Improved Dissolution of Dipyridamole with the Combination of pH-Modifier and Solid Dispersion Technology

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The aim of this study was to develop a pH-independent release formulation of dipyridamole (DP) by the combined use of pH-modifier technology and solid dispersion (SD) technology employing enteric polymer, Eudragit® S100 (Eud). Tartaric acid (TA) was selected as an appropriate pH-modifier in terms of improving the dissolution behavior of DP under neutral conditions. Upon optimization of the ratio of TA to DP, SD of DP with Eud and TA (SD-Eud/DP/TA) was prepared by a freeze-drying method. Scanning electron microscopic images revealed that DP was dispersed in the polymer in SD-Eud/DP/TA, and DP in SD-Eud/DP/TA was in an amorphous state, supported by powder X-ray diffraction and differential scanning calorimetry analyses. The dissolution behavior of SD-Eud/DP/TA was not dependent on the pH of the medium, although SD-Eud/DP exhibited very limited dissolution behavior under neutral conditions. Spectroscopic analysis suggested that there might be inter-molecular interaction among DP, TA and enteric polymer in SD-Eud/DP/TA, possibly leading to the stable pH-independent dissolution behavior of SD-Eud/DP/TA. TA in SD-Eud/DP/TA promoted the degradation of DP, suggesting that improving the stability of DP in SD-Eud/DP/TA might be key for its practical use. From these results, pH-independent dissolution behavior of SD-Eud/DP/TA could be achieved by an enteric polymer-based solid dispersion with a pH-modifier.

Key words dipyridamole; dissolution; enteric polymer; pH-modifier; solid dispersion

Recently, a lot of drug candidates with poor solubility have been developed and such drugs constituted about 40% of all drug products.1) In many cases, low solubility or slow dissolution of a poorly soluble drug in the gastrointestinal (GI) tract causes insufficient absorption of the drug for treatment. In order to improve the dissolution rate and solubility of poorly soluble drugs, various solubilization technologies have been developed, including amorphization, reduction of particle size, emulsification and solid dispersion (SD).3) However, these technologies might not always be effective for improving the dissolution behavior of drugs with pH-dependent solubility.3) Weak basic drugs are one included among pH-dependent soluble drugs, and exhibit high solubility under gastric pH conditions, but low solubility under intestinal pH conditions. Such pH-dependent solubility of weak basic drugs leads to high variability of absorption among individuals with different GI pH conditions.4) It has been reported that pH-modifier technology could effectively improve the dissolution of drugs with pH-dependent solubility.5) A pH-modifying agent could change the microenvironmental pH of the drug particles to a lower or higher pH at which the drug could dissolve easily.6) In order to improve the dissolution behavior of weak basic drugs, organic acids have been used as pH-modifying agents.7)

Dipyridamole [2,6-bis(diethanolamino)-4,8-dipiperidinopyrimido[5,4-d]pyrimidine] (DP), widely used as an antiplatelet for its attractive antithrombotic properties, is also a weak basic drug with relatively low solubility under neutral conditions, compared with its solubility under acidic conditions. In a previous study, pH-modifier technology was highly effective for improving the dissolution behavior of DP under neutral conditions, and the pharmacokinetic (PK) profile of DP in hypochlorhydric rats was also improved.8) However, even if the dissolution behavior of weak basic drugs under intestinal conditions could be improved by pH-modifying technology, the dissolution behavior of basic drugs can drastically change by the transition of pH conditions between stomach and intestine due to the pH-dependent solubility of the drug,9) possibly leading to poor and/or inconsistent oral absorption behavior. Thus, a stable dissolution profile at absorption site achieved by pH-independent dissolution character might be one of the key factors for the consistent oral absorption and pharmacological effect of DP. Several studies have revealed that solid dispersion with enteric polymer could control the dissolution rate of weak basic drugs under acidic conditions to avoid the precipitation of drug crystal caused by pH changes in GI tract.10)

The aim of the present study is development of pH-independent release formulation of DP with a combination of pH-modifier technology and SD technology with enteric polymer for achieving the stable dissolution behavior. An appropriate organic acid for pH-modification was selected by dissolution testing on DP granules with various acids. Eudragit® S100-based SD formulation of DP (SD-Eud/DP) with tartaric acid (SD-Eud/DP/TA) was prepared by a freeze-drying method. Eudragit® S100 was selected as a carrier polymer for solid dispersion of DP since it is widely used as a typical enteric polymer with wide safety margin in pharmaceutical research and has the wide applicability to solid dispersion systems.11) The morphology of each DP formulation was confirmed by

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scanning electron microscopy (SEM). The crystallinity of DP in each formulation was assessed by powder X-ray diffraction (PXRD) analysis and differential scanning calorimetry (DSC) for thermal behavior. The stability profile of DP in SD-Eud/DP/TA was investigated under stress conditions. Dissolution testing was conducted to confirm the pH-independent dissolution behavior of SD-Eud/DP/TA. Fourier transform IR (FT-IR) spectroscopic analysis was also carried out to investigate the possible interaction among DP, polymer and tartaric acid in SD-Eud/DP/TA.

**Experimental**

**Chemicals** Crystalline DP (purity: 99.5%) was supplied from Boehringer Ingelheim GmbH (Ingelheim, Germany). Amorphous DP was obtained by amorphization of crystalline DP using a freeze-drying method. Briefly, 5 mg of crystalline DP was dissolved in 1 mL of dimethyl sulfoxide (DMSO) and the solution was freeze-dried using an FD-81 freeze-drier (Tokyo Rikakikai, Tokyo, Japan). Hydroxypropyl cellulose (HPC) was purchased from IMCD Deutschland GmbH & Co., KG (Cologne, Germany). Mannitol was purchased from Roquette GmbH (Frankfurt, Germany). DMSO, p-toluenesulfonic acid monohydrate (TS) and l-tartaric acid (TA) were purchased from WakoPure Chemical Industries, Ltd. (Osaka, Japan). Adipic acid (AA) was provided by Asahi Kasei Corporation (Tokyo, Japan). Citric acid monohydrate (CA) was purchased from Jungbunzlauer Ladenburg GmbH (Ladenburg, Germany). dl-Malic acid (MLI) was provided by Showa Kasei Corporation (Osaka, Japan). Succinic acid (SA) was provided by Kawasaki Kasei Chemicals Ltd. (Kawasaki, Japan). l-Aspartic acid (D) and l-glutamic acid (E) were provided by Kyowa Hakko Bio Co., Ltd. (Tokyo, Japan). Eudragit® S100 was purchased from Evonik Industries (Essen, Deutschland). Erythritol was purchased from Nikken Chemical (Tokyo, Japan). All other chemicals were purchased from commercial sources.

**Preparation of DP Granules** DP granules with or without acidic pH-modifier were prepared by conventional wet granulation. Crystalline DP (15 wt%) and mannitol (70 wt%) and acid (15 wt%) were mixed and 5% HPC solution was added into the mixture, followed by granulation of the mixture with a mortar and pestle. Mannitol and HPC were added into DP granules as an excipient and binder, respectively. The wet granules were dried 60°C using a vacuum drying oven, DP23 (Yamato Scientific Co., Ltd., Tokyo, Japan), for 2 h. The dried granules were passed through a 1 mm mesh screen. To optimize the amount of pH-modifier in the DP granules, the dried granules were passed through a 1 mm mesh screen. To optimize the ratio of pH-modifier to DP was changed from 0.5 : 1 to 2 : 1.

**Preparation of Solid Dispersion of DP with TA (SD-Eud/DP/TA)** Crystalline DP (15%), TA (15%) and Eudragit® S100 (70%) were dissolved in DMSO (5 mg/DP/mL). The solution was frozen at −80°C and freeze-dried using an FD-81 freeze-dryer (Tokyo Rikakikai, Tokyo, Japan). Solid dispersion of DP without acid (SD-Eud/DP) and polymeric carrier (DP/TA) were also prepared by the same method as a reference formulation.

**Scanning Electron Microscopy (SEM)** Representative scanning electron microscopic images of DP samples were taken using a scanning electron microscope, VE-7800 (Keyence Corporation, Osaka, Japan), without Au or Pt coating. For the SEM observations, each sample was fixed on an aluminum sample holder using double-sided carbon tape.

**PXRD** The PXRD pattern was collected using D8 ADVANCE (Bruker AXS GmbH, Karlsruhe, Germany) with CuKα radiation generated at 40 mA and 35 kV. Data were obtained from 4º to 40º (2θ) at a step size of 0.014º and scanning speed of 4º/min.

**Thermal Analysis** DSC was performed using a DSC Q1000 (TA Instruments, New Castle, DE, U.S.A.). The DSC thermograms were collected in an aluminum close-pan system using a sample weight of about 3 mg and a heating rate of 5°C/min with nitrogen purge at 70 mL/min. The temperature axis was calibrated with indium (about 5 mg, 99.999% pure, onset at 156.6°C).

**Dissolution Testing of DP Formulations** For screening of pH modifiers, dissolution testing was carried out by the paddle method in 900 mL of 50 mM sodium phosphate buffer (NaPB) (pH 6.8) with constant stirring at 50 rpm in a dissolution test apparatus, NTR 6100 A (Toyama Sangyo, Osaka, Japan), at 37°C. For screening of pH modifiers, DP granule containing 25 mg of DP was weighed into 900 mL of dissolution medium (4.6-times of equilibrium solubility). For the optimization of formulation, DP granule containing 25 mg of DP was added into 900 mL of dissolution medium (4.6-times of equilibrium solubility). Samples were measured at the indicated times with an automatic UV flow cell at 298 nm for 50 mM NaPB (pH 6.8).

Dissolution testing of SD-Eud/DP/TA was also carried out in 50 mL of HCl solution (pH 1.2) or 50 mM NaPB (pH 6.8) with constant stirring at 50 rpm using a magnetic stirrer SST-66. The total amount of DP was adjusted to 2.8 mg in a beaker, equal to 9.3-times the equilibrium solubility at pH 6.8. Samples were diluted with acetonitrile by 2-fold and measured with a plate reader at a UV wavelength of 405 nm.

**FT-IR Spectroscopic Analyses** Powder samples were prepared by mixing approximately 2 to 3 mg with approximately 300 mg of KBr, and the mixture was pressed for preparation of a KBr disk. Spectra were recorded on IR Prestige-21 with IR solution software (Shimadzu, Kyoto, Japan), and 40 scans were performed with a resolution of 4 cm⁻¹.

**Stability Testing** For the stability testing, each DP formulation sample including 2 mg of DP was weighed and poured into a 25 mL closed amber bottle made of glass. The samples were stored at 40±2°C for 4 weeks in a stability chamber (Labcare Pvt. Ltd., Mumbai, India). After storage, the remaining DP was determined using a Waters Acquity ultra performance liquid chromatography (UPLC) system (Waters, Milford, MA, U.S.A.), which included binary solvent manager, sample manager, column compartment and SQD connected with MassLynx software. An Acquity UPLC BEH C 18 column (particle size: 1.7 µm, column size: 2.1×50 mm; Waters) was used, and the column temperature was maintained at 40°C. The sample was separated using a gradient mobile phase consisting of acetonitrile (A) and 5 mM ammonium acetate (B) with a flow rate of 0.25 mL/min. The gradient conditions of the mobile phase were 0–0.5 min, 40% A; 0.5–2.5 min, 40–95% A; 2.5–3.0 min, 95% A; and 3.0–3.5 min, 40% A. The peak for DP was detected at a retention time of 1.53 min. Analysis was carried out using selected ion recording (SIR) for specific m/z 429 and 505 for DP. The method was validated with respect to specificity, precision, accuracy and linearity in accordance with International Council for
Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guidelines (Q2B Validation of Analytical Procedures: Methodology).

Results and Discussion

Dissolution Behavior of DP Granules with Various pH-Modifiers

Theoretically, a pH-modifier could improve the dissolution behavior of weak basic drugs; for example, DP granules with the use of TS improved the dissolution behavior of DP under neutral conditions. In the present study, DP granules with various acidic pH-modifiers were prepared and subjected to dissolution testing to select a suitable organic acid as a pH-modifier. Dissolution testing in 50 mm NaPB (pH 6.8) of DP granules with various levels of each pH modifier was conducted for screening purposes (Fig. 1). The maximum drug concentration of DP granules with no acid was under 6 µg/mL at the observation time, which is the same value as the reported solubility of DP at pH 6.8. DP granules with D, E, AA and SA showed little improvement in the dissolution behavior, compared with DP granules with no acid. On the other hand, DP granules with CA, FA, MLI, TA, and TS showed highly improved dissolution behavior of DP at pH 6.8, and the supersaturation levels of these DP granules were found to be over 3-times higher than the original solubility of DP. The effect of pH modifier on the improvement of dissolution behavior of weak basic compound could depend on the acidity of the pH modifier. The pH values of CA, FA, MLI, TA, and TS in each saturated solution are lower than 2, and that of other pH modifiers including AA, SA, D, and E are above 2.5. Thus, there are relatively better dissolution behavior of DP granule with CA, FA, MLI, TA, and TS. In particular, DP granules with CA and TA exhibited around 4-times the supersaturation level, and DP granules with TA showed the highest drug concentration level among all tested DP granules. According to the results from dissolution testing on DP granules, DP granules with TA was selected as the most effective pH modifier among all tested organic acids. There were negligible changes of pH value in dissolution medium during dissolution testing of all DP granules (data not shown), suggesting the achievement of micro-environmental pH modification.

To optimize the ratio of TA to DP granules, another dissolution test was carried out on DP granules with various concentrations of TA (Fig. 2). The maximum DP concentration in the test medium of each DP granules with TA was higher than the equilibrium solubility of DP, and the supersaturation level depended on the ratio of TA to DP granules. DP granules with a TA ratio of 1 and 2 to DP demonstrated almost similar dissolution behavior, although the dissolved concentration in DP granules with a TA ratio of 2 to DP was slightly higher than that in DP granules with a TA ratio of 1 to DP. Generally, less excipient is preferable, considering the manufacturability and developability. Herein, the appropriate TA ratio to DP in DP granules was selected to be 1.

Physicochemical Properties of SD-Eud/DP/TA

SD-Eud/DP/TA was prepared with an optimized ratio of TA to drug, which was set according to the results from the dissolution testing of DP granules with TA under neutral conditions. The physicochemical properties of DP formulations were characterized by SEM (Fig. 3) and crystallinity assessment (Fig. 4). Crystalline DP appeared as plate-shaped particles in SEM images (Fig. 3-I). In contrast, DP particles were negligible in SD-Eud/DP (Fig. 3-II) and SD-Eud/DP/TA (Fig. 3-III), and the surface of these two formulations was textured. These findings may suggest that micronized DP was dispersed in the polymer in SD-Eud/DP or SD-Eud/DP/TA after lyophilization. PXRD (Fig. 4A) and DSC (Fig. 4B) analyses were also carried out to clarify the molecular state of inner DP. PXRD analysis revealed that crystalline DP retained a single crystalline form, suggested by the intrinsic PXRD pattern of crystalline DP. SD-Eud/DP also exhibited small diffraction peaks with different pattern from crystalline DP used in the present study possibly due to the formation of crystal polymorph of DP during freeze-drying process, since the crystal form of DP can be variable depending on the solvent for recrystallization. On the other hand, the halo pattern of SD-Eud/DP/TA in the PXRD pattern indicated that the amorphization of DP might have occurred in each SD formulation. In the DSC thermogram, crystalline DP showed a melting endotherm at about 168°C, which is almost the same as that in previous reports. SD-Eud/DP and SD-Eud/DP/TA did not exhibit any thermal events related to crystallinity changes of DP in the measuring range. The endothermic peaks observed at above 180°C could

Fig. 1. Dissolution Profiles of DP Granules at pH 6.8

DP granules with △, no acid; ○, TA; ▼, CA; ■, MLI; ▲, TS; △, FA; ◤, AA; ◀, SA; ◥, D; □, E. Degrees of supersaturation are expressed as measured concentration of dissolved DP (C) vs. equilibrium solubility of DP (Cs). Each bar represents the mean±S.E. of 3 independent experiments.

Fig. 2. Dissolution Profiles of DP Granules with Various TA Concentrations at pH 6.8

△, DP : TA = 1 : 0; ▼, 1 : 0.5; ◤, 1 : 1; and ◥, 1 : 2. Each bar represents the mean of 3 determinations.
be derived from thermal degradation of Eudragit® S100.15) The transition of endothermic peak might be an indicator that DP in SD-Eud/DP and SD-Eud/DP/TA is in a high energy amorphous state, in accordance with the PXRD data. Generally, the high energy amorphous state of a drug leads to supersaturation over the equilibrium solubility of a crystalline drug.16) Therefore, amorphization of DP in SD-Eud/DP and SD-Eud/DP/TA may have resulted in improved dissolution behavior under neutral conditions, at which the solubility of crystalline DP is low.

**Dissolution Behavior of SD-Eud/DP/TA** The dissolution behavior of SD-Eud/DP/TA was confirmed by dissolution testing under acidic and neutral condition (Fig. 5). Under acidic condition (pH 1.2), the dissolution behavior of crystalline DP was preferable, due to the high solubility of DP under such acidic conditions. On the other hand, SD-Eud/DP showed a low drug release rate, and the drug concentration was under 1µg/mL on average in the first 10 min. Eudragit® S100 is an enteric polymer, so its solubility is limited in acidic medium. Therefore, the release of DP from the SD-Eud/DP might have been interfered with by the poor dissolution property of Eudragit® S100. Compared with that of SD/DP, the dissolution behavior of SD-Eud/DP/TA was highly improved. Generally, a pH-modifier in an oral formulation could assist in adjusting the microenvironmental pH conditions at the surface of a drug to achieve better dissolution behavior. In the present study, TA could change the microenvironmental pH of DP in SD-Eud/DP/TA, resulting in rapid dissolution of DP, even when surrounded by enteric polymer. In 50mM NaPB (pH 6.8), DP and SD-Eud/DP exhibited very limited dissolution behavior and, even 120 min after the start of the dissolution test, the drug concentration was under 5µg/mL, due to the low solubility of DP under neutral conditions. In the SD-Eud/DP/TA system, TA might change the microenvironmental pH of DP to a lower level at which DP can dissolve more easily than at the pH of dissolution media without changing pH value of test medium. Therefore, as compared with DP and SD-Eud/DP, SD-Eud/DP/TA exhibited improved dissolution behavior of
DP in 50 mM NaPB (pH 6.8). Although the dissolved amount of DP in SD-Eud/DP/TA at pH 6.8 was much higher than that of DP and SD-Eud/DP as evidenced by DP concentration of ca. 30 µg/mL (ca. 54% dissolution of applied DP amount), further optimization of the formulation might be necessary for complete dissolution of DP. There was little difference in the dissolution behavior of SD-Eud/DP/TA between acidic and neutral media, suggesting that SD-Eud/DP/TA achieved pH-independent dissolution in spite of the weak basicity of DP.

**Interaction between DP and Polymer in SD-Eud/DP/TA**

The interaction of drug and polymer in SD formulation could give rise to attractive effects, including enhancement of the supersaturation of a drug, suppression of the precipitation of a drug, and stabilization of the amorphous state of a drug in SD. FT-IR spectroscopic analysis was performed in order to investigate the possible interaction between DP and polymer in SD-Eud/DP/TA (Fig. 6). Between 1300 and 1700 cm⁻¹, the peaks derived from C–N bonds (1360 cm⁻¹) and C=N ring (1540 cm⁻¹) of DP were observed in crystalline and amorphous DP. In contrast, the intensities of the absorption band in this region were decreased for SD-Eud/DP and SD-Eud/DP/TA compared with those for crystalline and amorphous DP, possibly due to the electrostatic interaction of carbonyl group in Eudragit® S100 with the C–N and/or O–H bond in DP. These results are corresponding to the previous report on the NMR analysis of molecular interaction between the carboxylic function of Eudragit® S100 and the nitrogen...
atom of DP. TA has the potential to form electrostatic interaction with DP owing to the existence of hydrogen bonding donors like carboxylic and hydroxyl groups in TA structure, resulting in the transition of the C–N and C=N stretch band of DP. Crystalline and amorphous DP also exhibited a strong absorption band between 2900 and 2950 cm⁻¹ derived from the stretching vibrations of the C–H bond of the piperidine unit in DP. Although Eudragit® S100 and TA did not exhibit an absorption band in that region, a slight transition was observed in SD-Eud/DP/TA to a higher wavenumber, but was not observed in SD-Eud/DP. These observations may indicate suppression of the stretching vibration of the C–H bond of the piperidine unit in DP, due to interaction with Eudragit® S100. When the binary component system composed of DP and TA was prepared, phase separation of components was observed after freeze-drying process, possibly suggesting the importance of polymer matrix for improving the miscibility of components in solid dispersion.

As shown in Fig. 5, although SD-Eud/DP exhibited very limited dissolution of DP in both pH 1.2 and 6.8 solution possibly due to the interaction between DP and Eudragit® S100 to prevent the DP release, the dissolution behavior of SD-Eud/DP/TA was better than that of SD-Eud/DP in both solution. This might have induced by the changes of interactions between DP, TA, and Eudragit® S100. TA could act as a pH-modifier in SD-Eud/DP/TA, so the possible interaction between DP and TA observed by FT-IR spectroscopy corresponds to the pH-modifying effect by TA.

Stability Profile of DP in SD-Eud/DP/TA

Organic acids sometimes decrease the chemical stability of a drug in formulation, due to acidic degradation or the promotion of hydrolysis of the drug. To clarify the possible influence of TA on the degradation profile of DP in SD-Eud/DP/TA, stability testing was conducted at 40°C for 4 weeks (Table 1). Crystal-line DP and SD-Eud/DP did not show significant degradation at least for 4 weeks of storage, and only 6% of DP degraded. On the other hand, DP in SD-Eud/DP/TA exhibited a strong degradation profile under stressed conditions. There was about 19% DP degradation after 2 weeks of storage, and the next 2 weeks led to about 24% degradation of DP in SD-Eud/DP/TA in total. This instability of DP in SD-Eud/DP/TA under accelerated conditions suggests that DP degradation caused by TA needs to be suppressed through the application of some formulation technology for the clinical use of SD-Eud/DP/TA. The degradation of DP could be mainly attributed to the hydrolysis by TA, so that the addition of desiccant could be effective way to prevent the degradation of DP.

Conclusion

In the present study, SD-Eud/DP/TA was developed with the combination of pH-modifier technology and solid dispersion technology. TA is the most promising pH-modifier among the tested organic acids for improving the dissolution behavior of DP in neutral conditions, and an appropriate ratio of TA to DP is determined to be 1:1, considering the improvement of dissolution behavior of DP. Although the solubility of DP is very poor in neutral conditions, SD-Eud/DP/TA showed pH-independent dissolution behavior. From the FT-IR spectroscopic analysis, the possible interaction among DP, Eudragit® S100 and TA might be attributable to the pH-independent dissolution behavior of SD-Eud/DP/TA. DP in SD-Eud/DP/TA was found not to be stable because of the added TA. In terms of clinical use, it is important to improve the stability of DP in SD-Eud/DP/TA. From these results, newly developed SD-Eud/DP/TA exhibited pH-independent dissolution of DP, and this technology could be useful for improving the dissolution behavior of other weak basic drugs.

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Conflict of Interest

The authors declare no conflict of interest.

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