International Journal of Pharmaceutics 419 (2011) 170–174

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Solvent shift method for anti-precipitant screening of poorly soluble drugs using biorelevant medium and dimethyl sulfoxide

Taro Yamashita*, Shunsuke Ozaki, Ikuo Kushida

Analytical Research, CMC Japan, Pharmaceutical Science & Technology Core Function Unit, Eisai Product Creation Systems, Eisai Co., Ltd., 5-1-3 Tokodai, Tsukuba, Ibaraki 300-2635, Japan

ARTICLE INFO

Article history:
Received 1 June 2011
Received in revised form 27 July 2011
Accepted 28 July 2011
Available online 4 August 2011

Keywords:
Anti-precipitant
FaSSIF
HPMC-AS
Itraconazole
High throughput screening
DMSO

ABSTRACT

96-well plate based anti-precipitant screening using bio-relevant medium FaSSIF (fasted-state simulated small intestinal fluid) is a useful technique for discovering anti-precipitants that maintain supersaturation of poorly soluble drugs. In a previous report, two disadvantages of the solvent evaporation method (solvent casting method) were mentioned: precipitation during the evaporation process and the use of volatile solvents to dissolve compounds. In this report, we propose a solvent shift method using DMSO (dimethyl sulfoxide). Initially, the drug substance was dissolved in DMSO at a high concentration and diluted with FaSSIF that contained anti-precipitants. To evaluate the validity of the method, itraconazole (ITZ) was used as the poorly soluble model drug. The solvent shift method resolved the disadvantages of the evaporation method, and AQOAT (HPMC-AS) was found as the most appropriate anti-precipitant for ITZ in a facile and expeditious manner when compared with the solvent evaporation method. In the large scale JP paddle method, AQOAT-based solid dispersion maintained a higher concentration than Tc-5Ew (HPMC)-based formulation; this result corresponded well with the small scale of the solvent shift method.

1. Introduction

Most drug candidates are identified from combinatorial and library approaches to find compounds that show high activity toward the target protein. However, selected compounds can have undesirable physicochemical properties such as high lipophilicity and poor solubility. Physicochemical properties (such as solubility, hydrophobicity, and permeability) are essential features for oral absorption of drug candidates (Martin, 2005; Kerns and Di, 2004). Drug candidates that have poor solubility and poor permeability tend to possess low oral bioavailability, thus resulting in low plasma concentrations (Lipinski, 2000; Waterbeemd et al., 2001).

To resolve poor solubility, studies of supersaturation and anti-precipitants have been reported (Brouwers et al., 2009; Gao et al., 2004; Varma and Panchagnula, 2005; Gao et al., 2003). To maintain a high concentration in the neutral pH of the intestine, supersaturation and anti-precipitant mechanisms that prevent precipitation have been studied. Solid dispersion is one of the technologies to maintain supersaturation in the intestine (Yamashita et al., 2003; Kushida et al., 2002). The drug was dispersed into carriers in an amorphous state and enhanced the apparent solubility in the intestine. For example, itraconazole (ITZ) is a poorly soluble compound and developed as a solid dispersion (Verreck et al., 2003; Six et al., 2005). To enhance the absorption of ITZ, market-available solid dispersion formulations have been developed (such as Sporanox®, Itrizole®); these formulations contain HPMC (hydroxypropyl methylcellulose) (ITZ/HPMC, 2/3, w/w). It has also been reported that HPMC-AS (hydroxypropyl methylcellulose-acetate succinate)-based solid dispersion enhanced the supersaturation of ITZ rather than HPMC-based solid dispersion (DiNunzio et al., 2010; Van Speybroeck et al., 2010).

96-well plate based anti-precipitant screening is a useful technique for discovering anti-precipitants that maintain the supersaturation of poorly soluble drugs with the advantages of utilizing a small quantity of the drug substance and high throughput (Shanbhag et al., 2008; Dai et al., 2008; Yamashita et al., 2010). Moreover, the screening results indicate the formulation strategy, such as lipid formulation or solid dispersion. In previous reports, the solvent evaporation method (solvent casting method) was used (Shanbhag et al., 2008; Dai et al., 2008). The drug substance was dissolved in the solvent (such as alcohol, acetone, etc.) that contained anti-precipitants, and the solvent was removed by evaporation. In a previous report, two disadvantages of the solvent evaporation method were raised (Dai et al., 2008): precipitation during the evaporation process and the necessity of volatile solvents to dissolve the compound. The solvent shift method using

* Corresponding author. Tel.: +81 29 847 5770; fax: +81 29 847 5771.
E-mail address: t5-yamashita@hhc.eisai.co.jp (T. Yamashita).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.07.045

simulated gastric fluid had also been reported for basic compounds (Yamashita et al., 2010), though this method is not applicable for poorly soluble compounds in an acidic medium.

The objective of this study was to develop a method that can find desirable anti-precipitants in a facile and expeditious manner. In this report, we propose a solvent shift method using DMSO (dimethyl sulfoxide) to resolve the disadvantages of the previous methods. Using this method, the drug substance was dissolved in DMSO with high concentration, and then a small aliquot of the DMSO solution was added to FaSSIF (fasted state simulated small intestinal fluid) that contained anti-precipitants. To evaluate the validity of this method, ITZ was used as the poorly soluble model drug. The result of the solvent shift method was compared with that of the solvent evaporation method and the large scale conventional dissolution method. Advantages of the solvent shift method will be discussed in this report.

2. Experimental

2.1. Materials and reagents

Itraconazole (ITZ, free base crystal) was purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Itrizole®, the itraconazole solid dispersion formulation, was purchased from Janssen Pharmaceutical K.K (Tokyo, Japan). SLS (sodium lauryl sulfate) and Tween 80 were purchased from Wako Pure Chemical Industries, Ltd. Pluronic F-68 was purchased from MP Biomedical Japan (Tokyo, Japan). Sucrose stearate S-570 was purchased from Mitsubishi-Kagaku Foods Co. (Tokyo, Japan). PEG 400 (polyethylene glycol 400) was purchased from NOF Co. (Tokyo, Japan). PG (propylene glycol) was purchased from Adeka Co. (Tokyo, Japan). Labrafil, Labrasol and Gelucire 44/14 were purchased from Gattefosse (Saint-Priest, France). Cremophor ELP, Cremophor RH40 and Kollidon 17PF were purchased from BASF Japan Ltd. (Tokyo, Japan). HCO-60 (polyethylene glycol-60 hydrogenated castor oil) was purchased from Nikko Chemicals Co. Ltd. (Tokyo, Japan). Tc-5Ew (HPMC: hydroxypropyl methylcellulose) and AQOAT (HPMC-AS: hydroxypropyl methylcellulose-acetate succinate) were purchased from Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan). Hydroxypropyl-β-cyclodextrin (HP-β-CD) was purchased from Mitsubishi Co. (Tokyo, Japan). Captisol was purchased from CyDex (Terrace Lenexa, KS).

Sodium taurocholate was purchased from Nacalai Tesque, Inc. (Kyoto, Japan). Lecithin was purchased from NOF Co. Potassium chloride (KCl), sodium hydroxide (NaOH), sodium dihydrogenphosphate (NaH_2PO_4), dimethyl sulfoxide (DMSO), HPLC-grade acetonitrile (MeCN), ethanol (EtOH), acetone and phosphoric acid were purchased from Wako. Water was purified using a Milli-Q Gradient A 10 system (Millipore, Billerica, MA). 70% MeCN was prepared by mixing 700 mL of MeCN and 300 mL of water.

2.2. Preparation of medium

In this study, FaSSIF was used as a test medium to compare our solvent shift method with the solvent evaporation method, though FeSSIF (fed state simulated small intestinal fluid) is another typical biorelevant medium (Bard et al., 2008). The composition of fasted state simulated small intestinal fluid (FaSSIF) was as follows: (pH 6.5: 3 mM sodium taurocholate, 0.75 mM lecithin, 29 mM NaH_2PO_4, 100 mM KCl in water). pH was adjusted to pH 6.5 by titration of NaOH using a pH meter (F-53, Horiba, Ltd., Fukuoka, Japan).

2.3. HPLC/UV condition

HPLC/UV analyses were performed using a 1100 series HPLC system fitted with a binary pump, plate auto sampler, thermostat in the column compartment, and diode array detector controlled by Chemstation, version 9.01 (Agilent Technologies, Palo Alto, CA). Chromatography was conducted using a YMC Pro C18 column (35 mm × 4.6 mm; particle size 3 μm; YMC, Kyoto, Japan). The mobile phase was composed of a mixture of 0.1% phosphoric acid in water (solvent A) and MeCN (solvent B). The gradient was delivered at 2 mL/min as follows: 0 min, 5% solvent B; 3.0 min, 90% solvent B; 3.5 min, 90% solvent B; 3.51 min, 5% solvent B; and 5 min, 5% solvent B; loop time = 5.0 min. The column was maintained at 40 °C. The diode array detector was set at 260 nm. The injection volume was 10 μL.

2.4. Anti-precipitant screening by the solvent shift method

Anti-precipitants were dissolved/suspended in FaSSIF at 0.015% (w/v). For the sample plate, 200 μL of anti-precipitant solution/suspension was placed in each well. Then, 4 μL of 5 mg/mL ITZ in DMSO solution was added to each well using an 8-channel electronic Biohit Proline pipette (Biohit OYJ, Helsinki, Finland) (time course 0: t_0), and the plate was sealed with a silicone pre-slit well cap. The concentration of ITZ at t_0 was 0.1 mg/mL, with 0.015% (w/v) anti-precipitant in FaSSIF (ITZ/anti-precipitant 2/3, w/w). The plate was shaken in a Taitec MicroMixer E-36 (Taitec Co., Saitama, Japan) at 25 °C. A volume of 100 μL of the sample was transferred into a MultiScreen HTS Solubility 0.45 μm filter plate (Millipore) using an 8-channel electronic pipette at the appropriate time and was filtered by MultiScreen Vacuum Manifold (Millipore) to separate the precipitate. The filtrates were diluted 4-fold with 70% MeCN (4-fold dilution sample). The 4-fold dilution samples were injected into the HPLC/UV, and the concentration of ITZ was measured.

As for the control crystalline powder, approximately 0.1 mg of ITZ free base crystalline powder was placed into each well, and 200 μL of FaSSIF that contained 2% (v/v) DMSO was added (t_0). The plate was shaken at 25 °C and the sample was filtered at the appropriate time. The 4-fold diluted filtrate was injected into the HPLC/UV, and the concentration of ITZ was measured.

2.5. Anti-precipitant screening by the solvent evaporation method

1 mg/mL of ITZ, 1.5 mg/mL of anti-precipitant solution in ethanol/acetone/water (10/10/1, v/v/v) was prepared, and 20 μL of solution was dispensed in each well. The solvent was evaporated by EYELA centrifugal evaporator NE-3100 for 1 h. 200 μL of FaSSIF was added (t_0), and then the plate was shaken at 25 °C. The sample was filtered at the appropriate time, and the filtrate was diluted 4-fold by 70% MeCN. The concentration of ITZ was measured by HPLC/UV analysis.

As for the control crystalline powder, approximately 0.1 mg of ITZ free base crystalline powder was placed into each well, and 200 μL of FaSSIF was added (t_0). The plate was shaken at 25 °C and the sample was filtered at the appropriate time. The 4-fold diluted filtrate was injected into the HPLC/UV, and the concentration of ITZ was measured.

2.6. Preparation of the solid dispersion

Solid dispersions were prepared by the solvent evaporation technique. 0.5 g of ITZ and 0.75 g of the anti-precipitant were mixed and dissolved into 525 mL of ethanol/acetone/water (10/10/1, v/v/v). The solvents were removed under reduced pressure using a rotary evaporator (NE-1, EYELA, Tokyo Rikakikai Co. Ltd., Tokyo, Japan) at 50 °C. After solvents were removed by drying under vacuum at room temperature, the solid dispersions were ground into powders with a mortar and pestle. In the solid dispersion, no

Table 1
Physicochemical properties of ITZ (Van Speybroeck et al., 2010).

Molecular weight	705.6 g/mol
c log *P*	6.2
pK_a	2 and 3.7
Solubility in water (pH 7)	1 ng/mL
Solubility in 0.1 N HCl (pH 1)	5 μg/mL
Solubility in FaSSIF	0.3 μg/mL

diffraction peaks relating to the ITZ crystal were observed by X-ray powder diffraction (XRPD, TTR-III, Rigaku, Tokyo, Japan).

2.7. Dissolution of the solid dispersion

All dissolution profiles of ITZ crystalline powder and solid dispersion were obtained by the JP paddle method (Toyama Sangyo NTR-VS3). 30 mg (as itraconazole) of sample was weighed and added into the apparatus with 300 mL of FaSSIF. The rotation speed and the sample temperature were set as 50 rpm and 37 °C, respectively. 2 mL aliquots were withdrawn at the appropriate time and filtered by 0.45 μm disc filter (GL Chromatodisc 13A, GL Sciences, Inc., Torrance, CA). The filtrate was diluted with the same volume of MeCN (2× dilution), and injected into HPLC/UV system. The concentration of ITZ was measured by HPLC/UV.

3. Results and discussion

3.1. Physicochemical properties of ITZ

Table 1 shows the physicochemical properties of ITZ (such as molecular weight, *c* log *P*, pK_a and solubility) (Van Speybroeck et al., 2010). ITZ is a weak base compound and has two pK_a values (2 and 3.7). The solubility of ITZ crystalline free base was 1 ng/mL in water at pH 7, 5 μg/mL at pH 1, and 0.3 μg/mL in FaSSIF. The clinical dose of ITZ ranges from 50 mg to 200 mg (from the label of Sporanox®). These values indicate that ITZ is classified as a poorly soluble drug. Fig. 1 shows the kinetic solubility and thermodynamic solubility of ITZ in FaSSIF with/without 2% DMSO using 96-well plate at 25 °C. "Kinetic solubility" indicates that 4 μL of 5 mg/mL ITZ DMSO solution was diluted by 200 μL of FaSSIF, and the concentration was then determined (the final DMSO concentration: 2%, v/v). "Thermodynamic solubility" indicates that an excess amount of the ITZ crystalline powder was added into FaSSIF with/without 2% (v/v) DMSO, and the concentration was then determined. These results show that the kinetic solubility was higher than the

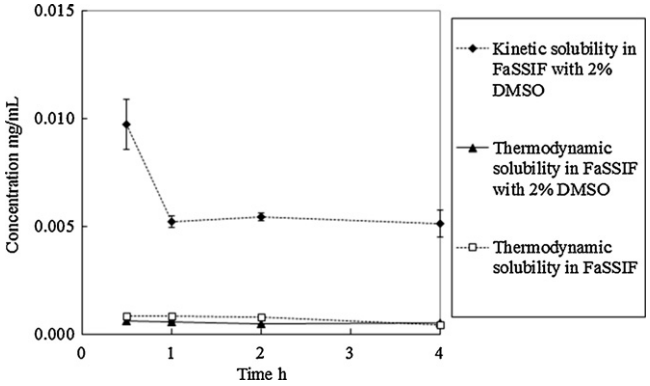

Fig. 1. The kinetic solubility and thermodynamic solubility of ITZ in FaSSIF with/without 2% DMSO using 96-well plate at 25 °C (S.D. $n = 3$).

thermodynamic solubility, and ITZ maintained a supersaturation state (ca. 5 μg/mL at 4 h). This phenomenon fully agrees with the result reported by Bevernage et al. (2010). Also, the kinetic solubility is usually higher than the thermodynamic one due to the supersaturation effects (Bard et al., 2008). 2% (v/v) of DMSO did not influence the solubility of ITZ crystalline powder.

3.2. Anti-precipitant screening by the solvent shift method

Seventeen kinds of polymers, surfactants, cyclodextrin, oil and excipients with a variety of structural and physical/chemical properties were investigated to find promising anti-precipitants for the supersaturation of ITZ in FaSSIF. The ratio of ITZ/anti-precipitant was selected as 2/3 w/w, because this ratio corresponded with market-available solid dispersion formulations (such as Sporanox® and Itrizole®) (Six et al., 2005). ITZ crystalline free base was dissolved in DMSO at 5 mg/mL; it was impossible to prepare 5 mg/mL solution due to poor solubility using other organic solvents (such as ethanol, acetone). To reduce the volume of the organic solvent in FaSSIF, DMSO was selected.

Fig. 2 shows the results of the anti-precipitant screening. AQOAT exhibited the highest concentration (ca. 20 μg/mL) from 1 to 2 h, meaning that only AQOAT acted as an anti-precipitant to prevent the precipitation of ITZ when compared with other anti-precipitants. In a previous report, HPMC-AS (AQOAT) showed a higher supersaturation than HPMC (TC-5Ew) in the dissolution study of FaSSIF (Van Speybroeck et al., 2010), and our results corresponded well with their results. HPMC (Tc-5Ew) is used with

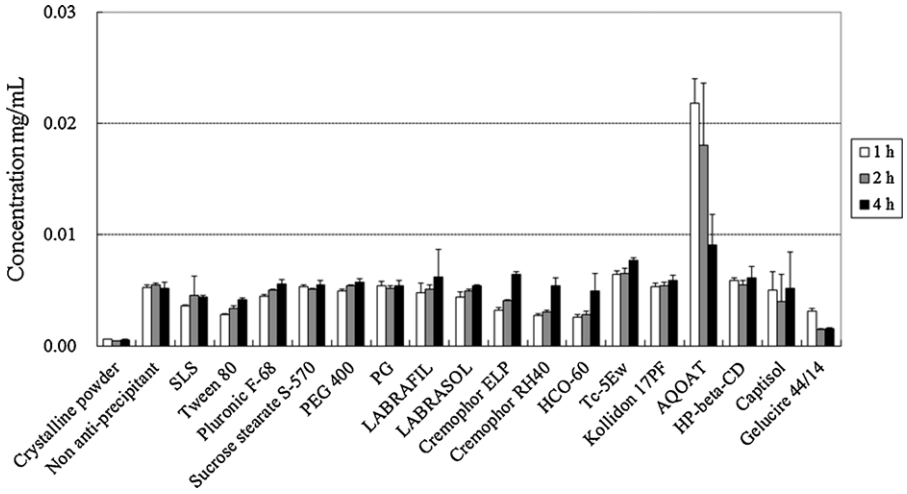

Fig. 2. The results of anti-precipitant screening by the solvent shift method (S.D. $n = 3$).

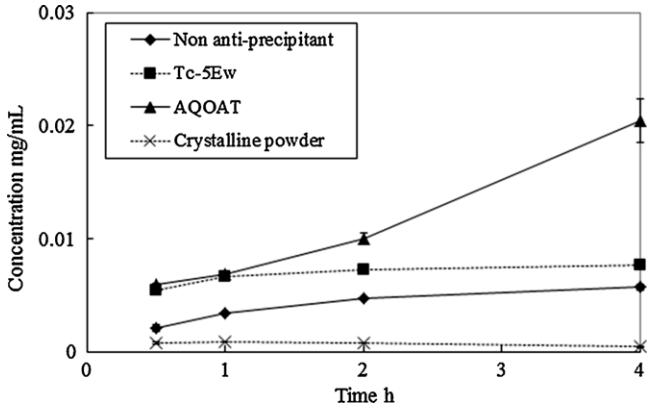

Fig. 3. The results of anti-precipitant screening by the solvent evaporation method (S.D. $n = 3$).

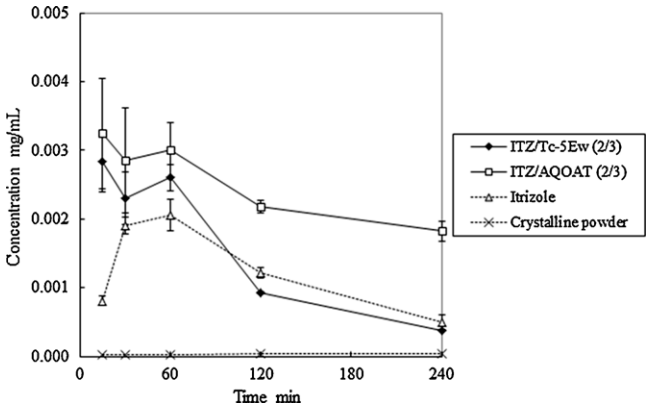

Fig. 4. Dissolution profiles of ITZ free base crystalline powder, Itrizole® (market-available solid dispersion), solid dispersion (ITZ/Tc-5Ew, 2/3, w/w) and solid dispersion (ITZ//AQOQT, 2/3, w/w,) in FaSSIF (S.D. $n = 3$).

market-available ITZ solid dispersions (Sporanox®, Itrizole®). In Fig. 2, Tc-5Ew showed a higher concentration than the crystalline powder, though it showed almost the same concentration with the non-anti-precipitant control. This result suggested that ITZ could maintain the supersaturation by itself, and Tc-5Ew does not affect the supersaturation of ITZ in FaSSIF. To corroborate, Bevernage et al. (2010) reported that ITZ maintained the supersaturation in FaSSIF alone. In the development history of HPMC-based solid dispersion, HPMC was selected by the enhancement of the physical stability of the solid state (Verreck et al., 2003). From the result of the solvent shift method, only AQOAT was found as an anti-precipitant that maintained the supersaturation of ITZ in FaSSIF.

3.3. The comparison of the solvent shift method and the solvent evaporation method

A 96-well plate based anti-precipitant screening by solvent evaporation method (solvent casting method) to find an anti-precipitant for poorly soluble drugs was previously reported (Shanbhag et al., 2008; Dai et al., 2008). To compare the solvent shift method with the solvent evaporation method, anti-precipitant screening of ITZ with Tc-5Ew and AQOAT was carried out. ITZ and anti-precipitant were dissolved in ethanol/acetone/water (10/10/1, v/v/v) with the ratio of ITZ/anti-precipitant (2/3, w/w). As for the solvent, ethanol/acetone/water (10/10/1, v/v/v) was selected because it was used as the solvent for preparation of the solid dispersion in Section 2.6. The solvent was evaporated by a centrifugal evaporator, and the concentration of ITZ was monitored in FaSSIF. Fig. 3 shows the results of the 96-well plate based anti-precipitant screening by the solvent evaporation method. In Fig. 3, AQOAT and Tc-5Ew showed almost the same concentration until 2 h, and AQOAT showed twice as high concentration as Tc-5Ew at 4 h. On the other hand, AQOAT showed the highest concentration from 1 to 2 h in the solvent shift method (Fig. 2). ITZ was precipitated with AQOAT during the evaporation process, and ITZ was gradually released from the precipitant in the evaporation method. Meanwhile the simple decrease in concentration was monitored in the solvent shift method. Thus, it took more time to find AQOAT by the solvent evaporation method than the solvent shift method. As a result, the solvent shift method could find the anti-precipitant in a facile and expeditious manner when compared with the solvent evaporation method.

In a previous report, two disadvantages of the solvent evaporation method were raised (Dai et al., 2008): precipitation during the evaporation process and the necessity of volatile solvents, such as alcohol, acetone, etc., to dissolve the compound. However, these two disadvantages were resolved in the solvent shift method. There is no precipitation of the starting material because the evaporation process is removed. In the previous report, the physical stability of the formulation could be simultaneously evaluated through the evaporation process (Dai et al., 2008). The objective of this study was to develop a method that can find the anti-precipitant for a poorly soluble drug in a facile and expeditious manner. Therefore, the solvent shift method is more suitable than the evaporation method. The second advantage of the solvent shift method is that it is unnecessary to dissolve in volatile solvents. In the solvent shift method, DMSO was used as the pre-solvent and could dissolve ITZ at high concentrations. On the other hand, ITZ was very slightly soluble in the alcohols (the label of Sporanox®). The solvent shift method using SGF (simulated gastric fluid) instead of DMSO was also previously reported for basic compounds (Yamashita et al., 2010). In the case of ITZ, it was impossible to use SGF as the pre-solvent because it was not dissolved in an acidic medium (Table 1). As a result, the solvent shift method is the most suitable method to find a desirable anti-precipitant for poorly soluble compounds.

3.4. The comparison between the solvent shift method and the performance of the solid dispersion

To compare the results of the solvent shift method with the large scale JP paddle method, a dissolution study was carried out. Fig. 4 shows the dissolution profiles of the crystalline powder, Itrizole® (market-available Tc-5Ew-based solid dispersion), the solid dispersion (ITZ/Tc-5Ew, 2/3, w/w) and the solid dispersion (ITZ/AQOAT, 2/3, w/w). AQOAT-based solid dispersion showed higher concentrations than Tc-5Ew-based solid dispersion and the market-available formulation (Itrizole®) from 2 to 4 h. As a result, AQOAT exhibited an anti-precipitant effect rather than Tc-5Ew in the large scale dissolution study and corresponded with the small scale of the solvent shift method.

Market formulations of ITZ (Sporanox®, Itrizole®) were developed as solid dispersions that contained HPMC (the ratio of ITZ/HPMC, 2/3, w/w). In the previous report, HPMC-based solid dispersion enhanced the *in vivo* absorption rather than the crystal (Van Speybroeck et al., 2010), and this result corresponded with that of the solvent shift method. As for *in vivo* performance of HPMC-AS, it was reported that HPMC-AS was not effective in enhancing *in vivo* performance due to its insolubility in the stomach (Van Speybroeck et al., 2010). Anti-precipitant screening using FaSSIF is an effective method for first screening to find an anti-precipitant that would maintain supersaturation of the drug substance in the intestine. After the first screening, further specific evaluation for the feature of the anti-precipitant (such as dissolution in the acidic media and the enhanced formulation of the dissolution rate, etc.) would be necessary.

4. Conclusions

In this study, we examined anti-precipitant screening using the solvent shift method. The objective of this study was to develop a method that could find desirable anti-precipitants in a facile and expeditious manner. In a previous report, the solvent evaporation method (solvent casting method) was reported with two disadvantages: precipitation of the drug during the evaporation process and the necessity of volatile solvents to dissolve compounds. The solvent shift method using simulated gastric fluid was also reported for basic compounds, though this method was not applicable for poorly soluble compounds in an acidic medium. The solvent shift method resolved these disadvantages and found AQOAT as the anti-precipitant in a simpler way and a shorter time than the solvent evaporation method. AQOAT also showed the anti-precipitant effect in the large scale dissolution study, so the result of the solvent shift method corresponded with that of the large scale study. The result of the solvent shift method will be a useful indicator for the formulation strategy in the early stages of drug development.

Acknowledgements

We thank all the staff members of the analytical research section at Tsukuba Research Laboratory (Eisai Co. Ltd.) for the discussion of this work.

References

Bard, B., Martel, S., Carrupt, P.A., 2008. High throughput UV method for the estimation of the thermodynamic solubility and the determination of the solubility in biorelevant media. Eur. J. Pharm. Sci. 33, 230–240.

Bevernage, J., Brouwers, J., Clarysse, S., Vertzoni, M., Tack, J., Annaert, P., Augustijns, P., 2010. Drug supersaturation in simulated and human intestinal fluids representing different nutritional states. J. Pharm. Sci. 99, 4525–4534.

Brouwers, J., Brewster, M.E., Augustinjns, P., 2009. Supersaturating drug delivery systems: the answer to solubility-limited oral bioavailability? J. Pharm. Sci. 98, 2549–2572.

Dai, W.G., Pollock-Dove, C., Dong, L.C., Li, S., 2008. Advanced screening assays to rapidly identify solubility-enhancing formulations: high-throughput, miniaturization and automation. Ad. Drug Deliv. Rev. 60, 657–672.

DiNunzio, J.C., Hughey, J.R., Brough, C., Miller, D.A., Williams III, R.O., McGinity, J.W., 2010. Production of advanced solid dispersions for enhanced bioavailability of itraconazole using KinetiSol® Dispersing. Drug Dev. Ind. Pharm. 36, 1064–1078.

Gao, P., Rush, B.D., Pfund, W.P., Huang, T., Bauer, J.M., Morozowich, W., Kuo, M., Hageman, M.J., 2003. Development of a supersaturable SEDDS (S-SEDDS) formulation of paclitaxel with improved oral bioavailability. J. Pharm. Sci. 92, 2386–2398.

Gao, P., Guyton, M.E., Huang, T., Bauer, J.M., Stefanski, K.J., Lu, Q., 2004. Enhanced oral bioavailability of a poorly water-soluble drug PNU-91325 by supersaturatable formulations. Drug Dev. Ind. Pharm. 30, 221–229.

Kerns, E.H., Di, L., 2004. Physicochemical profiling: overview of the screens. Drug Discov. Today Technol. 1, 343–348.

Kushida, I., Ichikawa, M., Asakawa, N., 2002. Improvement of dissolution and oral absorption of ER-34122, a poorly water-soluble dual 5-lipoxygenase/cyclooxygenase inhibitor with anti-inflammatory activity by preparing solid dispersion. J. Pharm. Sci. 91, 258–266.

Lipinski, C., 2000. Drug-like properties and the causes of poor solubility and poor permeability. J. Pharmacol. Toxicol. Methods 44, 235–249.

Martin, Y.C., 2005. A bioavailability score. J. Med. Chem. 48, 3164–3170.

Shanbhag, A., Rabel, S., Nauka, E., Casadevall, G., Shivanand, P., Eichenbaum, G., Mansky, P., 2008. Method for screening of solid dispersion formulations of low-solubility compounds-miniaturization and automation of solvent casting and dissolution testing. Int. J. Pharm. 351, 209–218.

Six, K., Daems, T., Hoon, J.D., Van Hecken, A., Depre, M., Bouche, M.P., Prinsen, P., Verreckd, G., Peeters, J., Brewster, M.E., Van den Mooter, G., 2005. Clinical study of solid dispersions of itraconazole prepared by hot-stage extrusion. Eur. J. Pharm. Sci. 24, 179–186.

Van Speybroeck, M., Mols, R., Mellaerts, R., Thi, T.D., Martens, J.A., Van Humbeeck, J., Annaert, P., Van den Mooter, G., Augustijns, P., 2010. Combined use of ordered mesoporous silica and precipitation inhibitors for improved oral absorption of the poorly soluble weak base itraconazole. Eur. J. Pharm. Biopharm. 75, 354–365.

Varma, M.V.S., Panchagnula, R., 2005. Enhanced oral paclitaxel absorption with vitamin E-TPGS: effect on solubility and permeability in vitro. Eur. J. Pharm. Sci. 25, 445–453.

Verreck, G., Six, K., Van den Mooter, G., Baert, L., Peeters, J., Brewster, M.E., 2003. Characterization of solid dispersions of itraconazole and hydroxypropylmethylcellulose prepared by melt extrusion. Int. J. Pharm. 251, 165–174.

Waterbeemd, H.V.D., Smith, D.A., Beaumont, K., Walker, D.K., 2001. Property-based design: optimization of drug absorption and pharmacokinetics. J. Med. Chem. 44, 1313–1333.

Yamashita, K., Nakate, T., Okimoto, K., Ohike, A., Tokunaga, Y., Ibuki, R., Higaki, K., Kimura, T., 2003. Establishment of new preparation method for solid dispersion formulation of tacrolimus. Int. J. Pharm. 267, 79–91.

Yamashita, T., Kokubo, T., Zhao, C., Ohki, Y., 2010. Antiprecipitant screening system for basic model compounds using bio-relevant media. JALA 15, 306–312.