% of PEG 400 was replaced with the excipient.

Table 2. Gel–Sol Transformation of Test Formulations Containing PEG 6000

	Initial	2 weeks			4 weeks			8 weeks		
		4 °C	RT	40 °C	4 °C	RT	40 °C	4 °C	RT	40 °C
Formula A	GH	GH	GH	SH	GH	GH	SH	GH	GH	SH
Formula B	GH	GH	GH	GH	GH	GH	GH	GH	GH	GH
Formula C	GH	GH	GH	GH	GH	GH	GH	GH	GH	GH

RT: room temperature, GH: gel state and homogeneous, SH: sol state and homogeneous.

also in clinical trials. In this study, the stability of the new vehicles containing an excipient (PEG 6000 or PVP K30) was preliminarily examined for utilization in clinical trials in terms of appearance (phase separated or not) and particle size distribution up to 8 weeks after preparation at storage temperatures of 4 °C, room temperature and 40 °C.

As summarized in Table 2, the appearance of the test samples containing PEG 6000 (formulas A, B and C) was, except for formula A stored at 40 °C, unchanged up to 8 weeks, and the gel state was maintained. For formula A stored at 40 °C, the vehicle was transformed from a gel state to a semi-clear sol state after 2 weeks of storage, and thereafter maintained in the same state up to 8 weeks, though it did not separate into two layers, unlike formulations containing PVP K30 as described below.

The particle size distribution profiles of those formulations containing PEG 6000 (formulas A, B and C) initially ranged from 0.5 to 100 μm and, except for formula A stored at 40 °C (Fig. 2-A), remained unchanged during storage up to 8 weeks, as shown for formulas B (Fig. 2-B) and C (Fig. 2-C) stored at 40 °C. The particle size distribution profile of formula A stored at 40 °C shifted to a larger particle size range after 2 weeks and thereafter remained unchanged up to 8 weeks.

The particle size distribution change was evaluated using parameters calculated from the accumulated frequency profiles of the particle size distribution. The 10 (D (10)), 50 (D (50)) and 90 (D (90)) v/v% diameters represent the diameter for 10, 50 and 90 v/v% accumulated frequency, respectively, and the ratio represents the ratio of each value to the initial value. The particle size distribution parameters of formulas A, B and C are listed in Table 3 under the initial condition and for 8 weeks after preparation at storage temperatures of 4 °C, room temperature and 40 °C. As shown in Table 3, for formulas A, B and C, each diameter value was unchanged and its ratio to the initial value was close to unity for every diameter under all storage conditions, except for formula A stored at 40 °C. For formula A stored at 40 °C, each diameter value was larger than that of the initial value by a factor of about 3, as represented by the ratio values. It appeared that particles coagulated in formula A during storage at 40 °C.

Thus, it was shown that PEG 6000 can improve the stability of new vehicles, in terms of appearance and particle size distribution, consistent with the result that it could reduce a temperature-dependent decrease in viscosity and prevent gel–sol transformation.

Effect of PVP K30 on the Stability of a New Vehicle As summarized in Table 4, the appearance of all test samples containing PVP K30 was unchanged, with the gel state maintained up to 8 weeks after preparation at the storage temperatures of 4 °C and room temperature. However, with the storage temperature of 40 °C, all the test samples became clear sol, separating into two layers after 2 weeks of storage, and thereafter remained separated up to 8 weeks.

The particle size distribution profiles for the above three modified formulations (formulas D, E and F) were initially similar to that of the basic formulation, and unchanged up to 8 weeks after preparation at the storage temperatures of 4 °C and room temperature (profiles not shown). However, for the storage temperature of 40 °C, the particle size distribution profile shifted to a larger particle size range and was broader after 2 weeks and remained constant up to 8 weeks storage at 40 °C, as shown for formula D (Fig. 2-D).

The particle size distribution parameters are listed in Table 5 for the initial condition and for 8 weeks after preparation at the storage temperatures of 4 °C, room temperature and 40 °C. At storage temperatures of 4 °C and room temperature, each diameter value for 8 weeks was comparable with the initial value and, accordingly, its ratio to the initial value was close to unity for these diameters. However, for storage at 40 °C, each diameter value for 8 weeks was larger than that of the initial value, and the ratio values were larger than those for storage at 4 °C and room temperature.

Thus it was shown that PVP K30 cannot improve the stability of the new vehicle, in terms of appearance and particle size distribution, consistent with the result that it could not

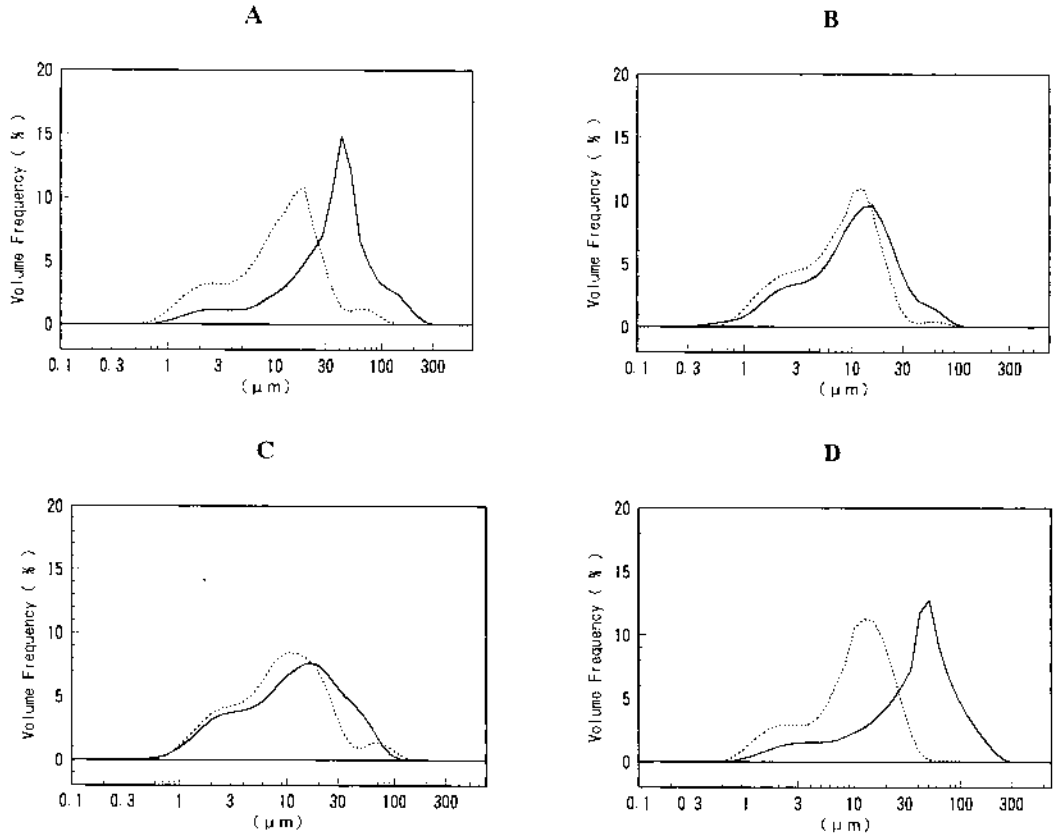

Fig. 2. Change in the Volume Frequency Profile of the Particle Size Distribution of Formulas A, B, C and D after 8 Weeks of Storage at 40 °C
Initial (------), after 8 weeks (——). A: Formula A, B: formula B, C: formula C, D: formula D.

Table 3. Particle Size Distribution Parameters of Test Formulations Containing PEG 6000 after 8 Weeks Storage at 4 °C, Room Temperature and 40 °C (n=3)

		Initial diameter±S.D. (μm)	Diameter±S.D. after 8 weeks (μm)		
			4 °C (ratio)	RT (ratio)	40 °C (ratio)
Formula A	D (10)	1.96±0.07	2.06±0.18 (1.05)	2.31±0.54 (1.18)	6.56± 2.13 (3.35)
	D (50)	10.68±0.56	11.31±1.28 (1.06)	12.37±4.38 (1.16)	33.78± 2.23 (3.16)
	D (90)	27.82±4.72	30.28±1.30 (1.09)	33.85±7.80 (1.22)	86.03±21.33 (3.09)
Formula B	D (10)	1.67±0.04	1.72±0.06 (1.03)	1.75±0.04 (1.05)	2.03± 0.11 (1.22)
	D (50)	7.51±0.74	8.11± 0.65 (1.08)	8.27±0.11 (1.10)	9.92± 0.90 (1.32)
	D (90)	17.55±1.62	17.39±0.59 (0.99)	17.86±0.80 (1.02)	27.26± 1.54 (1.55)
Formula C	D (10)	1.88±0.02	2.56 ±0.04 (1.37)	2.62±0.06 (1.40)	2.03± 0.11 (1.08)
	D (50)	8.35±0.09	14.17±0.08 (1.70)	13.95±0.30 (1.67)	11.02± 0.66 (1.32)
	D (90)	25.31±1.89	33.14±2.02 (1.31)	33.10±1.14 (1.31)	37.70± 1.10 (1.49)

D (10), D (50) and D (90) represent the diameter for 10, 50 and 90 v/v% accumulated frequency, respectively. The ratios represent the ratios of the value for each storage condition to the initial value. RT means room temperature.

Table 4. Gel–Sol Transformation of Test Formulations Containing PVP K30

	Initial	2 weeks			4 weeks			8 weeks		
		4 °C	RT	40 °C	4 °C	RT	40 °C	4 °C	RT	40 °C
Formula D	GH	GH	GH	SS	GH	GH	SS	GH	GH	SS
Formula E	GH	GH	GH	SS	GH	GH	SS	GH	GH	SS
Formula F	GH	GH	GH	SS	GH	GH	SS	GH	GH	SS

RT : room temperature, GH : gel state and homogeneous, SS : sol state and separated.

Table 5. Particle Size Distribution Parameters of Test Formulations Containing PVP K30 after 8 Weeks Storage at 4 °C, Room Temperature and 40 °C ($n=3$)

		Initial diameter±S.D. (μm)	Diameter±S.D. after 8 weeks (μm)		
			4 °C (ratio)	RT (ratio)	40 °C (ratio)
Formula D	D (10)	1.94±0.04	2.32±0.28 (1.19)	1.83±0.21 (0.94)	4.69± 0.36 (2.42)
	D (50)	9.83±0.15	13.06±2.16 (1.33)	10.26±2.34 (1.04)	38.30± 5.19 (3.89)
	D (90)	21.91±0.47	35.25±8.21 (1.61)	27.94±5.76 (1.28)	89.23±27.25 (4.07)
Formula E	D (10)	1.56±0.04	1.82±0.02 (1.16)	1.77±0.15 (1.13)	6.68± 1.53 (4.27)
	D (50)	8.05±2.09	10.63±0.06 (1.32)	10.17±2.18 (1.26)	52.20± 2.65 (6.48)
	D (90)	20.24±1.04	23.82±1.44 (1.18)	25.11±1.76 (1.24)	145.95± 0.74 (7.21)
Formula F	D (10)	1.78±0.05	1.80±0.12 (1.01)	1.99±0.07 (1.12)	6.94± 0.91 (3.90)
	D (50)	7.46±0.27	7.75±1.48 (1.04)	10.84±1.36 (1.45)	54.03± 4.01 (7.24)
	D (90)	19.21±1.32	20.17±1.89 (1.05)	24.93±1.10 (1.30)	151.75± 9.98 (7.90)

D (10), D (50) and D (90) represent the diameter for 10, 50 and 90 v/v% accumulated frequency, respectively. The ratios represent the ratios of the value for each storage condition to the initial value. RT means room temperature.

prevent temperature-dependent decrease in viscosity and gel–sol transformation.

Discussion

To prevent temperature-dependent gel–sol transformation, the use of an additional surfactant (polyoxyl 60 hydrogenated castor oil) was proposed for the development of a vehicle for a hard gelatin capsule.[18] However, this would lead to an increased surfactant content that may cause adverse effects, *e.g.*, damage to Kupffer cells.[12,13] Therefore, we explored an alternative method to prevent temperature-dependent gel–sol transformation, using PEG 6000 or PVP K30 instead of surfactants. These compounds are often used in an inner solution of soft gelatin capsules as viscosity increasing agents, but are not surface active.

The partial (2 or 3%) replacement of PEG 400 with PEG 6000 (formulas B and C) was suggested to be effective in preventing the temperature-dependent gel–sol transformation of our newly developed vehicle system at about 37 °C. It was considered that the improved stability of the new vehicle system was presumably brought about by tightened cross linking (hydrogen bonding with polyoxyethylene units)[16,17] between the surplus surfactant and the outer PEG 400 phase or, in other words, by an increased melting point of the outer PEG phase (mixture of PEG 400 and PEG 6000). This seems to have resulted in increased viscosity, which was constant at temperatures above 34 °C (Fig. 1-A). Because the kinematic viscosity value (700–900 cSt at 99 °C) of PEG 6000 solution was much higher than that (7.3 cSt at 99 °C) of PEG 400 solution,[26] it was considered that replacing only a small fraction of PEG 400 with PEG 6000 could extensively increase the viscosity of the new vehicle. Because both PEG 400 and PEG 6000 consist of the same polyethylene unit and are highly miscible, it seems that PEG 6000 is quite useful as an excipient to partially replace PEG 400 and increase the viscosity of the new vehicle. However, PVP K30 could not improve the stability of the new vehicle at the storage temperature of 40 °C (Table 5), presumably because PVP K30 could not tighten the cross linking, as suggested by the result that the viscosity decreased with an increase in temperature from 20 to 40 °C (Fig. 1-B) and temperature-dependent gel–sol transformation was not prevented. Although we did not examine whether PVP K30 could stabilize the vehicle at replacement contents higher than 3%, it is obvious that PEG 6000 works more efficiently than PVP K30 at low contents of 2 or 3%.

In conclusion, it was found that PEG 6000 is an excipient that is capable of preventing the coagulation of particles in the new vehicle system by increasing its viscosity at 40 °C, but PVP K30 is not. It was considered that formulations in which more than 2% of PEG 400 is replaced with PEG 6000 have sufficient stability as dosage forms for preclinical studies and also clinical trials, and are pharmaceutically viable as a soft gelatin capsule. Our study is currently focused more on characterization of the vehicle than on the elucidation of a stabilization mechanism, though the latter would also be a good subject for future investigation. We are now conducting stability experiments with a hydrophobic drug in the improved new vehicle for a soft gelatin capsule.

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