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# Combination of Pluronic/Vitamin E TPGS as a potential inhibitor of drug precipitation

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**Abstract**

In this study, we screened surfactants and their combinations at low concentrations as potentially potent inhibitors of drug precipitation in an aqueous medium. Nine surfactants (including Pluronic F127, Pluronic F108, and Pluronic F68) were evaluated at concentrations below their critical micelle concentrations (CMCs) using an in vitro precipitation assay. A model compound used in this study showed a sharp pH-dependent solubility profile and was much more soluble in simulated gastric fluid (SGF) (pH 1.2) than in simulated intestinal fluid (SIF) (pH 7.4). The compound was first dissolved in SGF with each surfactant, and the solutions were dispensed into the wells of a 96-well microtiter plate by a TECAN robot and diluted 10-fold with SIF. After a preset incubation time at room temperature, the solutions were filtrated through a 96-well filter plate, and the compound concentration in the filtrate was measured using an HPLC method. At concentrations below their CMCs, Pluronic F127 and Pluronic F108, but not Pluronic F68, inhibited the compound precipitation in SIF. Combinations of Pluronic F127 or Pluronic F108 with Vitamin E TPGS showed significantly stronger inhibition than the individual surfactants, indicating synergistic effects on inhibition of drug precipitation.


*Keywords:* Precipitation inhibitor; Pluronic; Vitamin E TPGS; Poorly water-soluble compound

## 1. Introduction

It is a challenge to develop oral dosage forms for highly lipophilic compounds because they are poorly soluble in an aqueous medium (Lipinski et al., 1997; Gardner et al., 2004). A variety of strategies have been proposed to improve solubility of such compounds; however, drug precipitation in vivo may limit the performance of solubility-enhancing formulations (Hoener and Benet, 2002). For example, basic drugs with higher solubility in gastric fluid than in intestinal fluid may precipitate with the sharp pH increase in the intestine (Kostewicz et al., 2003; Perng et al., 2003; Gu et al., 2005) or when there is extensive dilution of excipients (Schroeder and DeLuca, 1974; Pouton, 1999, 2000). Although supersaturable, lipid-based formulations have become popular choices for improving the solubility and, thus, the bioavailability of poorly water-soluble compounds (Gao et al., 2003, 2004), drugs may still precipitate rapidly in vivo before they are absorbed, limiting oral bioavailability. Therefore, one of the key aims in formulation development for poorly water-soluble drugs is to prevent or retard drug precipitation in vivo (Pouton, 2000).

Water-soluble amphiphilic surfactants have been widely used to prevent drug precipitation and increase the aqueous solubility of poorly water-soluble drugs. For example, Pluronics (poloxamers) (BASF, Mount Olive, NJ), which are polyoxyethylene–polypropylene oxide block copolymer surfactants, have been incorporated into aqueous formulations to increase drug solubility, or formulated with drugs to form a drug/polymer solid solution or solid dispersion to improve dissolution and bioavailability (Reddy et al., 1976; Shin and Cho, 1997; Chutimaworapan et al., 2000; Rouchotas et al., 2000). The increased drug aqueous solubility and improved dissolution have been also found with other water-soluble amphiphilic surfactants such as Vitamin E TPGS and Gelucire 44/14 (Sethia and Squillante, 2002). In these studies, a high concentration of surfactants, usually well above the critical micelle concentration (CMC), was required to solubilize drugs because of micellar effects. Unfortunately, a high concentration of surfactants may

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irritate the gastrointestinal tract and cause moderate, reversible changes in intestinal wall permeability (Swenson et al., 1994).

Compared with lipid-based amphiphilic surfactants, some water-soluble polymers without intrinsic solubilizing properties can inhibit drug precipitation in aqueous media at lower concentrations. For example, polyvinylpyrrolidone (PVP) reduced the precipitation of a number of poorly soluble compounds (Simonelli et al., 1970; Chemtob, 1989; Doherty and York, 1989; Raghavan et al., 2001). Other studies have focused on water-soluble cellulosic polymers such as hydroxypropylmethylcellulose (HPMC), methylcellulose, hydroxypropyl methylcellulose phthalate, and sodium carboxylmethylcellulose (Kohri et al., 1999; Raghavan et al., 2001; Gao et al., 2003; Li et al., 2005). At low concentrations (0.001–1 mg/mL), these cellulosic polymers inhibited drug precipitation and prolonged the supersaturated state of the drugs (Usui et al., 1997). Compared to formulations without precipitation inhibitors, those including the polymeric precipitation inhibitors significantly increased oral bioavailability by generating and maintaining a supersaturated concentration of drug (Gao et al., 2003, 2004; Gao and Morozowich, 2006). Although the use of precipitation inhibitors for improving the oral bioavailability of poorly water-soluble drugs has been studied, most of the research has focused on cellulosic polymers and PVP. There have been relatively few reports regarding the use of low concentrations of surfactant polymers as precipitation inhibitors.

In this study, we found that Pluronics inhibited precipitation of a poorly water-soluble compound in an aqueous medium at concentrations below their CMCs. In order to screen potential precipitation inhibitors, we first dissolved all tested surfactants and the compound in simulated gastric fluid (SGF) (pH 1.2). The formulations were then diluted with simulated intestinal fluid (SIF) (pH 7.4), and the compound concentration following dilution was measured. Nine surfactants including three Pluronics (Pluronic F127, Pluronic F108 and Pluronic F68) were evaluated, and the effects of combinations of Pluronics and Vitamin E TPGS on compound precipitation were investigated.

## 2. Materials and methods

### 2.1. Compounds

A poorly water-soluble compound was obtained from the Johnson and Johnson Pharmaceutical Research and Development compound collection. It consists of C, H, F, N, O and S, with a molecular weight of 676.77 g/mol. The compound does not contain any acidic groups, but two basic groups (a piperidine and a pyridine group). Table 1 summarizes the molecular weight, p$K_a$, log $P$, solubility, solubility parameter, and melting point of the compound.

### 2.2. Formulation excipients and biorelevant media

The following excipients were evaluated as potential precipitation inhibitors in the in vitro precipitation studies: d-Alpha Tocopheryl Polyethylene Glycol 1000 Succinate (Vitamin E TPGS) (Eastman Chemical, Kingsport, Tennessee); Tween 40, Tween 60, and Tween 80 (Sigma–Aldrich, St. Louis, MO); polyethylene glycol hydroxystearate (Solutol HS15), Cremophor EL, Pluronic F127, Pluronic F108, and Pluronic F68 (BASF); Gelucire 44/14 (Gattefossé, Paramus, NJ); and Volpo 10 (Croda USA, Edison, NJ).

SGF (pH 1.2) and SIF (pH 7.4) were prepared according to USP without enzymes.

Table 1
Physicochemical properties of the tested compound

| Property | Value |
|---|---|
| Molecular weight (g/mol) | 676.77 |
| p$K_a$[a,b] | 3.59, 7.8 |
| log $P$[c,b] | 2.14 |
| Solubility[d,b] | 0.6 mg/mL in SGF (pH 1.2), <0.0002 mg/mL in SIF (pH 7.4) |
| Solubility parameter ($MPa^{1/2}$)[e] | 27.77 |
| Melting point[f] (°C) | 167.4, 190.4 |

[a] p$K_a$ was measured by potentiometric titration in a water/methanol mixture with a UV absorption measurement.
[b] All measurements were conducted at ambient temperature.
[c] log $P$ was determined by the shake-flask method with 1-octanol and buffer pH 10.
[d] Equlibrium solubility.
[e] Solubility parameter was estimated computationally using Molecular Modeling Pro Plus (ChemSW, Fairfield, CA).
[f] Melting point was measured by a differential scanning calorimeter (HyperDSC, PerkinElmer, Boston, MA).

### 2.3. In vitro precipitation method

The in vitro drug precipitation upon dilution in an aqueous medium was assessed as described previously (Dai et al., 2007). All tested excipients in the study are soluble in SGF (pH 1.2) at concentration of 8 mg/mL. In addition, the compound in free-base form could be solubilized in SGF (pH 1.2) at 10 mg/mL as a supersaturated solution. In this study, the stock solutions of the base compound and the excipients were first prepared in SGF (pH 1.2) at concentrations of 6 and 8 mg/mL, respectively. Then, 50 μL of compound and 25 μL of each excipient solution were automatically dispensed into each well of a 96-well microtiter plate (Scienceware, Bel-Art Products, Pequannock, NJ) by a TECAN robot (Tecan US Inc., Research Triangle Park, NC). Each well in the 96-well microtiter plate contained 0.3 mg of compound and an excipient mass of 0.2 mg (single excipient) or 0.4 mg (binary combination). After a 30-min gentle shaking at room temperature, 900 μL of SIF (pH 7.4) was added to each well of the plate, yielding an approximately 10-fold dilution of the formulations. Following a 30-min gentle shaking (unless specified otherwise), all solutions in each well in the plate were transferred by a TECAN robot to a 0.2-μm polyvinylidene fluoride (PVDF) filter plate (pION, Inc., Woburn, MA). The solutions were passed through the filter plate under the vacuum to remove compound particles. The filtrate was then collected by a 96-well collection plate underneath the filter plate. After discarding the first 40 μL of the filtrate, the filtrate was diluted with $n$-propanol, and the concentration of the compound in the filtrate was determined using a high-performance liquid chro-

matographic (HPLC) method with a lower quantification limit of 0.1 μg/mL. The maximum concentration of the compound was approximately 300 μg/mL if the compound dissolved entirely in an aqueous medium without precipitation. The in vitro precipitation method is usually performed at ambient temperature. The lead formulations identified from this method are then evaluated and confirmed at 37 °C using an USP dissolution bath.

As discussed previously (Dai et al., 2007), the in vitro precipitation method in the study measures drug apparent solubility or concentration following addition of an aqueous medium into formulation. Since drug precipitation upon dilution is a kinetic process, drug concentration determined by this method could be a non-equilibrium value if an adequate period of time is not permitted to reach the equilibrium solubility. Unlike the equilibrium solubility which is a function of only the medium and temperature, the apparent solubility determined by the method in this study depends not only on medium and temperature, but also on time and concentration.

### 2.4. Characterization of the compound precipitates

The compound precipitates in an aqueous medium upon dilution were collected as follows. The stock solutions of the compound and the excipients were first prepared in SGF at concentrations of 6 and 8 mg/mL, respectively. Then, 500 μL of the compound and 250 μL of the corresponding excipient solutions were mixed, and the solutions were stirred for a 30 min at room temperature. Then, 9 mL of SIF (pH 7.4) was added to each solution (approximately 10-fold dilution of the formulations). After shaking at room temperature for additional 30 min, all of the solution was centrifuged at 16,000 rpm for 5 min. The white precipitate was washed twice with deionized water, lyophilized, and stored at −20 °C.

X-ray powder diffraction (XRPD) of the precipitates was performed using a PANalytical X'Pert Pro Powder X-ray Diffraction System (PANalytical, Natick, MA). The data were collected with an angular range between 3° and 35° 2$\Theta$, using a 0.0167°/step with a scan rate of 0.209° 2$\Theta$/s.

Differential scanning calorimetry (DSC) measurements were carried out using a Hyper-DSC system (PerkinElmer, Boston, MA). A 3- to 7-mg sample was accurately weighed and placed in a hermetic aluminum pan with a lid and crimp sealed. The sample was heated from 25 to 200 °C at 10 °C/min in aluminum pans under nitrogen atmosphere.

### 2.5. HPLC method

An Agilent 1100 HPLC instrument with an auto-sampler module for a 96-well microtiter plate (Agilent, Palo Alto, CA) was used to analyze compound concentrations. A Waters Xterra RP18 column (150 mm × 4.6 mm, 3.5 μm) (Waters, Milford, MA) was used at 30 °C. The mobile phase consisted of 70% (v/v) acetonitrile with 0.1% trifluoroacetic acid (TFA) and 30% (v/v) water with 0.1% TFA. The flow rate was controlled at 1 mL/min with an injection volume of 20 μL; the effluent was assayed for the compound concentration at a wavelength of 245 nm. The retention time of the compound was 2.5 min during a total 4.25-min run time per sample. None of the excipients used in the study interfere with the assay.

## 3. Results and discussion

The compound used in the study is a free-base form. It has a pH-dependent aqueous solubility of 0.6 mg/mL at pH 1.2 (SGF) and <0.0002 mg/mL at pH 7.4 (SIF) (Table 1). In addition, the compound in free-base form could be solubilized in SGF (pH 1.2) at 10 mg/mL as a supersaturated solution, and the compound retained soluble in this supersaturated solution for at least 2 h at room temperature before precipitation occurred. Also the compound was found to be chemically stable in SGF (pH 1.2) for at least 2 h (degradant <0.01% by HPLC analysis). The reasonably high apparent aqueous solubility and good chemical stability of the compound in SGF allowed us to dissolve the compound at the concentrations below 10 mg/mL in SGF (pH 1.2), and to investigate in vitro precipitation by dilution of the compound solution in SIF (pH 7.4).

Due to its relatively high apparent solubility at low pH, this compound was initially completely soluble at 6 mg/mL in SGF (pH 1.2) in the in vitro precipitation study; however, a cloudy solution was observed immediately when the compound solution was diluted with SIF (pH 7.4). The concentration of the compound without any excipients was 1.43 μg/mL following precipitation upon dilution with SIF (Table 2) but would have been 300 μg/mL if no precipitation occurred. Thus, almost all the compound precipitated out due to low solubility when SIF was added.

Addition of a non-ionic surfactant reduced or minimized the compound precipitation to some extent, depending on the type of surfactants used (Table 2). Among the nine surfactants tested individually at a concentration of 0.2 mg/mL after dilution, addition of Pluronic F127 or Vitamin E TPGS inhibited precipitation more effectively than the others. Following a 30-min incubation after dilution with SIF, the compound concentrations in the presence of Pluronic F127 or Vitamin E TPGS were 69.5 and 45.2 μg/mL, respectively, compared with 1.43 μg/mL for the solution without any excipients, and were significantly higher than those achieved with the other tested surfactants (all <10 μg/mL) (Table 2).

Although Pluronic F127 and Vitamin E TPGS significantly inhibited compound precipitation, their inhibitory effects were limited at the weight ratio of compound/excipient (3/2); only 23.2% and 15.1% of the compound remained solubilized, respectively, and the majority of the compound precipitated out after dilution (Table 2). Combining Pluronic F127 with Vitamin E TPGS, however, inhibited the compound precipitation significantly (Table 2), and approximately 70% of the compound remained solubilized following 30-min incubation upon dilution. The compound concentration increased to 207 μg/mL, much higher than that with individual Pluronic F127 (69.5 μg/mL) or Vitamin E TPGS (45.2 μg/mL). This concentration was also statistically significantly higher than the sum of the individual compound concentrations ($p < 0.001$). Combining Pluronic F127 and Vitamin E TPGS resulted in synergistic

Table 2
Inhibition of the precipitation of compound in an aqueous medium by Pluronic F127 formulations

| Formulation (single excipient) | Compound concentration (μg/mL) ($n=3$) | Formulation (surfactant with Pluronic F127) | Compound concentration (μg/mL) ($n=3$) |
|---|---|---|---|
| Compound only | 1.43 ± 0.03 | | |
| Pluronic F127 | 69.5 ± 7.88 | | |
| Vitamin E TPGS | 45.2 ± 17.1 | Vitamin E TPGS + Pluronic F127 | 207 ± 15.50 |
| Tween 40 | 8.44 ± 0.54 | Tween 40 + Pluronic F127 | 24.20 ± 18.10 |
| Tween 60 | 8.20 ± 1.11 | Tween 60 + Pluronic F127 | 8.98 ± 1.02 |
| Tween 80 | 9.57 ± 1.97 | Tween 80 + Pluronic F127 | 43.5 ± 23.1 |
| Cremophor EL | 5.90 ± 0.51 | Cremophor EL + Pluronic F127 | 22.2 ± 21.3 |
| Volpo 10 | 4.73 ± 1.18 | Volpo 10 + Pluronic F127 | 6.77 ± 2.60 |
| Solutol HS 15 | 2.42 ± 0.58 | Solutol HS 15 + Pluronic F127 | 6.91 ± 2.70 |
| Gelucire 44/14 | 1.52 ± 0.05 | Gelucire 44/14 + Pluronic F127 | 3.05 ± 0.46 |

effects on inhibiting drug precipitation. However, the antagonistic behavior, not synergism, was seen when Pluronic F127 was combined with each the other tested surfactants (Table 2). When Pluronic F127 is combined with the other tested surfactants rather than Vitamin E TPGS, the compound concentration after precipitation was significantly lower than that with Pluronic F127 alone (69.5 μg/mL).

We also found that this increased compound concentration in the presence of excipients upon dilution was not due to a pH change which could be potentially caused by the presence of compound and excipients tested. All the formulations containing the compound and the tested excipients in SGF maintained the same pH at 1.2. After dilution with SIF (pH 7.4), re-measurement of the pH of the formulations showed the similar pH (7.0) for all formulations in each well. This could be explained by the buffer capacity of SIF and the use of non-ionic excipients in the study.

Reproducibility between replicates is shown by the standard deviation ($n=3$) for replicate formulations at the same time point. It can be seen that for most data points, the standard deviations are less than 15%. However, for some data points the standard deviations are significantly larger. The in vitro precipitation method determines drug concentration following precipitation. Larger standard deviations seem to occur for samples that have begun to precipitate or have been in the process of precipitation (no longer supersaturated) but which have not yet reached equilibrium. Samples that are supersaturated but have not yet begun to precipitate (e.g., for effective precipitation inhibitors) have standard deviations less than 10%.

In addition to Pluronic F127, we studied the inhibitory effects of Pluronic F108 and its combinations on compound precipitation. Similar to the findings in Pluronic F127 studies, Pluronic F108 at 0.2 mg/mL inhibited compound precipitation in aqueous media significantly compared with the other surfactants tested in the F127 study. The compound concentration upon dilution in aqueous media with 0.2 mg/mL of Pluronic F108 was increased to 36.4 μg/mL for the solution without any excipients. This increased concentration was also significantly higher than those achieved with the other tested surfactants (all <10 μg/mL) (Table 2). In addition, combining Pluronic F108 and Vitamin E TPGS resulted in synergy that further inhibited compound precipitation, leading to an increased compound concentrations (187 μg/mL) following dilution. However, as observed in the Pluronic F127 study, no such synergistic effect was seen when Pluronic F108 was combined with any of other tested surfactants.

In addition, Pluronics types and amounts in the formulations affected the extent of inhibition of drug precipitation in an aqueous medium upon dilution (Fig. 1). Pluronic F127 and Pluronic F108, but not Pluronic F68, inhibited the compound precipitation in SIF. Increasing amount of Pluronic F127 in the formulations also further inhibited compound precipitation upon dilution (Fig. 1). In sharp contrast to the results achieved with Pluronic F127 and Pluronic F108, Pluronic F68 did not inhibit compound precipitation, even when the final Pluronic F68 concentration in aqueous medium upon dilution was high. No synergistic effect on inhibition of compound precipitation was seen when Pluronic 68 and Vitamin E TPGS were combined.

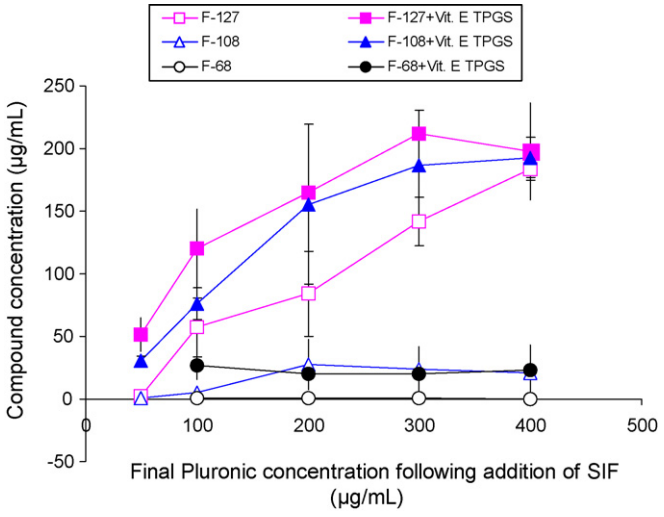


Fig. 1. The effect of Pluronic types and amounts on inhibition of compound precipitation in an aqueous medium. In the precipitation assay, each well in the 96-well microtiter plate contained 0.3 mg of compound and a range of Pluronics mass (0.05, 0.1, 0.2, 0.3 and 0.4 mg). For the wells with combination of Pluronics and Vitamin E TPGS, an additional 0.1 mg Vitamin E TPGS was added. The final aqueous volume in each well was 1 mL following a 30-min incubation upon dilution with SIF. The maximum concentration of compound would be 300 μg/mL if the compound dissolved entirely in an aqueous medium without precipitation (see Section 2 for details). The error bars represent standard deviations of four measurements.

The study results suggest Pluronic F127 and Pluronic F108, particularly when combined with Vitamin E TPGS, were potent inhibitors for drug precipitation. The underlying mechanisms for inhibition of drug precipitation with low concentrations of Pluronics and Vitamin E TPGS are not yet clear. The inhibition of drug precipitation observed in the study may be due to solubilization of poorly water-soluble drug by micellization. Other factors that inhibit precipitation may include an increase in solution viscosity and interaction between the drug and surfactants that impact drug nucleation and crystal growth. In our study, the final Pluronics concentrations in an aqueous medium upon dilution were in the range of 0.05–0.4 mg/mL (Fig. 1), well below their CMC values (>0.9 mg/mL) (Alexandridis et al., 1994; Sezgin et al., 2006). The Vitamin E TPGS concentration (0.1 mg/mL) in the formulation upon dilution (Fig. 1) was also below its CMC value (>0.2 mg/mL) (Ismailos et al., 1994; Yu et al., 1999). In addition, we estimated the micropolarity of microenvironments in the formulations using pyrene probe. The results indicated that while Pluronic F127 became more hydrophobic in the presence of Vitamin E TPGS compared with Pluronic F127 alone, no corresponding micelles were formed at the concentrations of Pluronic F127 and Vitamin E TPGS used in the study. However, in those media with 0.1 mg/mL Vitamin E TPGS and Pluronic F127 or Pluronic F108 (0.05–0.4 mg/mL), the compound concentration increased up to 200 μg/mL upon dilution (Fig. 1). Therefore, the inhibition of drug precipitation (and concomitant increase in drug concentration) is not likely a result of micellization, which often contributes to solubilization of poorly water-soluble drugs in formulations containing Pluronics (Prancan et al., 1980; Shin and Cho, 1997). In our study we also noticed that the compound concentration was directly proportional to the Vitamin E TPGS concentration once this surfactant concentration was above its CMC value.

Addition of Pluronics and Vitamin E TPGS into an aqueous medium may increase solution viscosity that slow or inhibit crystal growth and precipitation; indeed, drug crystal growth for recrystallization is directly proportional to the diffusion rate of a compound. The effective concentration of Pluronics for inhibition of drug precipitation, however, was as low as 0.05 mg/mL (Fig. 1), and the viscosity increase of the solution with low concentrations of polymers was negligible. The extent to which drug precipitation was inhibited was much greater than the change in viscosity that has been previously described by others (Usui et al., 1997). Furthermore, other surfactants such as Tween 40, Tween 60, Tween 80, Solutol HS15, Cremophor EL, Gelucire 44/14, and Volpo 10 were tested at a higher concentration (0.2 mg/mL). They generated more viscous solutions than Pluronics at 0.05 mg/mL, but no inhibitory effect on drug precipitation was seen (Table 2). Thus, it was not an increase in viscosity that slowed the diffusion rate during crystal growth and inhibited drug precipitation.

We believe the interaction between the drug and a Pluronic/Vitamin E TPGS mixture inhibits drug precipitation. It has been reported that water-soluble polymer inhibitors such as HPMC may adsorb on the surface of the nuclei and inhibit drug nucleation in the supersaturated solution (Raghavan et al., 2001). These polymers may also adsorb on the surface of drug crystals and form a mechanical barrier that inhibits the contact of crystals for growth (Ziller and Rupprecht, 1988). A similar mechanism may apply for the inhibition of drug precipitation in an aqueous medium by Pluronic/Vitamin E TPGS. In particular, steric hindrance by Pluronic/Vitamin E TPGS may separate the crystal particles. The hydrophilic polyoxyethylene (POE) moiety of Pluronic is likely to be desirable in achieving steric stabilization of colloid systems (Woodle et al., 1992; Castile et al., 2001).

The interactions which lead to inhibition of drug precipitation might be hydrophobic interactions or hydrogen bonding between drug and polymer molecules (Doherty and York, 1987; Raghavan et al., 2001). We speculate that the blocklength of the hydrophobic polypropylene oxide (PPO) segment in Pluronics is critical in terms of inhibiting drug precipitation. Pluronic F127 and Pluronic F108 have the MWs of the PPO segments of 3600 and 3000, respectively, which are significantly larger than that in Pluronic F68 (1800). A strong hydrophobic interaction between Pluronic F127 or Pluronic F108 and the compound is expected, which may lead to the inhibition of compound precipitation (Fig. 1). Pluronic F68 did not exhibit an inhibitory effect on compound precipitation. We speculate that the blocklength of the PPO segment in Pluronic F68 might be below the critical value required for inhibition of compound precipitation. A further study is needed to confirm our hypothesis.

In addition, the in vitro precipitates upon dilution were characterized by XRD and DSC. Fig. 2 shows the XRD patterns of the precipitates upon dilution from the different formulations. Compared to the compound without any excipients, compound precipitates from Pluronic F127 or Vitamin E TPGS upon dilution displayed similar peak locations in XRD patterns, and no obvious peak broadening was observed (Fig. 2). However, the precipitates from a combination of Pluronic F127 and Vitamin E TPGS upon dilution were amorphous. The findings were further confirmed by DSC results (Fig. 3). We speculate that Pluronics/Vitamin E TPGS mixture may be incorporated in the drug precipitates, thereby inhibiting the formation of regular crystalline structure. The study results suggest that, like other

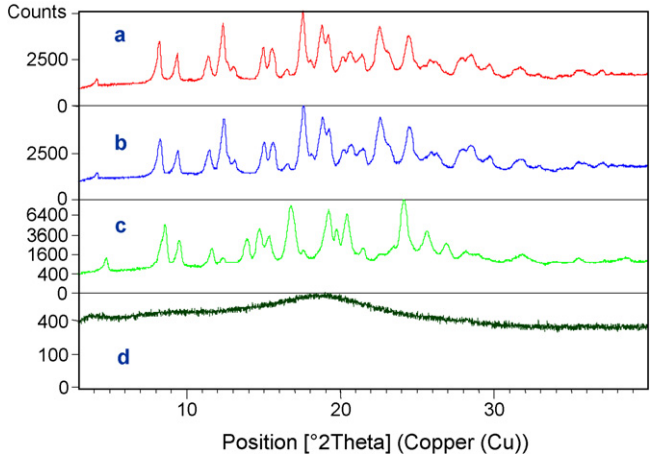


Fig. 2. XRD patterns of the precipitates upon dilution from (a) the compound, (b) the Vitamin E TPGS formulation, (c) the Pluronic F127 formulation, and (d) the Pluronic F127/Vitamin E TPGS formulation.

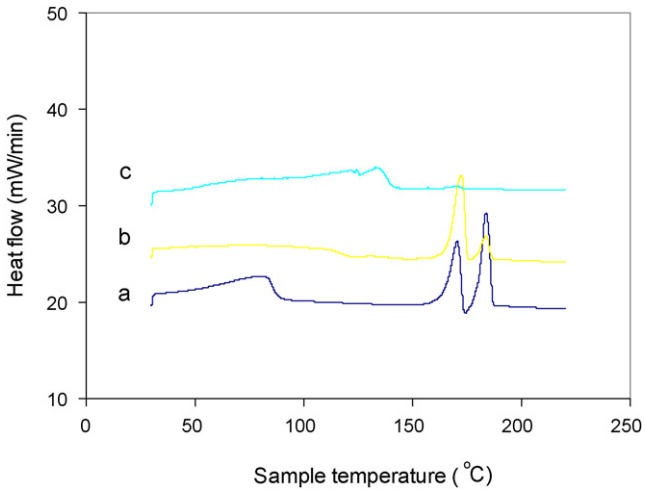


Fig. 3. DSC patterns of the precipitates upon dilution from (a) the Vitamin E TPGS formulation, (b) the Pluronic F127 formulation, and (c) the Pluronic F127/Vitamin E TPGS formulation.

additives, Pluronics alone may inhibit drug nucleation, prevent crystal growth, and modify recrystallization and crystal habits, but does not change the internal structure of the crystal (Chow et al., 1995; Usui et al., 1997). In contrast, a combination of Vitamin E TPGS with Pluronics may change crystal structures of drug precipitates (Figs. 2 and 3).

## 4. Conclusions

We demonstrated that low concentrations of Pluronic F127 and Pluronic F108 inhibited precipitation of a poorly water-soluble compound in an aqueous medium, and that a combination of Pluronics with Vitamin E TPGS resulted in a synergy that inhibited compound precipitation even more significantly. Little is known about the mechanism for this inhibition of drug precipitation, and further studies are needed to reveal the mechanism. It would be also interesting to test other low-solubility compounds with different properties in future studies. The study results suggest that Pluronic F127 and Pluronic F108, particularly when combined with Vitamin E TPGS, were potent inhibitors for drug precipitation.

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