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Improvement of physicochemical properties of N-4472 part I formulation design by using self-microemulsifying system

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Abstract

The optimization of oral dosage form formulation has been developed for N-4472, *N*-[2-(3,5-di-tert-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-*N'*-[4-(*N*-benzylpiperidyl)] urea, which was a poorly water-soluble drug having a lipid-lowering effect. Formulations that contained various surfactants and water-soluble polymers were prepared and the solubility of N-4472 was evaluated in JP XIV first fluid (pH 1.2), JP XIV second fluid (pH 6.8), and distilled water. The highest solubility of N-4472 was achieved when L-ascorbic acid (VC), Gelucire® 44/14, and HCO-60® were used as additives. It was confirmed that this formulation could create microemulsion droplets with a mean droplet size of approximately 20 nm and a sharp droplet distribution pattern in JP XIV first fluid, JP XIV second fluid, and distilled water. When JP XIV second fluid was used as a dissolution medium, however, an eventual decrease of solubility was observed, that is, the fluid became white and cloudy as time passed. It was found that the addition of sodium dodecyl sulfate (SDS) was effective to prevent the lowering of solubility, and that a weight ratio of 1.0/1.5/11.4/4.9/3.8 for N-4472/VC/Gelucire® 44/14/HCO-60®/SDS was optimum for the self-microemulsifying formulation. It was assumed that electrostatic repulsion of microemulsion droplets and an increase of the cloud point by the addition of SDS were responsible for the successful formation of a stable microemulsion.

Keywords: Optimized formulation; Microemulsions; Self-emulsifying systems; Solubility enhancement; N-4472

1. Introduction

Recently, studies on oral dosage forms using a self-microemulsifying system have been performed for the purpose of improving the solubility and absorption of poorly water-soluble drugs (Constantinides and Scalart, 1997; Matuszewska et al., 1996; Hauss et al., 1998; Khoo et al., 1998, 2000; Kommura et al., 2001). Commercially available drugs that use this self-microemulsifying system include cyclosporin A as well as preparations of ritonavir and saquinavir (HIV protease inhibitors), and the usefulness of this system has also been demonstrated clinically (Cooney et al., 1998; Porter and Charman, 2001).

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Self-microemulsifying formulations consist of a mixture of drugs, oils, and surfactants, and the gentle mixing of these ingredients in aqueous media can generate microemulsion droplets (with a mean droplet size ≤ 100 nm) of drugs that have been solubilized (Constantinides, 1995; Pouton, 1997). It is considered that this self-microemulsifying system may improve absorption of drugs by rapid self-microemulsification in the stomach, with the microemulsion droplets subsequently dispersing in the gastrointestinal tract to reach sites of absorption (Shah et al., 1994).

However, microemulsions are not always stable, and at higher temperatures than the cloud point of microemulsion consisting non-ionic surfactants irreversible phase separation can occur due to the dehydration of polyethylene oxide moiety in non-ionic surfactants, which results in cloudiness of the preparation (Chen et al., 2000). Since an improvement of absorption cannot be expected if such phase separation occurs in the gastrointestinal tract, the cloud point of the microemulsion should be over 37 °C. The cloud point is also affected by the amount and hydrophobicity of any drugs in the microemulsion as well as the kind, combination, mixing ratio, and amount of each of the oils and surfactants that are used (Chen et al., 2000; Warisnoicharoen et al., 2000). Therefore, when designing a self-microemulsifying drug formulation, it is essential to find the optimal combination of carriers that will create stable microemulsion droplets having a cloud point over 37 °C.

N-[2-(3,5-di-*tert*-butyl-4-hydroxyphenethyl)-4,6-difluorophenyl]-*N*′-[4-(*N*-benzyl-piperidyl)] urea (N-4472, Fig. 1) is a newly developed drug with lipid-lowering activity. This drug shows poor oral absorption, because, it has a low aqueous solubility (less than 0.2 μg/ml in JP XIV second fluid and distilled water). As reported previously, when N-4472 was evaporated specifically with VC at a molar ratio of 1/5 (N-4472/VC), marked improvement of the N-4472 solubility (>20 mg/ml) in distilled water was observed. This result was explained by means of the formation of surface-active complex between N-4472 and VC, resulting in micelle formation. However, the solubility of N-4472/VC evaporate (1/5) was observed to decrease in JP XIV second fluid (N-4472 solubility: ≤ 0.2 μg/ml), because, the complex was dissociated due to the change in then ionic state (Itoh et al., 2001). In this study, we developed an optimized formulation using a self-microemulsifying system in order to improve the solubility of N-4472 in JP XIV second fluid.

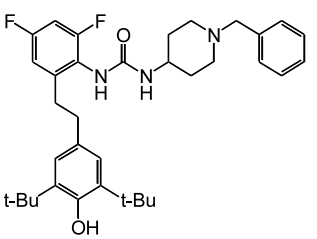
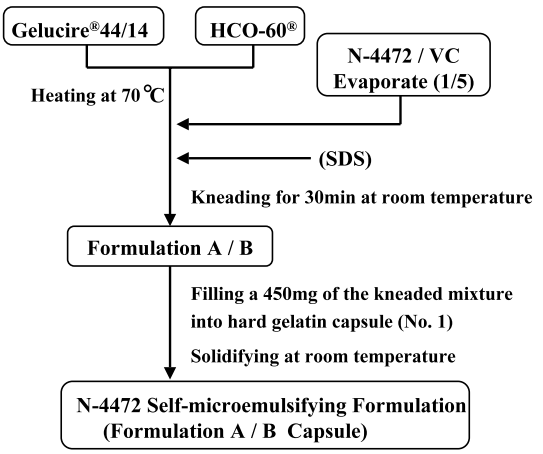


Fig. 1. Chemical structure of N-4472.

2. Materials and methods

2.1. Materials

N-4472 was synthesized by Nisshin Seifun Group Inc. (Japan). Gelucire® 44/14 (mixture of 30% glycerolester and 70% PEG-ester with fatty acids) and Labrasol® were obtained from Gattefosse Co. (France). Polysorbate 80 (Tween 80, NOF Co., Japan), polyoxyethylene (60) hydrogenated castor oil (HCO-60®, Nikko Chemicals Co. Ltd., Japan), polyoxyl (40) stearate (MYS-40®, Nikko Chemicals Co. Ltd., Japan), hydroxypropylmethylcellulose (HPMC, TC-5EW, Shin-Etsu Chemical Co., Ltd., Japan), methylcellulose (MC, SM-4, Shin-Etsu Chemical Co., Ltd., Japan), hydroxypropylcellulose (HPC, SSL, Nippon Soda Co., Ltd., Japan), povidone (PVP, K-30, BASF Japan Ltd., Japan), gelatin (Gelatin U, Nitta Gelatin Inc., Japan), and guar gum (PF-20, Dainippon Pharmaceutical Co., Ltd., Japan) were used as received. L-Ascorbic acid (VC), dodecyltrimethylammonium bromide (DTMA-Br) and sodium dodecyl sulfate (SDS) were of reagent grade and purchased from Wako Pure Chemical Industries, Ltd. (Japan). All other chemicals and solvents used were of analytical reagent grade.



Scheme 1. Preparation method of N-4472 self-microemulsifying formulations.

2.1.1. Preparation of N-4472/VC evaporate (molar ratio: 1/5)

The 4.0 g of N-4472 and 6.0 g of VC were dissolved in 300 ml of ethanol. The solution was evaporated at 60 °C in a vacuum. The solid mass obtained was further dried in a vacuum drier at 70 °C for 2 h and then pulverized.

2.1.2. Preparation of N-4472 self-microemulsifying formulations

Formulation A was prepared by kneading a mixture of Gelucire® 44/14 (8.4 g) and HCO-60® (3.6 g) with a 1.5 g of N-4472/VC evaporate (1/5) by using a vibrational rod mill (TI-200, CMT CO., Ltd., Japan). To prepare Formulation B, Gelucire® 44/14 (6.825 g), HCO-60® (2.925 g) and SDS (2.25 g) were used as carrier and prepared by same method as described above. The 450.0 mg of kneaded mixture (Formulation A or B) was filled into hard gelatin capsule, and then solidified at room temperature. (Scheme 1 and Table 1)

2.2. Solubility determination

Each specimen containing 0.1 mg of N-4472 was dispersed into 5 ml of the JP XIV second fluid in which various carriers were dissolved. The dispersions in test tubes were shaken for 5 or 60 min at 150 strokes per min in a water bath thermostatted at 37 °C. The dispersions were filtered through a membrane filter (0.45 μm, GL Sciences Inc., Japan) and the filtered solutions were appropriately diluted with the HPLC mobile phase solution. The concentrations of N-4472 in the solution were measured by HPLC.

2.3. Dissolution studies

Dissolution studies were performed according to the JP XIV paddle method. The JP XIV first fluid, JP XIV second fluid and distilled water were used as dissolution media. A specimen containing 20 mg of N-4472 was introduced into 900 ml of a dissolution medium thermostatted at 37, 50 or 60 °C. The revolution speed of the paddle was adjusted to 100 rpm. The 5 ml of solution was pipetted out at definite intervals, and filtered through a membrane filter (0.45 μm, GL Sciences Inc., Japan). The filtered solutions were appropriately diluted with the HPLC mobile phase solution. The concentrations of N-4472 in the solution were measured by HPLC.

2.4. HPLC analysis

HPLC analysis was carried out using LC-6A and SPD-6A (Shimadzu Co, Japan). The mobile phase (acetonitrile/distilled water/phosphoric acid (100:100:1, V/V/V)) was delivered at a flow rate of 1.0 ml/min through a L-Column® ODS (4.6 mm I.D. × 15 cm: CERI, Japan) at 40 °C. The detection wavelength was 274 nm.

Table 1
N-4472 self-microemulsifying formulations

Formulation	mg per capsule	
	A	B
N-4472/VC evaporate[a]	50	50
Gelucire® 44/14	280	227.5
HCO-60®	120	97.5
SDS	–	75
Total (mg)	450	450

[a] VC, L-ascorbic acid, N-4472/VC (molar ratio: 1/5).

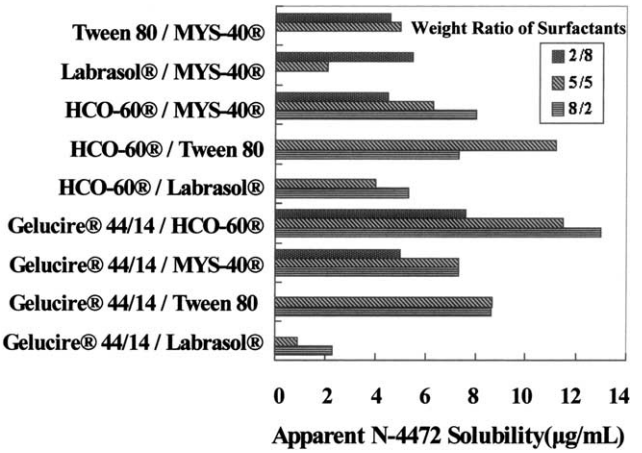


Fig. 2. Apparent solubility of N-4472 in JP XIV second fluid (pH 6.8) containing binary non-ionic surfactants at 37 °C.

2.5. Measurement of particle size distribution

A volumetric particle size distribution for each microemulsion was determined on a Microtrac® UPA (UPA150, Nikkiso Co., Ltd., Japan) by dynamic light scattering operating with heterodyne detection. The UPA system possesses a detection range from 3.2 to 6540 nm.

2.6. Zeta potential measurement

A zeta potential for each microemulsion was determined using a ZetaPALS® (Nikkiso Co., Ltd., Japan). Each sample was analyzed in triplicate.

3. Results and discussion

3.1. Improvement of the solubility of N-4472

As described in the introduction section, the N-4472/VC evaporate (1/5) provided improved aqueous solubility of N-4472 due to micelle formation. However, the micelle was not physicochemically stable enough in JP XIV second fluid, resulting in decrease of N-4472 solubility (≤ 0.2 μg/ml). In order to stabilize the micellar solution of N-4472 to optimize the formulation, we estimated effects of surfactants addition. As a screening of surfactants for self-microemulsifying system, several kinds of surfactants (i.e. Gelucire® 44/14, HCO-60®, Labrasol®, Tween 80, MYS-40®) were added (0.05 W/V%) into JP XIV second fluid and the change in the solubility of N-4472 was evaluated. Although an addition of each surfactant improved the N-4472 solubility in JP XIV second fluid (3.3–11.0 μg/ml), the effect of one-surfactant system seemed not sufficient enough to be applied for oral administration. With the expectation of further improvement of the solubility of N-4472 in JP XIV second fluid, two kinds of surfactants were combined and the effect on stabilizing the micellar system was also investigated. Fig. 2 shows the solubility of N-4472 when surfactants were added at various ratios (weight ratio of two surfactants: 8/2, 5/5, and 2/8). With a combination of Gelucire® 44/14 and HCO-60®, N-4472 showed the highest solubility in JP XIV second fluid, and it was found that N-4472 could be solubilized in the microemulsion in the neutral pH condition. Fig. 3 shows the changes in the solubility of N-4472 when the ratio of Gelucire® 44/14 to HCO-60® was altered incrementally. The ratio at which N-4472 showed the highest solubility in JP XIV second fluid was Gelucire® 44/14: HCO-60® = 7:3.

As described in Scheme 1, Formulation A capsules were prepared by filling the kneaded mixtures of which formulation was shown in Table 1. Fig. 4 shows the dissolution profile of N-4472 from Formulation A capsules in JP XIV second

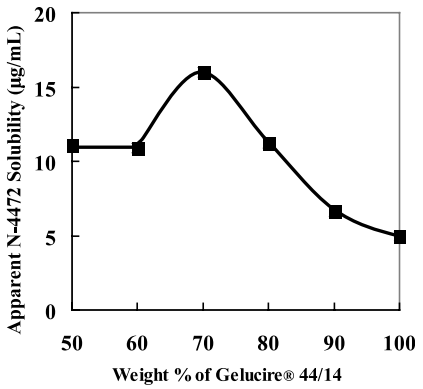


Fig. 3. Variation of apparent N-4472 solubility in JP XIV second fluid (pH 6.8) at 37 °C as a function of Gelucire® 44/14 and HCO-60® mixing ratio.

fluid. The complete dissolution of N-4472 was observed at 10 min, and the test fluid became clear. However, at 20 min, the test fluid became white and cloudy and the N-4472 concentration started to decrease. Moreover, the concentration of N-4472 decreased further and reached a level below the detection limit (0.2 μg/ml) at 40 min. Fig. 5 shows the particle size distribution patterns of the test fluids at 10 and 40 min after the start of the dissolution test. Ten minutes after the start of the test, microemulsion droplets with a mean size of approximately 20 nm were observed. After 40 min, no microemulsion droplets were observed, but the formation of large particles were observed with a mean size of about 2 μm and a wide distribution in the range of 0.2–6.5 μm. As a

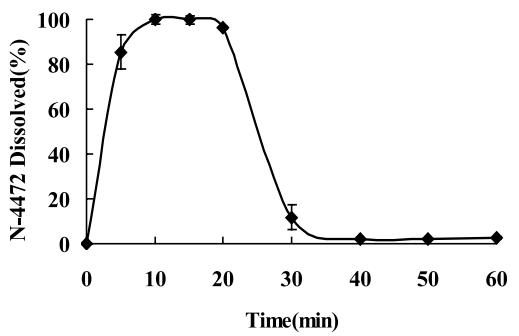


Fig. 4. Dissolution profile of N-4472 from Formulation A capsule in JP XIV second fluid (pH 6.8) at 37 °C (Mean ± S.D., $n = 3$).

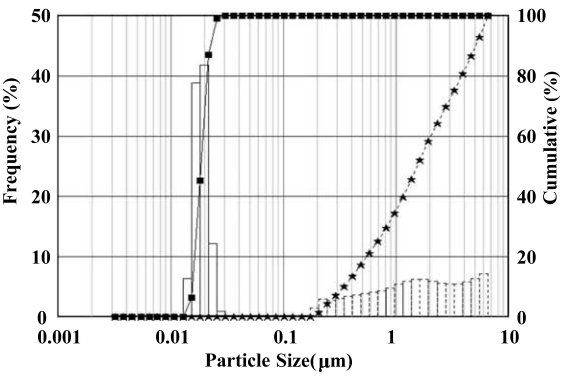


Fig. 5. Change in the particle size distributions after dispersing Formulation A capsule in JP XIV second fluid (pH 6.8) key: frequency: —; after 10 min, ·····; after 40 min; cumulative: ■; after 10 min, ★; after 40 min.

result of powder X-ray diffraction analysis for the formed large particles (data not shown), it was recognized that the fall of the N-4472 concentration observed in Fig. 4 was attributable to the precipitation of N-4472 that had previously been soluble.

3.2. Formation of a stable microemulsion

We made further investigations whether additional excipients to Formulation A could prevent phase separation of the microemulsion in JP XIV second fluid. In expectation of hydrophobic interaction with N-4472 that had been solubilized in microemulsion droplets and electrostatic repulsion between the droplets, six kinds of water-soluble polymers and two kinds of ionic surfactants were chosen as potent candidate excipients for stabilizing microemulsion (Scherlund et al., 1998; Kita et al., 1999; Schulz and Daniels, 2000). Screening of excipients was performed by the evaluation of solubility of N-4472 after Formulation A was added to the fluid that was prepared by dissolving each candidate excipient (0.1%) in JP XIV second fluid and shaking for 60 min. The dissolved fraction ($C_{60\ \mathrm{min}}/C_{\mathrm{total}}$) of N-4472 was calculated after shaking for 60 min, where $C_{60\ \mathrm{min}}$ and C_{total} mean the concentration of N-4472 at 60 min and the concentration of N-4472 completely dissolved, respectively.

Fig. 6 shows the values of $C_{60\ min}/C_{total}$ for each excipient in JP XIV second fluid. The water-soluble polymers that achieved a $C_{60\ min}/C_{total}$ value of over 0.5 were HPMC and MC, which contain hydrophobic methoxyl group at a level of approximately 30%. On the other hand, a $C_{60\ min}/C_{total}$ value of HPC, which does not contain methoxyl group, was only 0.05, suggesting that the hydrophobic part of water-soluble cellulose polymers might suppress a decrease in the concentration of N-4472 and contribute to stabilization of the microemulsion. In addition, cationic DTMA-Br showed a $C_{60\ min}/C_{total}$ value of 0.0, while anionic SDS showed a value of 0.98 even though both are ionic surfactants possessing dodecyl moiety.

Based on the above findings, it was recognized that SDS was the most effective excipient to stabilize the microemulsion, and that a stable microemulsion would be formed in JP XIV second fluid after addition of SDS to Gelucire® 44/14 and HCO-60® as carriers in the self-microemulsifying formulation of N-4472.

3.3. Optimization of the N-4472 self-microemulsifying formulation

In order to determine the optimal amount of SDS for the N-4472 self-microemulsifying formulation, 2.5 mg of Formulation A was added to 5 ml of JP XIV second fluid which contained varied amount of SDS. Then, the mixture was shaken for 60 min at 37 °C. Fig. 7 shows the relationship

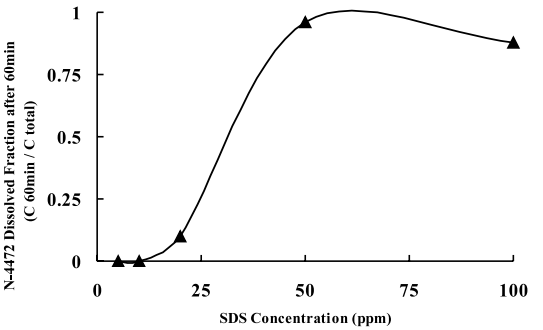


Fig. 7. Effect of SDS concentration on the formation of stable N-4472 microemulsion in JP XIV second fluid (pH 6.8) at 37 °C.

between the $C_{60\ min}/C_{total}$ values and SDS concentration. It was found that the microemulsion was stabilized at an SDS concentration of more than 50 ppm.

These results suggested that more than 45 mg of SDS should be added to the N-4472 self-microemulsifying Formulation A in order to stabilize the microemulsion in subsequent dissolution tests using 900 ml of JP XIV second fluid. Therefore, to ensure that the microemulsion was stabilized, we determined that 75 mg of SDS should be added to the N-4472 self-microemulsifying formulation as shown in Table 1.

Formulation B capsules were prepared using Gelucire® 44/14, HCO-60® and SDS as carriers according to the method described in Scheme 1. Fig. 8 shows the dissolution profiles of N-4472

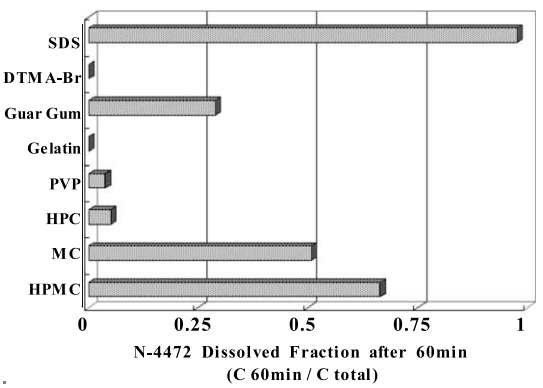


Fig. 6. Effect of excipient on the stability of N-4472 microemulsion in JP XIV second fluid (pH 6.8) at 37 °C.

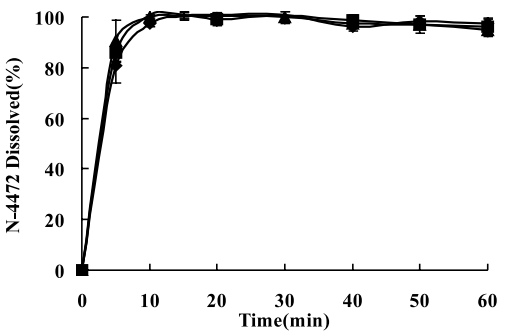


Fig. 8. Dissolution profiles of N-4472 from Formulation B capsule in JP XIV first fluid (pH 1.2), JP XIV second fluid (pH 6.8) and distilled water at 37 °C (Mean ± S.D., $n = 3$) key: ◆; JP XIV first fluid, ■; JP XIV second fluid, ▲; distilled water.

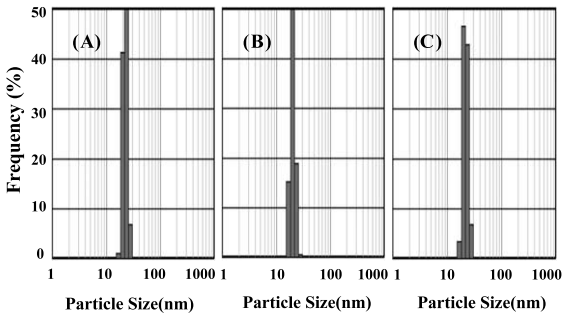


Fig. 9. Particle size distributions of the microemulsions generated from Formulation B in (A): JP XIV first fluid (pH 1.2), (B): JP XIV second fluid (pH 6.8) and (C): distilled water.

from Formulation B capsules in JP XIV first fluid (pH 1.2), JP XIV second fluid (pH 6.8), and distilled water at 37 °C. Since N-4472 was immediately and completely dissolved in every test fluid without any decrease of the concentration thereafter, Formulation B was recognized to be the optimum N-4472 self-microemulsifying formulation.

Fig. 9 shows the results of measurement of the particle size distribution in transparent fluids after N-4472 had completely dissolved from Formulation B capsules.

It was found that a stable microemulsion having a sharp distribution and a mean droplet size of approximately 20 nm was generated in all of JP XIV first fluid, JP XIV second fluid, and distilled water. Formulation B was considered to generate fine emulsified droplets containing N-4472 and to solubilize the drug by microemulsification in each test fluid.

3.4. Factors contributing to formation of a stable microemulsion

From the comparison of the dissolution behavior of N-4472 in JP XIV second fluid at 37 °C (Figs. 4 and 8), factors related to success in obtaining the stable microemulsion after SDS addition were investigated. Generally, a decrease of electrostatic repulsive forces between microemulsion droplets or an increase of the temperature above the cloud point will cause phase separation of a microemulsion. The zeta potentials of microemulsion droplets were determined. When Formulation A or B were added to JP XIV second fluid, the zeta potential values were found as 0.31 ± 0.09 and -6.91 ± 1.96 mV, respectively, indicating that the electrostatic repulsive force of the latter was greater than the former.

In order to evaluate the cloud point of the microemulsion obtained with Formulation B, the changes of the N-4472 concentration were monitored at different temperature. Fig. 10 shows the dissolution profiles of N-4472 from Formulation B capsules when the temperature of JP XIV second fluid was maintained at 37, 50, and 60 °C. Compared with the dissolution pattern at 37 °C, a slight decrease of solubility was observed at 50 °C. At 60 °C, there was a marked fall of the N-4472 concentration due to phase separation of the microemulsion, similarly to the dissolution behavior of Formulation A at 37 °C as shown Fig. 4.

Based on the above findings, the factors contributing to successful formation of a stable microemulsion in JP XIV second fluid by Formulation B were assumed to be as follows, (1) coalescence of microemulsion droplets was prevented due to an increase of electrostatic repulsion among the droplets since the surface charge was negative, because of adsorption of SDS. (2) As the hydrophilicity of the surfactant mixture obtained by addition of SDS to Gelucire® 44/14 and HCO-60® increased, the cloud point of the microemulsion was raised to 50–60 °C, and

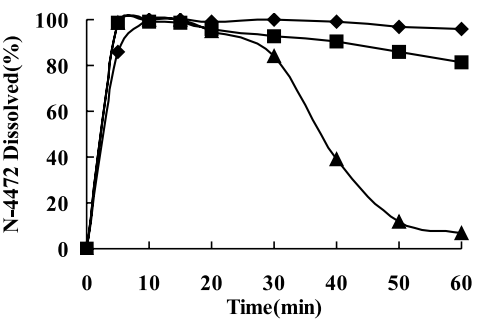


Fig. 10. Effect of temperature on the decrease in N-4472 concentration after dispersing Formulation B capsule in JP XIV second fluid (pH 6.8) key: ◆; 37 °C, ■; 50 °C, ▲; 60 °C.

therefore, a stable microemulsion was formed at 37 °C.

In conclusion, we found that Formulation B consisting of N-4472, VC, Gelucire® 44/14, HCO-60®, and SDS was the optimum self-microemulsifying formulation of N-4472, a poorly water-soluble drug. This formulation showed rapid self-microemulsification in various aqueous media, and formed stable microemulsion droplets with a mean droplet size of about 20 nm. Regarding stabilization of the microemulsion droplets, the addition of anionic surfactant, SDS, played an important role.

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