Development of Emulsion Type New Vehicle for Soft Gelatin Capsule. I. Selection of Surfactants for Development of New Vehicle and Its Physicochemical Properties

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Screening of surfactants was carried out to develop an oil in water (o/w) emulsion type new vehicle for a soft gelatin capsule (SGC), using polyethyleneglycol 400 (PEG 400) as hydrophilic phase and medium chain triglyceride (Miglyol 810®), propyleneglycol dicaprylate (Sefsol 228®) or soybean oil as hydrophobic phase (PEG 400: hydrophobic phase: surfactant = 87 : 10 : 3) and by means of simple homogenization.

Polyoxyethylene (20) cetylether (BC-20TX®), which can form homogeneous and viscous white gels using the above hydrophilic and hydrophobic phase combination, was selected as a model surfactant for developing the new vehicle. Using Miglyol 810® as hydrophobic phase, a model new vehicle formulation (PEG 400 : water : Miglyol 810® : BC-20TX® = 77 : 10 : 10 : 3) was prepared, and its physicochemical properties were evaluated.

The particle size distribution of the new vehicle, after diluting about 3000 times with water, ranged from about 0.5 to 50 μm. Furthermore, the new vehicle had thixotropic property at room temperature (about 25 °C) and temperature-dependent gel–sol transforming property with the transformation temperature of about 37 °C.

These properties meet the requirement for encapsulation of the new vehicle in SGC and suggest that it can be expected to form the o/w emulsion state in the aqueous environment in the stomach. The rheological properties would also make it advantageous for use in other dosage forms such as suppository, cataplasm or liniment.

Key words soft gelatin capsule; o/w emulsion; surfactant; polyoxyethylene (20) cetylether

Soft gelatin capsule (SGC) is an oral dosage form which generally encapsulates such a drug as water soluble non-aqueous solution, oil solution, or suspension. This dosage form can improve bioavailability of a drug by accelerating disintegration, dispersion and dissolution in the gastrointestinal tract. However, the administration of a drug in oil solution or a hydrophobic drug in SGC dosage form may be less advantageous because of the poor miscibility of the oil with the aqueous environment of the gastrointestinal tract. This poor miscibility would lead to variable absorption of a drug in the small intestine, for example, as a consequence of highly variable gastric emptying.

To improve the performance of SGCs containing a hydrophobic drug, self-emulsifying drug delivery systems[2–4)] and microemulsions[5,6)] have been proposed. In these systems, high content of a surfactant (approximately 30 to 60 w/w% of formulation) is required to form and maintain an emulsion state in the gastrointestinal tract. A large quantity of a surfactant, however, may irritate the gastrointestinal tract and, if absorbed, may damage Kupffer cells.[7,8)] It may also lead to unexpectedly high and variable absorption of a drug used simultaneously. To avoid these potential problems, the content of a surfactant should be reduced. We, therefore, tried to develop a new vehicle of a fine dispersed emulsion type for SGC, using minimal surfactant content.

Generally, water, glycerol,[9)] ethylene glycol[10)] and some other substances[11,12)] are used as the hydrophilic phase of o/w emulsion. However, these hydrophilic solvents cannot be encapsulated by themselves because they migrate into the shell of SGC. In this study, we selected PEG 400 as hydrophilic phase that can be encapsulated in SGC, and a medium chain triglyceride as hydrophobic phase. Nineteen surfactants, which are allowed as oral pharmaceutical excipients, were screened and physicochemical properties of the newly developed model vehicle were evaluated.

Experimental

Materials Polyethyleneglycol 400 (JP: Macrogol 400 or PEG 400) was purchased from NOF Corporation (Japan). Medium chain triglyceride (JPE: Miglyol 810®) was purchased from Hüls AG (Germany). Propyleneglycol dicaprylate (Sefsol 228®) was purchased from Nikko Chemicals Co., Ltd. (Japan). Soybean oil was purchased from Ajinomoto Co., Inc. (Japan).

Nineteen surfactants used in this work are shown in Table 1. They were supplied by each supplier as samples.

Methods Screening of Surfactants: The primary screening of surfactants was carried out using PEG 400 as hydrophilic phase and Miglyol 810® as hydrophobic phase, both of which are frequently used as filling solvents for SGC. The secondary screening was carried out by evaluating the suitability of selected surfactants with two types of oil (Sefsol 228® and soybean oil).

Three components (87 g of PEG 400, 10 g of an oil and 3 g of a surfactant) were weighed in a disposable polypropylene beaker and then homogenized with Polytron® homogenizer (PCU-11, Kinematica AG, Switzerland, Graduation 6—2 min) at room temperature. Formula of blank sample consisted of 90 g of PEG 400 and 10 g of an oil.

Part (50 ml) of each sample was transferred to a Nessler tube and left standing at room temperature. After 24 h, the sample was examined for phase separation and, if separated, the volume of the separated phase was measured.

Preparation of a New Vehicle for Evaluation of Physicochemical Properties: Among several emulsion preparation methods,[13–17)] the mechanical method using a high-pressure homogenizer[13,14)] was selected as that for development of a new vehicle.

Experientially, it is known that water in the shell migrates to the inner solution when PEG 400 is encapsulated as the only hydrophilic solvent for SGC. This water amounts to about 10% of the inner volume in the final product. Therefore, 10% of water was included in advance in the new vehicle to evaluate the physicochemical properties.

Four components (77 w/w% of PEG 400, 10 w/w% of purified water,

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Table 1. Surfactants for Screening

Surfactant			Supplier	Lot No.
Product	Chemical name	HLB		
HCO-40	POE(40) hydrogenated castor oil	12.5	Nikko Chemicals Co., Ltd.	4772
HCO-50	POE(50) hydrogenated castor oil	13.5	Nikko Chemicals Co., Ltd.	4566
HCO-60	POE(60) hydrogenated castor oil	14.0	Nikko Chemicals Co., Ltd.	4317
Tween65	POE(20) sorbitan tristearate	10.5	Kao Chemicals Co., Ltd.	3135
Tween60	POE(20) sorbitan monostearate	14.9	Kao Chemicals Co., Ltd.	1011
Tween80	POE(20) sorbitan monooleate	15.0	Nikko Chemicals Co., Ltd.	5273
Tween40	POE(20) sorbitan monopalmitate	15.6	Kao Chemicals Co., Ltd.	3129
MYS-25	POE(25) monostearate	15.0	Nikko Chemicals Co., Ltd.	4478
MYS-40	POE(40) monostearate	17.5	Nikko Chemicals Co., Ltd.	4789
GO-460	POE(60) sorbit tetraoleate	14.0	Nikko Chemicals Co., Ltd.	4244
BC-10TX	POE(10) cetyl ether	13.5	Nikko Chemicals Co., Ltd.	4463
BC-20TX	POE(20) cetyl ether	17.0	Nikko Chemicals Co., Ltd.	4485
BL-2	POE(2) lauryl ether	9.5	Nikko Chemicals Co., Ltd.	3084
BL-4.2	POE(4.2) lauryl ether	11.5	Nikko Chemicals Co., Ltd.	4267
BL-9EX	POE(9) lauryl ether	14.5	Nikko Chemicals Co., Ltd.	4379
BL-21	POE(21) lauryl ether	19.0	Nikko Chemicals Co., Ltd.	4131
BL-25	POE(25) lauryl ether	19.5	Nikko Chemicals Co., Ltd.	3264
Nonion LP20R	Sorbitan monolaurate	8.6	NOF Corporation	30907B
Nonion LP60R	Sorbitan monostearate	4.7	NOF Corporation	40225B

POE = polyoxyethylene. HLB = hydrophile lipophile balance.

10 w/w% of Miglyol 810® and 3 w/w% of BC-20TX®) were weighed in a stainless steel beaker, heated to about 60 °C in a water bath, and then mixed using a high-speed mixer (Cell-master® CM-100, SMT Co., Ltd., Japan, 15000 rpm–10 min) followed by homogenization using a high-pressure homogenizer (Mini-Lab® 8.30H, Rannie, Denmark, 10000 psi–5 treatments).

Evaluation of Particle Size Distribution of the New Vehicle: The particle size distribution of the new vehicle was measured using a laser diffraction particle size analyzer (SALD®-2000A, Shimadzu Corporation, Japan) after diluting about 3000 times with water; the measurement could not be made without this dilution.

Evaluation of Viscosity of the New Vehicle: The viscosity of the new vehicle was measured using a cone-and-plate viscometer (Visconic ED®, Standard cone: R = 24 mm, $\psi = 1.34'$, Tokimec Inc., Japan).

Evaluation of Thermogram of the New Vehicle: The thermogram of the new vehicle was measured using a differential scanning calorimeter (DSC-50®, Shimadzu Corporation, Japan).

Results

Screening of Surfactant The primary screening of surfactants was carried out using PEG 400 as hydrophilic phase and Miglyol 810® as hydrophobic phase, both broadly/commonly used as filling solvents for SGC. In general, this content of emulsion ranges from about 0.5 to 5.0 w/w% for the system[9-17]; for example, this content for parenteral nutrition is 1.2%.[13,14] Therefore, the surfactant content was set at 3.0 w/w% in this study, the component ratio of PEG 400, Miglyol 810® and surfactant was 87 : 10 : 3. The selection was made by examining whether the sample is homogeneous or not under this experimental condition. The results are summarized in Table 2 and typical photographs of emulsions using Miglyol 810® are shown in Fig. 1. Only three surfactants of polyoxyethylene (20) cetylether (BC-20TX®), polyethylene glycol (40 Ethylene oxide) monostearate (MYS-40®) and polyethylene glycol (60) sorbit tetraoleate (GO-460®) gave homogeneous and viscous white gels like the one shown in Fig. 1(A).

The stability of emulsion is known to be dependent on the combination of oil and surfactant.[13] A secondary screening was carried out by evaluating the suitability of these selected surfactants with other oils. Two types of oil were tested, Sefsol 228® and soybean oil. These are also widely used as filling solvents for SGC. Preparation and evaluation of samples were carried out by the same method as the primary screening described above. BC-20TX® and MYS-40® gave homogeneous and viscous white gels like the one shown in Fig. 1 (A) for both oils. GO-460® also gave a homogeneous and viscous white gel for Sefsol 228®, however, phase separation like type D in Fig. 1 was observed when soybean oil was used as hydrophobic phase. Thus, it was suggested that BC-20TX® and MYS-40® could be used with a greater variety of oils than GO-460® and would be better for developing the new vehicle preparation. In this work, BC-20TX® was selected as a model surfactant for the development of a new vehicle and further experiments were carried out.

Preparation of a New Vehicle and Evaluation of Physicochemical Properties Based on the results of the preceding screening study, a model formulation for a new vehicle development was decided. In this stage, purified water was used as one of the hydrophilic phase components to avoid the migration effect of shell water of SGC in the encapsulation process. The model formulation consisted of 77 w/w% of PEG 400, 10 w/w% of Miglyol 810®, 10 w/w% of purified water and 3 w/w% of BC-20TX®. This new vehicle in the form of homogeneous and viscous white gel was found to be satisfactorily stable, and was subjected to evaluation of its physicochemical properties.

To confirm that the new vehicle is in the emulsion state, particle size distribution was determined using a laser diffraction particle size analyzer. The new vehicle was finely dispersed in water, and the particle size ranged between

Table 2. Results of Screening for Surfactants

Product	Volume of separated phase (ml)			Judgment	Type in Fig. 1	Remarks
	Upper layer	Middle layer	Bottom layer			
Blank	5.0			×	E	Separated
HCO-40	5.0			×	E	Separated
HCO-50	5.0			×	E	Separated
HCO-60	7.0			×	C	Oil phase was whitely turbid.
Tween65	3.0			△	D	PEG phase was gelled.
Tween60	3.0			△	B	PEG phase was whitely turbid.
Tween80	1.0			△	B	PEG phase was whitely turbid.
Tween40	3.0			△	D	PEG phase was gelled.
MYS-25	19.0			△	C	Oil phase was gelled.
MYS-40	0.0			○	A	Viscous white gel
GO-460	0.0			○	A	Viscous white gel
BC-10TX	5.0			×	D	Middle layer was gelled.
BC-20TX	0.0			○	A	Viscous white gel
BL-2	5.0			×	E	Separated
BL-4.2	5.0			×	E	Separated
BL-9EX	5.0			×	E	Separated
BL-21	4.0	34.0		△	D	Middle layer was gelled.
BL-25	3.0	28.0		△	D	Middle layer was gelled.
Nonion LP20R	4.5			×	E	Separated
Nonion LP60R	8.0			×	C	Oil phase was gelled.

The formulation of test samples consisted of PEG 400 (87 w/w%), Miglyol 810 (10 w/w%) and a surfactant (3 w/w%). A part (50 ml) of each sample was transferred to a Nessler tube and left standing at room temperature. After 24 h, the sample was examined for phase separation and, if separated, the separated phase volume was measured. In judgment column, ○, △ and × represent the excellent, good and poor, respectively, with regard to emulsion state. In type in Fig. 1 column, A, B, C, D and E refer to the indications in Fig. 1.

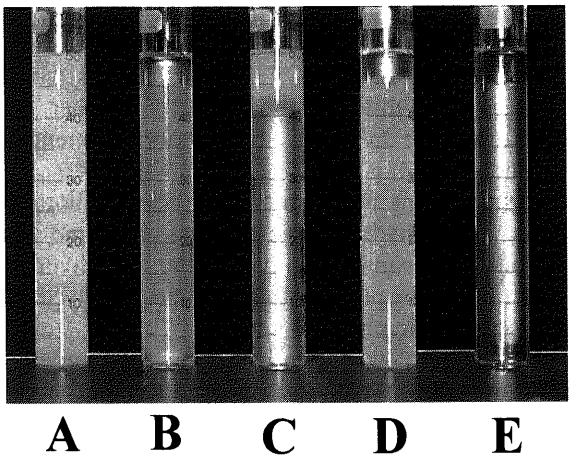

Fig. 1. Typical Photographs of Emulsions in Screening for Surfactants

PEG 400 was used as water phase and Miglyol 810® as hydrophobic phase. The surfactant was varied as follows: type A, BC-20TX®, homogeneous and viscous white gel; type B, Tween-80®, PEG 400 phase was white and turbid; type C, HCO-60®, hydrophobic phase was white and turbid; type D, BL-21®, PEG 400 phase was gelled; type E, blank, separated.

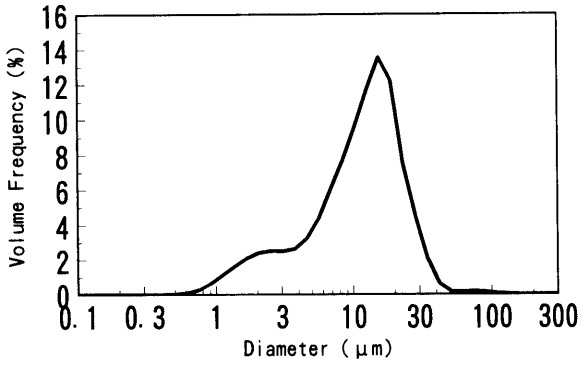

Fig. 2. Particle Size Distribution of the New Vehicle Dispersed in Water

The particle size distribution of the new vehicle was measured after diluting about 3000 times with water. The formulation of the new vehicle consisted of PEG 400 (77 w/w%), Miglyol 810® (10 w/w%), purified water (10 w/w%) and BC-20TX® (3 w/w%).

about 0.5 and 50 μm (Fig. 2), suggesting that this new vehicle can be expected to form o/w emulsion in the aqueous environment in the stomach.

The new vehicle maintained a gel state at room temperature (about 25 °C). The viscosity was measured using a cone-and-plate viscometer. The viscosity decreased with an increase in the rotative velocity of a cone at 20 °C and 25 °C (Fig. 3), and reverted to its former state when the sample was left standing for a while, suggesting that the new vehicle has thixotropic property at temperatures below 25 °C. The viscosity also decreased with temperature and

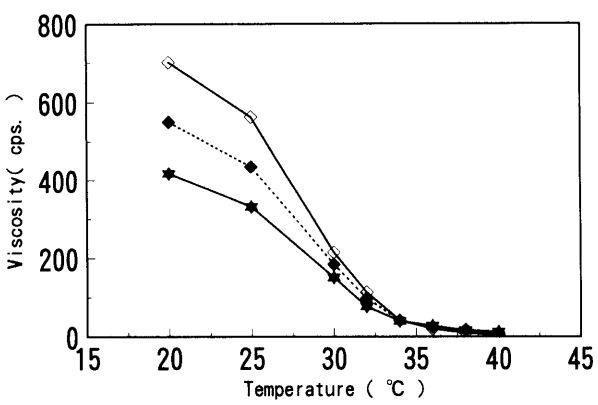

Fig. 3. Viscosity of the New Vehicle

10 rpm (—◇—), 20 rpm (---◆---), 50 rpm (—✱—).

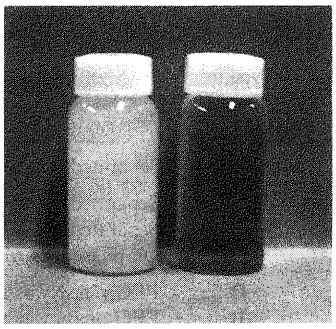

Fig. 4. Photographs of the New Vehicle Showing Gel–Sol Transformation

A, gel state (20 °C); B, sol state (40 °C).

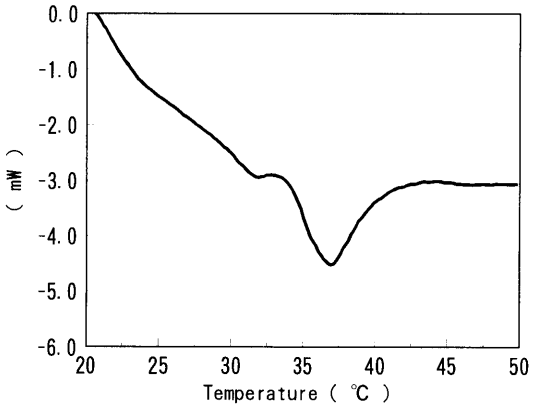

Fig. 5. DSC Thermogram of the New Vehicle

was independent of rotative velocity at temperatures above 30 °C. The new vehicle also maintained a state of clear solution at 40 °C as shown in Fig. 4, suggesting that it has a gel–sol transformation property between 30 and 40 °C. According to DSC (differential scanning calorimeter) thermogram (Fig. 5), the gel–sol transformation temperature was about 37 °C, which is close to body temperature. Thus, it was demonstrated that this new vehicle has temperature-dependent thixotropic and gel–sol transformation properties. The observed viscosity range suggested to us that this vehicle can be encapsulated into SGC.

Discussion

The purpose of this study was to select surfactants to form a new o/w emulsion type vehicle for SGC using PEG 400 as hydrophilic phase. The surfactant content in this study was set at 3 w/w% (an approximate median value from the contents commonly used for o/w emulsions)[9-17] to avoid potential adverse effects[7,8]; these which might be caused by high surfactant content (approximately 30 to 60 w/w% of formulation) of existing dosage forms,[2-6] as described in the previous section. It is further known that various factors (characteristics or amounts of hydrophilic phase, surfactant and hydrophobic phase, and method of preparation) influence emulsification.[9-17] Therefore, to carry out a surfactant screening study, the test formulation was fixed at 87 w/w% of PEG 400 as hydrophilic phase, 10 w/w% of oil and 3 w/w% of surfactant.

Three surfactants were found to form homogeneous and viscous white gels for three types of oil (for BC-20TX® and MYS-40®: Miglyol 810®, Sefsol 228® and soybean oil) or two types of oil (for GO-460®: Miglyol 810® and Sefsol 228®). Thus, it seemed feasible to form emulsion states using less than 3 w/w% of these surfactants with PEG 400 and some oil. Surplus surfactant and the outer PEG 400 phase reportedly bound cross linking (hydrogen bonding with polyoxyethylene units) and formed a gel state.[18,19] In the combination of GO-460®, PEG 400 and soybean oil, the emulsion state was not formed, however. This difference in the results between GO-460® and others when soybean oil was used may be explained by the difference in hydrophile lipophile balance (HLB) values. BC-20TX® and MYS-40® have larger HLB values (about 17) than GO-460® (about 14). Since the required HLB value was determined by compatibility between hydrophilic phase and hydrophobic phase, the most suitable HLB value was believed to be about 17 in the system using PEG 400 as outer hydrophilic phase with various oils. We therefore selected three types of surfactants which can potentially form emulsion state, and from among them chose BC-20TX® as a model surfactant for further study, because it was the one most generally used as a pharmaceutical excipient among these.

Evaluation of the physicochemical properties demonstrated that this new vehicle had some interesting rheological properties. It had thixotropic property at room temperature (about 25 °C) and temperature-dependent gel–sol transforming property with the transformation temperature of about 37 °C. These properties would be advantageous in utilizing the vehicle for other dosage vehicle forms, for example, suppository, liniment, cataplasm and others.

In addition, this new vehicle can contain both a hydrophilic and a hydrophobic drug at the same time; a hydrophilic drug can be dissolved in the outer hydrophilic phase and a hydrophobic drug can be dissolved in the inner hydrophobic phase.

In conclusion, it was found that 1) a low content (3% for system) of BC-20TX® could form a homogeneous and viscous white gel with PEG 400, purified water and Miglyol 810®, 2) the new vehicle was finely dispersed in water although the formulation was prepared with very low surfactant content, and 3) it had thixotropic property at room temperature (about 25 °C) and temperature-dependent gel–sol transforming property with the transformation temperature of about 37 °C.

In this study, no detailed evaluation of component ratio of developed formulation or selection of a candidate model drug for this system were carried out. These experiments will be done in future.

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