Difference in the Dissolution Behaviors of Tablets Containing Polyvinylpolypyrrolidone (PVPP) Depending on Pharmaceutical Formulation After Storage Under High Temperature and Humid Conditions

Yoh Takekuma, Haruka Ishizaka, Masato Sumi, Yuki Sato, Mitsuru Sugawara.

Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan.

Received, August 25, 2016; Revised, November 25, 2016; Accepted, December 9, 2016; Published, December 11, 2016.

ABSTRACT PURPOSE. Storage under high temperature and humid conditions has been reported to decrease the dissolution rate for some kinds of tablets containing polyvinylpolypyrrolidone (PVPP) as a disintegrant. The aim of this study was to elucidate the properties of pharmaceutical formulations with PVPP that cause a decrease in the dissolution rate after storage under high temperature and humid conditions by using model tablets with a simple composition. **METHODS.** Model tablets, which consisted of rosuvastatin calcium or 5 simple structure compounds, salicylic acid, 2-aminodiphenylmethane, 2-aminobiphenyl, 2-(*p*-tolyl)benzoic acid or 4.4'-biphenol as principal agents, cellulose, lactose hydrate, PVPP and magnesium stearate as additives, were made by direct compression. The model tables were wrapped in paraffin papers and stored for 2 weeks at 40°C/75% relative humidity (RH). Dissolution tests were carried out by the paddle method in the Japanese Pharmacopoeia 16th edition. **RESULTS.** Model tablets with a simple composition were able to reproduce a decreased dissolution rate after storage at 40°C/75% RH. These tablets showed significantly decreased water absorption activities after storage. In the case of tablets without lactose hydrate by replacing with cellulose, a decreased dissolution rate was not observed. Carboxyl and amino groups in the structure of the principal agent were not directly involved in the decreased dissolution. 2-Benzylaniline tablets showed a remarkably decreased dissolution rate and 2-aminobiphenyl and 2-(*p*-tolyl)benzoic acid tablets showed slightly decreased dissolution rates, though 4,4'-biphenol tablets did not show a decrease dissolution rate. **CONCLUSIONS.** We demonstrated that additives and structure of the principal agent were involved in the decreased in dissolution rate for tablets with PVPP. The results suggested that one of the reasons for a decreased dissolution rate was the inclusion of lactose hydrate in tablets. The results also indicated that compounds as principal agents with low affinity for PVPP may be easily affected by airborne water under high temperature and humid conditions.

INTRODUCTION

Tablets have been widely used because of their superior portability and usability. Tablets contain some additives such as excipients, binders and lubricants other than the principal agents. Recently, the market share of generic drugs in Japan has increased to more than 20% due to a national policy, though Japan is still lagging behind Europe and North America. Differences between additives in brand name and generic products are permitted. Therefore, there are many generic drugs that contain different additives from those in brand name drugs, and it is possible that the stabilities of brand name and generic products are different. Therefore, we previously evaluated the stabilities of tablets containing various statins, HMG-CoA reductase inhibitors, after blister packs (BP) had been opened. The results demonstrated that the dissolution rates for several brand name and generic tablets decreased after storage for more than 6 months at 40°C/75% relative humidity (RH), and these phenomena were observed for all tablets of tested drugs containing polyvinylpolypyrrolidone (PVPP) (1). PVPP is produced by cross-linking polyvinylpyrrolidone (PVP) (2).

It is water-insoluble and has adsorption ability to polyphenolic compounds such as flavonoids.

Corresponding Author: Yoh Takekuma, Ph. D., Faculty of Pharmaceutical Sciences, Hokkaido University Kita-12-jo, Nishi-6-chome, Kita-ku, Sapporo 060-0812, Japan**;** E-mail: y-kuma@pharm.hokudai.ac.jp

Hence, PVPP has been used to remove polyphenolic compounds in wines that may cause undesirable flavor astringency and color (3). In addition, the binding capacity of PVPP for flavonoids increases with an increase in the number of hydroxyl groups on the flavonoid nucleus (4). On the other hand, in the field of pharmaceutical formulation, PVPP has used as a superdisintegrant for orally disintegrating tablets (5) because PVPP has the property of swelling by absorbing water, and its swelling rate is very fast (6).

There have been several studies on dissolution behaviors of tablets containing PVPP after storage under high temperature and humid conditions (7-9); however, the results of those studies are not consistent. Yamazaki *et al*. studies the stabilities of famotidine orally disintegrating tablets of one brand name and six generic drugs (four of the drugs containing PVPP) after BP had been opened and they observed a decrease in the dissolution rate for only one generic drug after storage for more than 4 weeks at 27°C/55% RH (9). These studies indicate that the cause of the decrease in dissolution rate is not only PVPP but also pharmaceutical formulations of tablets; however, it is difficult to clarify the factors causing a decrease in dissolution rate by using commercial drugs because of the variety of compositions including the principal agent composition of commercial tablets.

Hence, the aim of this study was to elucidate the properties of pharmaceutical formulations containing PVPP that cause a decrease in dissolution rate after storage under high temperature and humid conditions by using model tablets with a simple composition. Model tablets containing PVPP with a decreased dissolution rate after storage at 40°C/75% RH were prepared by direct compression, and the effects of differences in additives and structures of the principal agents on dissolution behavior of model tablets were investigated.

MATERIALS AND METHODS

Chemicals and reagents

Rosuvastatin calcium tablets (Crestor tablets) were purchased from AstraZeneca K.K. (Osaka, Japan). PVPP (Kollidon CL) was kindly supplied by BASF Japan Ltd. (Tokyo, Japan). Rosuvastatin calcium, Cellulose Powder (through 400 mesh), salicylic acid and 2-aminobiphenyl were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). 4.4'-Biphenol, 2-(*p*-tolyl)benzoic acid and 2-aminodiphenylmethane were purchased from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). Magnesium stearate and lactose hydrate were obtained from Taihei Chemical Industrial Co., Ltd. (Osaka, Japan) and Yakuhan Pharmaceutical Co., Ltd. (Hokkaido, Japan), respectively. All other reagents were of the highest grade available and used without further purification.

Preparation of model tablets

Rosuvastatin calcium, salicylic acid, 2-aminodiphenylmethane, 2-aminobiphenyl, 2-(*p*-tolyl)benzoic acid and 4.4'-biphenol were used as the principal agents. Rosuvastatin calcium was extracted from grinded Crestor tablets by methanol and evaporated to dryness. Pharmaceutical formulations of model tablets are shown in Table 1. All ingredients were sieved through 100 mesh and weighed as shown in Table 1. Cellulose and lactose hydrate were mixed thoroughly in a mortar, and PVPP and the principal agent were added to the mixture sequentially and mixed. Then magnesium stearate was added through 100 mesh to the mixture and mixed gently. Model tablets (3 mm in diameter, 1.5 mm in thickness, approximately 15 mg in weight) were made from the mixture by using a hand press tableting machine (MP-1 Mini Press, JASCO Corporation, Tokyo, Japan). Model tablets without cellulose or lactose hydrate were made by replacing with lactose hydrate and cellulose, respectively.

Table 1. Basic pharmaceutical formulation of model direct compression tablets

Ingredient	Percentage	Purpose of use
Principal agent	3.3%	
PVPP	0% - 15%	Disintegrant
Cellulose	30%	Binder, excipient
Lactose hydrate	50.7% - 65.7%	Binder, excipient, adjusted to total 100%
Magnesium stearate	1%	Lubricant

Each preparation of mixture of all ingredients before tableting is 5 g or 7 g.
PVPP; polyvinylpolypyrrolidone

Storage condition for model tablets

Tested drugs were wrapped in four tablets by paraffin paper and stored for 2 weeks at 40°C/75% RH. Control tablets were placed in polyethylene bags, and the bags were heat-sealed. They were stored the under same condition.

Dissolution test

Dissolution profiles of model tablets were determined using the paddle method in the Japanese Pharmacopoeia 16th edition (NTR-6200A, Toyama Sangyo Co., Ltd., Osaka, Japan) with a paddle speed of 50 rpm (10). Dissolution was performed in 900 mL purified water at 37°C ± 0.5°C. Four tablets were dropped into each vessel. Samples (each 10 mL) were collected at 2, 5, 10, 15, 30, 45 and 60 min after dropping the tablets, and the same volume of purified water was immediately refilled by using an AUTO SAMPLER-W (Toyama Sangyo Co., Ltd). Collected samples were immediately filtrated through membrane filters (Mixed cellulose ester type membrane filter, pore size: 0.45 μm, 13 mm in diameter, Advantec Toyo Kaisha Ltd., Tokyo, Japan). Drug concentrations of samples were determined by a UV-HPLC method described below.

Measurement of absorption of water into model tablets

Measurement of absorption of water into model tablets was performed using the swelling-water tester reported by Kondo *et al*. with some modifications (11). A 30 mm×30 mm paper filter was placed on top of a polypropylene bottle filled with purified water with a temperature of approximately 20°C. Purified water was added to the bottle using a syringe connected to the lower part of the bottle via a polyethylene tube until the filter paper was completely wet. After excess water had been removed from the filter paper, 6 tablets were placed on the center of the paper filter. The volume of water absorbed into the tablets was measured 30 sec after placing tablets on the paper filter using a graduated pipette at room temperature.

Measurement of moisture contents of model tablets

Moisture contents of control and tested model tablets were measured using a moisture analyzer (LIBROR ED-200MO, Shimadzu Corporation, Kyoto, Japan) after storage for 2 weeks at 40°C/75% RH.

Drug assay

The concentrations of tested drugs (rosuvastatin, salicylic acid, 2-aminobiphenyl, 4.4'-biphenol, 2-(*p*-tolyl)benzoic acid and 2-aminodiphenylmethane) were determined using an HPLC system equipped with an L-7110 pump, L-7300 column oven, L-7420 UV-VIS detector and L-7200 autosampler (HITACHI, Tokyo, Japan). The column for HPLC was an Inertsil ODS-4 (3 mm in inside diameter × 150 mm) (GL Sciences Inc., Tokyo, Japan). Mixtures of 2.5 mM ammonium acetate/acetonitrile (2/1, v/v) for rosuvastatin (1), distilled water/methanol/acetic acid (60/75/1, v/v) for salicylic acid (10) and acetonitrile/distilled water (67/33, v/v) for the other tested drugs (12) were used as mobile phases. Column temperature and flow rate were 40°C and 0.4 mL/min, respectively. The ultraviolet wavelengths for detection were 238 nm for rosuvastatin, 270 nm for salicylic acid and 283 nm for the other tested drugs. Twenty μL of a sample was injected into the HPLC system. The lower limit of quantitation for all tested agents were 0.3 μg/mL. Coefficients of variation were under 10% in the range of 0.3-10 μg/mL (n = 5).

STATISTICAL ANALYSIS

Data are expressed as means with standard deviation (S.D.). Student's *t*-test was used to determine the significance of differences between control and unpacked group in the result of measurement of absorption of water into model tablets. Statistical significance was defined as $p<0.05$.

RESULTS

Effects of PVPP contents in rosuvastatin model tablets on dissolution profiles

It was investigated whether dissolution rates for rosuvastatin model tablets containing 3% PVPP and those not containing PVPP decreased after storage for 2 weeks at 40°C/75% RH (Figure 1). It was observed that the dissolution rate for model tablets with 3% PVPP decreased remarkably in the early phase compared with the dissolution rate for control tablets. Although the dissolution rate for model tablets without PVPP also decreased, the decreased rate was much smaller than that for tablets with 3% PVPP. We also investigated the effects of PVPP contents in rosuvastatin model tablets on dissolution profiles after storage for 2 weeks at 40°C/75% RH.

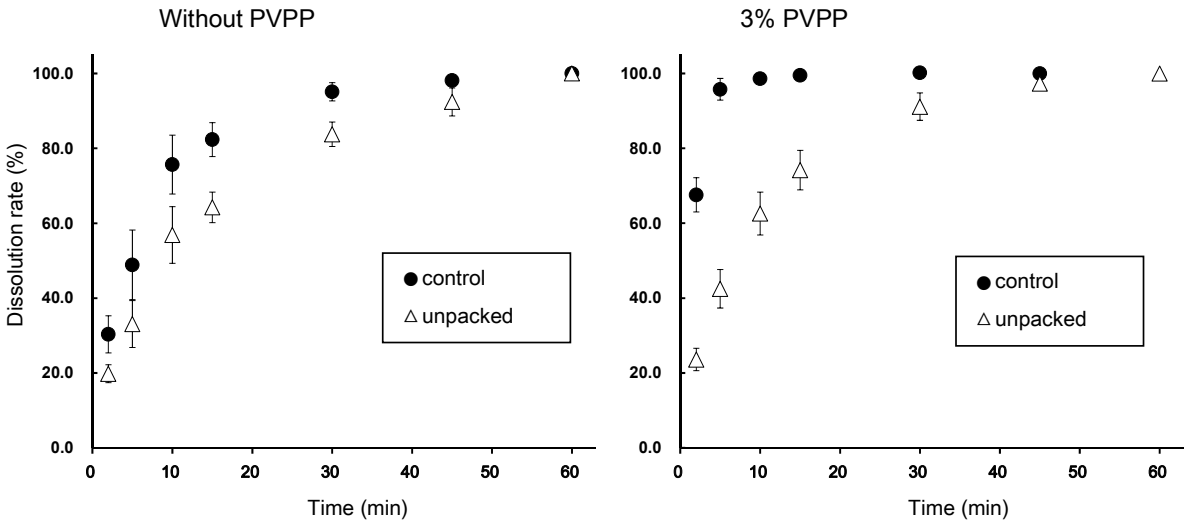

Figure 1. Dissolution profiles of rosuvastatin model tablets containing 3% PVPP (right) and not containing PVPP (left) after storage for 2 weeks at 40°C/75% RH. Four tablets were dropped into each vessel. Each point represents the mean ± S.D. of 6 measurements.

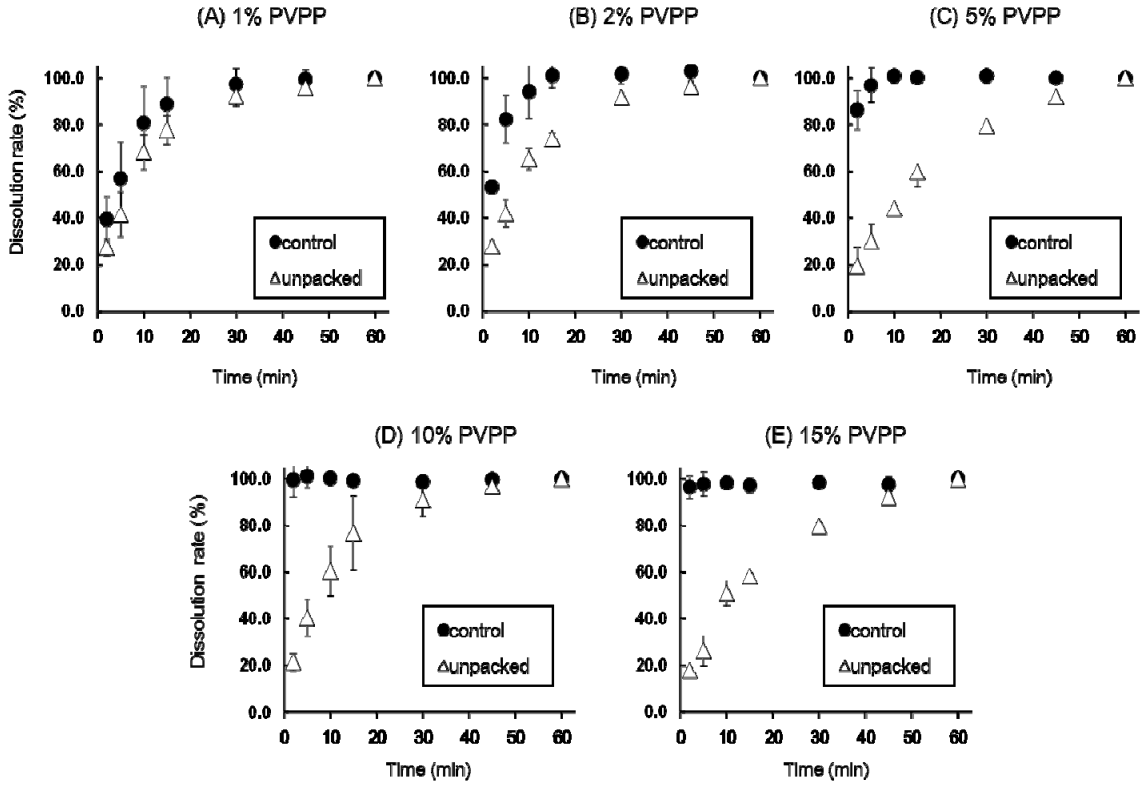

Figure 2. Effects of PVPP contents in rosuvastatin model tablets on dissolution profiles of the tablets after storage for 2 weeks at 40°C/75% RH. Four tablets were dropped into each vessel. Each point represents the mean ± S.D. of 6 measurements.

The results are shown in Figure 2. Dissolution rates for all tested tablets with 1-15% PVPP decreased compared with the dissolution rate for control tablets, and the magnitude of decrease in dissolution rate depended on the PVPP content.

Absorption of water into model tablets

PVPP has the property of swelling by absorbing water, and this property is important for rapid disintegration. We therefore evaluated the water absorption activities of rosuvastatin model tablets with 1-15% PVPP after storage for 2 weeks at 40°C/75% RH (Figure 3). It was found that volume of water absorbed into all tested tablets was significantly decreased compared with that in control tablets. The volume of water absorbed into control tablets with 15% PVPP was much higher than those in the other control tablets. Therefore, the difference in water absorption between control and unpacked tablets with 15% PVPP was remarkably large compared with the others. We also examined moisture contents of tested tablets before measurement of water absorption, but no significant difference was found between control and unpacked tablets with any PVPP content (data not shown). Based on these results, PVPP content in the model tablets was fixed to 10%.

Effects of additives other than PVPP on dissolution profiles for rosuvastatin model tablets

We investigated the effects of additives other than PVPP on dissolution profiles for rosuvastatin model tablets. The model tablets consisted of cellulose, lactose hydrate and magnesium stearate, PVPP and rosuvastatin as the principal agents (Table 1). Hence, we focused on cellulose and lactose hydrate, which were major contents in the model tablets. As shown in Figure 4, dissolution rates for model tablets without cellulose (82% lactose hydrate) after storage for 2 weeks at 40°C/75% RH remarkably decreased compared with the rates for control tablets, though these phenomena were not observed for model tablets without lactose hydrate (82% cellulose).

Effect of structures of the principal agent on dissolution profiles for model tablets

To examine the effects of structures of the principal agent on dissolution profiles for model tablets containing PVPP, rosuvastatin in model tablets was replaced with various compounds with simple structures as the principal agents. Chemical structures of the five tested compounds are shown in Figure 5. The magnitude of decrease in dissolution rate for 2-benzylaniline tablets after storage for 2 weeks at 40°C/75% RH was largest of all tested compounds (Figure 6). On the other hand, a difference in dissolution rate for salicylic acid tablets between control and unpacked tablets was not observed. The dissolution profile of the control of 4,4'-biphenyl tablets was different from the dissolution profiles of other tested compounds. Namely, the dissolution rate for the control of 4,4'-biphenyl tablets was lower than those for the controls of other tested tablets. As a result, a decrease in the dissolution rate for 4,4'-biphenyl tablets was not observed.

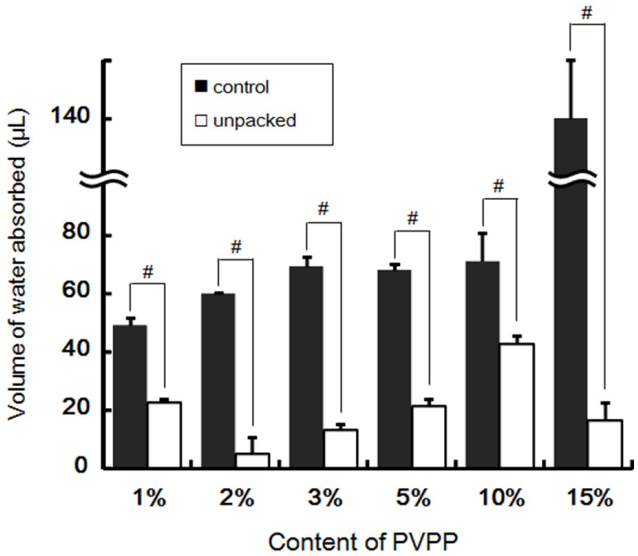

Figure 3. Amounts of water absorbed into rosuvastatin model tablets with various PVPP contents for 30 sec. Each column represents the mean with S.D. of 3-4 measurements. #; $p<0.01$

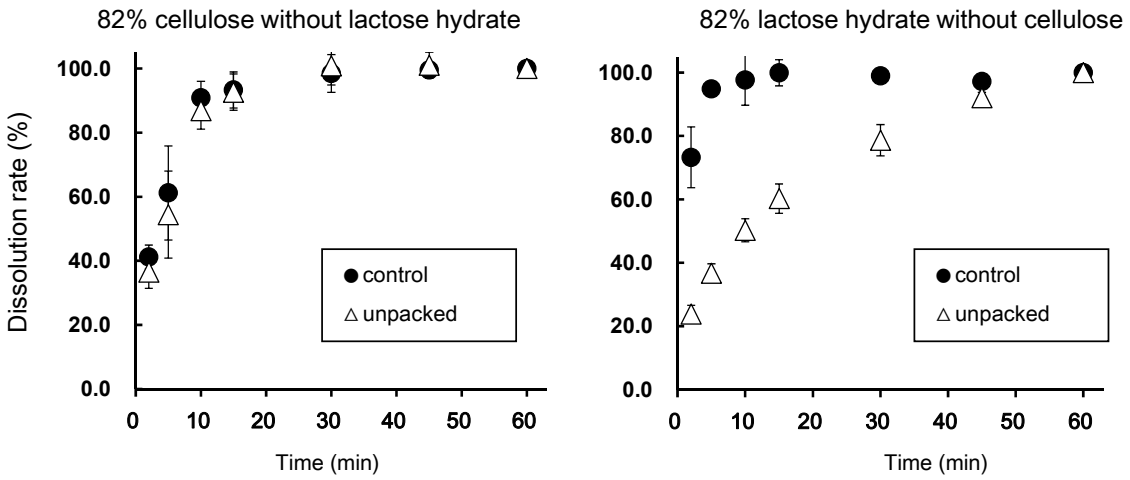

Figure 4. Dissolution profiles of rosuvastatin model tablets containing 10% PVPP without cellulose or lactose hydrate after storage for 2 weeks at 40°C/75% RH. Four tablets were dropped into each vessel. Each point represents the mean ± S.D. of 6 measurements.

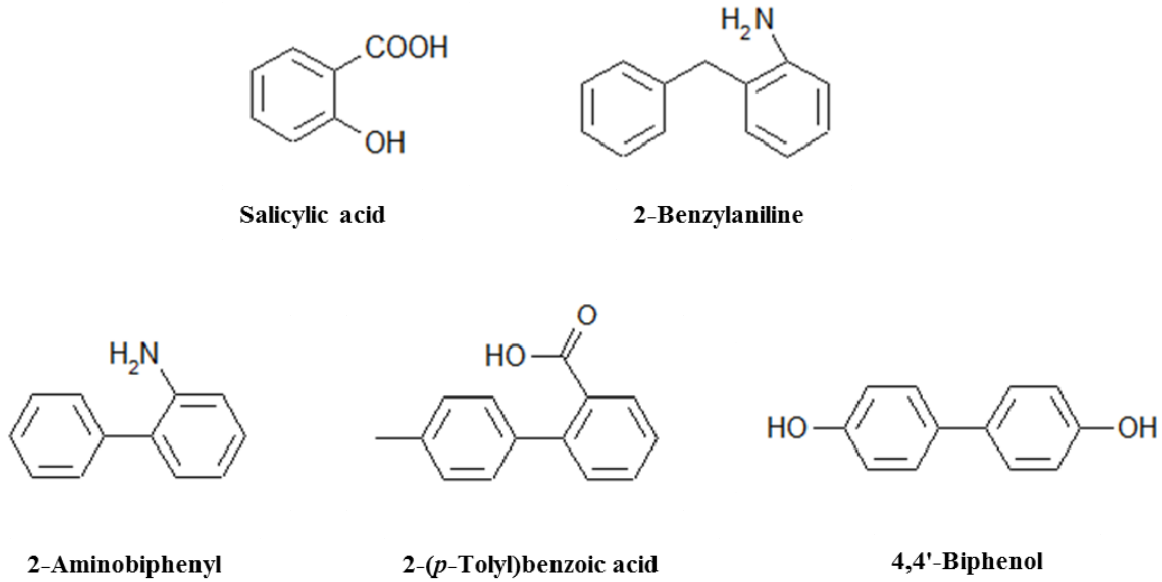

Figure 5. Chemical structures of tested compounds as the principal agents in model tablets containing 10% PVPP.

DISCUSSION

In this study we investigated the effects of differences in pharmaceutical formulations of tablets on dissolution behavior of tablets containing PVPP after storage under high temperature and humid conditions. Several previous studies have shown a decrease in dissolution rate for tablets containing PVPP after storage under high temperature and humid conditions (7, 9), as was shown in our previous study (1); however, conflicting results were also reported (8, 9). The kinds of additives and their contents in commercially available tablets are too variable to examine the effects of differences in pharmaceutical formulations of tablets. We therefore prepared rosuvastatin model tablets with a simple composition. The dissolution rate for the model tablets containing PVPP after storage for 2 weeks at 40°C/75% RH remarkably decreased

compared with the dissolution rate for tablets without PVPP by replacing PVPP with lactose hydrate (Figure 1). These results indicated that it is possible to reproduce changes in dissolution behaviors depending on PVPP content after storage under high temperature and humid conditions using model tablets with a simple composition.

The magnitude of decrease in dissolution rate depended on the PVPP content in the tablets (Figure 2), and all of the tested tablets containing 2-15% PVPP, but not those containing 1% PVPP, could not maintain bioequivalence compared with each control according to criteria in Guidelines for Bioequivalence Studies of Generic Products (13). Conversely, it was clarified that the tablets containing 1% PVPP could maintain bioequivalence after storage at 40°C/75% RH. On the other hand, dissolution profiles of the tested tablets with various PVPP contents after storage at 40°C/75% RH were similar. The dissolution rate for control tablets increased with an increase in PVPP content in the tablets and, as a result, the magnitude of decrease in dissolution rate after storage also increased with an increase in PVPP content. Furthermore, a decrease in the volumes of water absorbed in the tested unpacked tablets with any PVPP content after storage compared with each control was observed. These results indicated that the reason for the decrease in dissolution rate for tablets containing PVPP after storage at 40°C/75% RH was that exposure to high temperature and humid conditions impaired the superior water absorption and disintegration activities of the tablets containing PVPP.

We then examined whether differences in additives or the principal agents in tablets cause a decrease in dissolution rate for tablets containing PVPP after storage under high temperature and humid conditions. We prepared rosuvastatin tablets containing PVPP without cellulose or lactose hydrate. Both cellulose and lactose are widely used as a binder and excipient for preparation of tablets. A decrease in the dissolution rate was observed only for tablets without cellulose (82% lactose hydrate) (Figure 4). It was thought that airborne water hardly affected the tablets without lactose hydrate because lactose is hydrophilic but cellulose is not so hydrophilic.

As for the effect of the principal agent, we examined 5 compounds with simple structures and high melting points (solid at room temperature). We had predicted that the carboxyl group in the principal agents plays an important role in the decrease in dissolution rate since statin-based medicines, for which we previously reported this phenomenon, are anionic compounds.

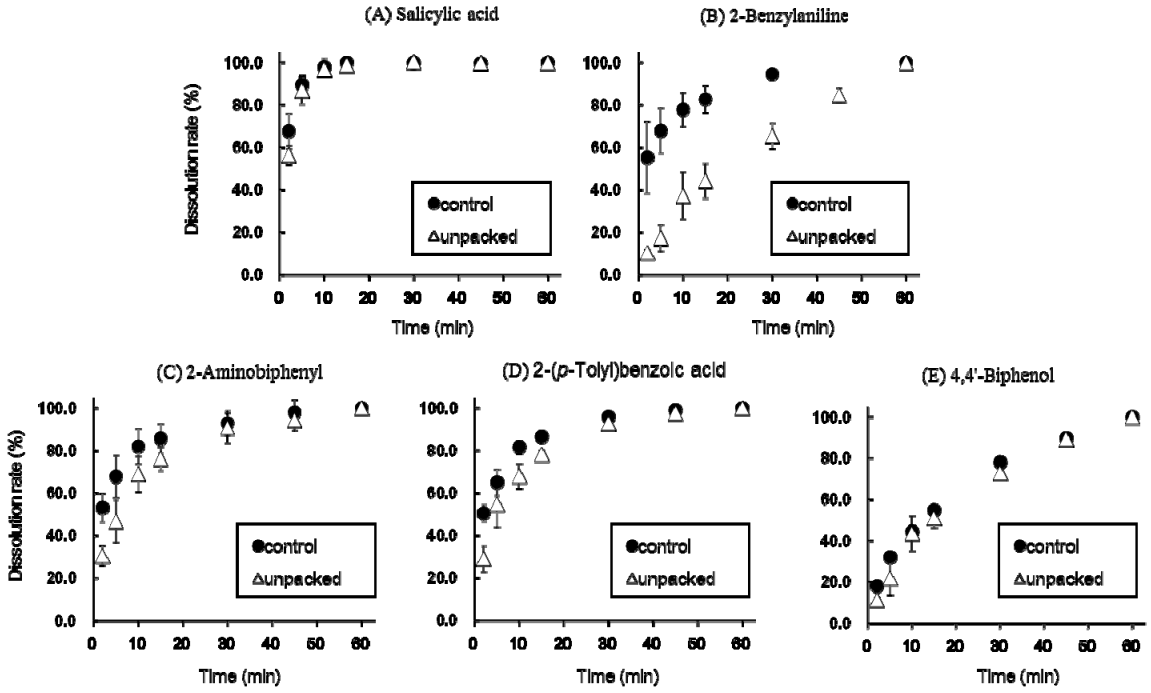

Figure 6. Effects of differences in structures of the principal agents in model tablets containing 10% PVPP on dissolution profiles of the tablets after storage for 2 weeks at 40°C/75% RH. Four tablets were dropped into each vessel. Each point represents the mean ± S.D. of 6 measurements.

However, the results in this study suggested that effects of the carboxyl group and amino group in the principal agent on the dissolution rate are small because the dissolution rate for salicylic acid tablets did not decrease (Figure 6 (A)) and the dissolution profiles for 2-aminobiphenyl and 2-(*p*-tolyl)benzoic acid were similar as shown in Figure 6 (C) and (D). Both compounds as the principal agents have a biphenyl backbone, and an amino group for the former and a carboxyl group for the latter are attached to the same position (Figure 5).

Although the dissolution rate for 2-benzylaniline tablets remarkably decreased after storage at 40°C/75% RH, the magnitude of the decrease in dissolution rate for 2-aminobiphenyl tablets was very small. The structures are similar, and the methylene group in 2-benzylaniline is inserted into the phenyl-phenyl bond in 2-aminobiphenyl. In the case of 4,4'-biphenyl, dissolution rate for the control of 4,4'-biphenyl was slow compared with the dissolution rates for controls of other tested drugs, while a decrease in the dissolution rate was not observed. All tested agents in this study were chemically stable under this study condition in 2 weeks because actual measurements of dissolution rate (percent of cumulative amount dissolved) reached almost of 100% of theoretical value finally. Duran-Lara *et al*. reported that affinity of phenolic compounds for PVPP tended to increase with an increase in the length of the resonant structure (14). It is known that the binding capacity of PVPP for compounds with similar backbones increases with an increase in the number of hydroxyl groups. Hence, compounds with low affinity for PVPP may be easily affected by airborne water under high temperature and humid conditions. However, the reason for the slow dissolution rate of the control of 4,4'-biphenyl is not known. It was reported that when PVPP is mixed with other compounds, the interaction between PVPP and the compounds involves hydrophobic interaction, van der Waals force and hydrogen bonding (15). Hence, the complicated mechanism involved in these forces as well as resonance energy of compounds may cause the slow dissolution rate of the control of 4,4'-biphenyl. Further investigations to elucidate the mechanism of the interaction are required.

CONCLUSION

Model tablets with PVPP that reproduce a decrease in dissolution rate after storage under high temperature and humid conditions were prepared. We showed that additives and structure of the principal agent were involved in the decrease in dissolution rate. A decrease in dissolution rate was not observed for tablets containing PVPP without lactose hydrate. The results indicated that compounds as the principal agents with low affinity for PVPP may be easily affected by airborne water under high temperature and humid conditions. The results suggested that it is possible to avoid a decreased dissolution rate for tablets with PVPP according to the pharmaceutical formulation.

DISCLOSURE

The authors report no conflicts of interest in this work.

REFERENCES

1. Takekuma Y, Takachi R, Ishizaka H, Sato Y, Sumi M, Sugawara M. Effects of Light, Temperature, Humidity on the Stability of Each Opened Tablet Formula. Japanese journal of pharmaceutical health care and sciences. 2014;40(3):135-46.
2. Bühler V, Kollidon® - Polyvinylpyrrolidone excipients for the pharmaceutical industry 9th revised edition, Ludwigshafen, Germany, pp11-14, 2008.
3. Caceres-Mella A, Pena-Neira A, Parraguez J, Lopez-Solis R, Laurie VF, Canals JM. Effect of inert gas and prefermentative treatment with polyvinylpolypyrrolidone on the phenolic composition of Chilean Sauvignon blanc wines. J Sci Food Agric. 2013;93(8):1928-34.
4. Doner LW, Becard G, Irwin PL. Binding of Flavonoids by Polyvinylpolypyrrolidone. Journal of Agricultural and Food Chemistry. 1993;41(5):753-7.
5. Zhao N, Augsburger LL. Functionality comparison of 3 classes of superdisintegrants in promoting aspirin tablet disintegration and dissolution. AAPS PharmSciTech. 2005;6(4):E634-40.
6. Desai PM, Liew CV, Heng PW. Understanding disintegrant action by visualization. J Pharm Sci. 2012;101(6):2155-64.
7. Ota M, Fukami T, Arakawa M, Hayashi H, Suzuki T, Iwata M, et al. Examination of factors that delay the elution of acetaminophen from over-the-counter drugs. Pharmazie. 2012;67(12):1018-25.
8. Bindra DS, Stein D, Pandey P, Barbour N. Incompatibility of croscarmellose sodium with alkaline excipients in a tablet formulation. Pharm Dev Technol. 2014;19(3):285-9.
9. Yamazaki N, Iizuka R, Miyazawa S, Wada Y, Shimokawa K, Ishii F. Selection of generic preparations of famotidine orally disintegrating

tablets for use in unit-dose packages. Drug Discov Ther. 2012;6(5):263-8.
10. MInistry of Health L, and Welfare. The Japanese Pharmacopoeia, 16th edition. Hirokawa Shoten Co, Tokyo, Japan, pp.284-287, 2011
11. Kondo K, Niwa T, Danjo K. Evaluation of disintegration properties of orally rapidly disintegrating tablets using a novel disintegration tester. Chem Pharm Bull. 2012;60(10):1240-8.
12. Alizadeh N, Farokhcheh A. Simultaneous determination of diphenylamine and nitrosodiphenylamine by photochemically induced fluorescence and synchronous fluorimetry using double scans method. Talanta. 2014;121:239-46.
13. National Institute of Health Sciences. Guideline for Bioequivalence Studies of Generic Products. 2012.
14. Duran-Lara EF, Lopez-Cortes XA, Castro RI, Avila-Salas F, Gonzalez-Nilo FD, Laurie VF, et al. Experimental and theoretical binding affinity between polyvinylpolypyrrolidone and selected phenolic compounds from food matrices. Food chemistry. 2015;168:464-70.
15. Laborde B, Moine-Ledoux V, Richard T, Saucier C, Dubourdieu D, Monti JP. PVPP-polyphenol complexes: a molecular approach. J Agric Food Chem. 2006;54(12):4383-9.