Effect of Grinding with Hydroxypropyl Cellulose on the Dissolution and Particle Size of a Poorly Water-Soluble Drug

Tatsuhiko YAMADA,*[,a] Noriyasu SAITO,[a] Teruko IMAI,[b] and Masaki OTAGIRI[b]

Pharmaceutical Laboratories, Kissei Pharmaceutical Co., Ltd.,[a] 4365–1 Kashiwabara Hotaka, Minamiazumi, Nagano 399–8304, Japan and Faculty of Pharmaceutical Sciences, Kumamoto University,[b] 5–1 Oe-honmachi, Kumamoto 862–0973, Japan. Received April 2, 1999; accepted June 17, 1999

A new benzofuroquinoline derivative, 3,9-bis(*N*,*N*-dimethylcarbamoyloxy)-5*H*-benzofuro[3,2-*c*]quinoline-6-one (KCA-098), shows poor oral absorption due to practical insolubility in water. In this study, a co-grinding technique employing a water-soluble polymer was used for improvement of the dissolution rate of KCA-098. Powder X-ray diffraction patterns and IR spectra of KCA-098 showed the conversion of the drug from a crystal state to an amorphous state by grinding with a polymer such as hydroxypropyl cellulose (HPC-SL) or polyvinylpyrrolidone (PVP K30). The particle size of KCA-098 was remarkably reduced to a submicron size by grinding with HPC-SL. The co-ground mixture with HPC-SL showed a rapid dissolution rate and maintained supersaturation for more than 1 h. On the other hand, the co-ground mixture with PVP K30 showed rapid dissolution and supersaturation for a shorter period. These data suggest that the rapid dissolution rate was obtained by the conversion of the drug particles from a crystal to amorphous state by grinding with water-soluble polymers and that a reduction in particle size to the submicron level led to the maintenance of supersaturation due to good dispersion.

Key words KCA-098; grinding; hydroxypropyl cellulose; dissolution; particle size

The new benzofuroquinoline derivative, 3,9-bis(*N*,*N*-dimethylcarbamoyloxy)-5*H*-benzofuro[3,2-*c*]quinoline-6-one (KCA-098), has promising pharmacological activity for the treatment of osteoporosis, as it inhibits bone resorption and stimulates bone formation.[1—3] We previously reported that KCA-098 has three kinds of crystal forms, I, II and III, which are transformed at 260 °C, 152 °C, and 93 °C from the hydrate.[4] Forms I and II showed the same dissolution profile, whereas form III, a metastable form, showed a faster dissolution rate. However, all crystal forms finally showed the same solubility as a hydrate because of the transformation of each crystal form to its hydrate form in water. From the results of stability and the preparation of crystals, we selected form II as a desirable crystal for pharmaceutical formulation. However, some pharmaceutical technique was considered necessary to increase the dissolution rate of form II in order to obtain adequate oral bioavailability of KCA-098. The co-grinding method with a water-soluble polymer is one of the useful pharmaceutical techniques for improving the dissolution and bioavailability of poorly water-soluble drugs. Microcrystalline cellulose (MCC),[5,6] polyvinylpyrrolidones (PVPs),[7] and polyethyleneglycols[8] are extensively used as carrier for co-grinding. In addition, it has been reported that a co-ground mixture incorporating hydroxypropyl cellulose (HPC) improves the dissolution rate of drugs.[9] In this study, ground mixtures of KCA-098 (form II) were prepared with HPC-SL and PVP K30, used as water-soluble polymers, and their dissolution behaviors were examined. Further, some additional factors influencing the dissolution were examined.

Experimental

Materials Form II of KCA-098 was prepared according to the previously reported method.[4] HPC (HPC-SL, MW 73500, Nippon Soda Co., Ltd., Tokyo, Japan) and PVP (PVP K30, MW40000, Gokyo Industries, Ltd., Osaka, Japan) were used. Other chemicals were of reagent grade.

Preparation of Co-ground Mixtures KCA-098 and polymers were combined at a 1 : 4 drug : polymer weight ratio, then transferred into a mill jar filled with stainless steel balls (V-IM, Irie Shokai Co., Ltd., Tokyo, Japan). The sealed jar was set in motion on driven rolls for 1 to 21 h. A physical mixture of the drug and polymer was also prepared by roughly mixing each component.

Powder X-Ray Diffraction Study The powder X-ray diffraction pattern was recorded on a Rigakudenki RINT-1400 X-ray diffractometer with nickel-filtered CuKα radiation at room temperature. The operating conditions were as follows: voltage, 30 kV; current, 100 mA; time constant, 1 s; diffraction angle, range 3—40° (2θ); scanning speed, 2°/min.

FT-IR Measurement The FT-IR of samples prepared with KBr was measured with a Nicolet 510 FT-IR spectrophotometer.

Particle Size Analysis Particle size was determined by a laser diffraction method using an SK laser diffraction particle-sizer analyzer (PRO-7000S, Seishin Enterprise Co., Ltd., Tokyo, Japan) at room temperature, after the sample (30 mg) had been dispersed in 20 ml of water for 20 s by sonication.

Dissolution Study The dissolution of the sample was determined according to the dissolution test prescribed in the JPXIII. An accurately weighed sample, equivalent to 50 mg of KCA-098, was put into 900 ml of water at 37 °C and stirred at 90 rpm. At appropriate time intervals, samples were removed, filtered through a 0.2 μm-membrane filter (Ekikurodisc, Gelman Science Japan, Ltd.), and assayed by the HPLC method described in a previous paper.[4]

Results and Discussion

Particle State of Drug in Co-ground Mixture Figure 1 shows the powder X-ray diffraction pattern of the ground mixture of KCA-098 with HPC-SL. The intensities of the crystal peaks of KCA-098 decreased with an increase in the grinding period, and a halo pattern was obtained after 3 h of grinding. The grinding of KCA-098 with PVP K30 also induced halo patterns of the drug after 3 h (data not shown). In addition, the grinding of KCA-098 without polymers also induced a decrease in its diffraction intensities; however, all of the diffraction peaks still remained after 3 h of grinding. The grinding of the drug alone for more than 21 h shifted KCA-098 from the crystal to the amorphous state (data not shown), as reported earlier for another mixture,[10] and either polymer enhanced the transformation of the drug to the amorphous state by dispersion of the drug into the polymer network by mechanical stress.[11] Further, FT-IR spectra supported the

* To whom correspondence should be addressed.

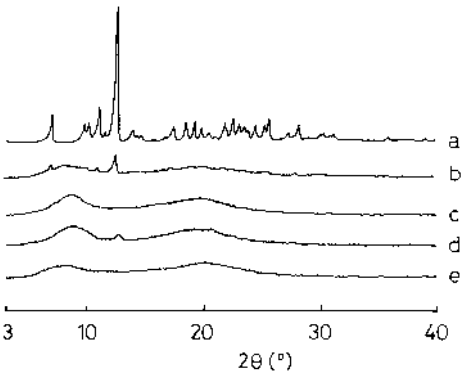

Fig. 1. Effect of Grinding on Powder X-Ray Diffraction Patterns of KCA-098 Co-ground with HPC-SL (1 : 4)

a, KCA-098 (form II); b, physical mixture; c, HPC-SL; d, co-ground for 1 h; e, co-ground for 3 h.

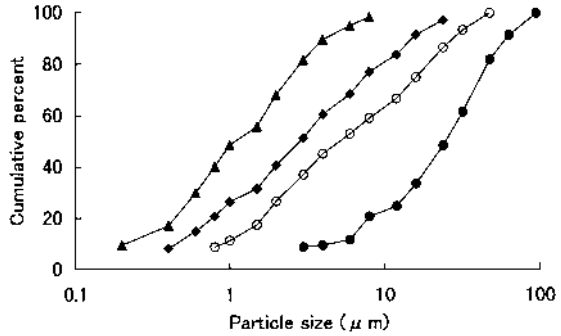

Fig. 2. Particle Size Distribution of KCA-098, the Drug Ground Alone, and Co-ground Mixture with Polymer (1 : 4)

○, KCA-098; ●, KCA-098 ground alone for 3 h; ▲, co-ground with HPC-SL for 3 h; ◆, co-ground with PVP K30 for 3 h.

molecular dispersion and disappearance of the crystal state by the grinding of KCA-098 for 3 h with polymers and for 21 h without polymers, respectively. That is, the N–H stretching band at 2861 cm^{-1} disappeared, and the pyridone ring carbonyl stretching at 1659 cm^{-1} and two carbamate carbonyl stretchings at 1716 cm^{-1} were shifted to a higher frequency and were observed around 1668 cm^{-1} and 1723 cm^{-1} (spectra not shown). These changes in IR peaks for the N–H and carbonyl groups are explained by the destruction of intermolecular hydrogen bonding.[12,13]

The particle size distribution of KCA-098 particles in the co-ground mixture with PVP K30 or HPC-SL was examined. In order to estimate the particle size of KCA-098 itself, we measured the sample dispersed in water after the dissolution of the water-soluble polymer from the co-ground mixture. As shown in Fig. 2, KCA-098 particles in the HPC-SL co-ground mixture showed a considerably smaller size than those in that with PVP K30. In addition, the size of KCA-098 particles ground alone was greater than that of those before grinding, suggesting aggregation of microparticles in water. Because the particle size for the co-ground mixtures was measured after dissolution of the polymer, its particle size reflects crystallization and/or aggregation of KCA-098 in water. Therefore, the fine particles of KCA-098 in the co-ground mixture indicate not only a reduction in particle size by grinding with a polymer, but also the possible inhibition of aggregation and crystallization of KCA-098 particles by

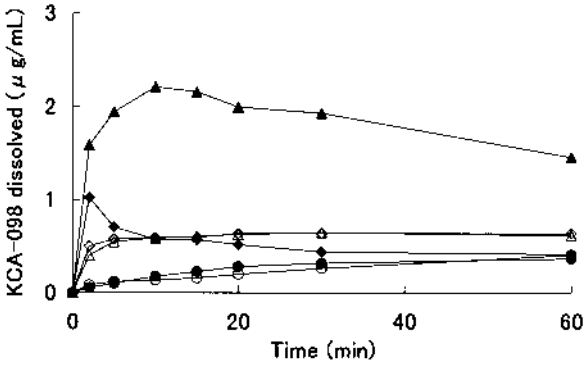

Fig. 3. Dissolution Profiles of KCA-098 in Physical Mixture and Co-ground Mixture with Either Polymer (1 : 4)

○, intact KCA-098; ●, KCA-098 ground alone for 3 h; △, physical mixture with HPC-SL; ▲, co-ground with HPC-SL; ◇, physical mixture with PVP K30; ◆, co-ground with PVP K30.

HPC-SL or PVP K30 in water. The above data indicate that the grinding of KCA-098 with HPC-SL or PVP K30 is useful for transformation from the crystal state to the amorphous state and that an even greater reduction in particle size is achieved by grinding with HPC-SL.

Dissolution Study Figure 3 shows dissolution profiles of KCA-098 in its physical and co-ground mixture with HPC-SL or PVP K30 in water at 37 °C. The dissolution of KCA-098 ground alone, an amorphous form, was the same as that of the intact crystal KCA-098. The physical mixture of KCA-098 and either of the two kinds of polymers showed a faster dissolution rate compared with the drug alone because of the solubilization effect of polymers. The water-soluble polymer might thus stabilize a good dispersion of the drug particles in water. The co-ground mixture with PVP K30 showed a rapid initial dissolution but the same solubility as its physical mixture after 10 min in the dissolution test. Furthermore, the dissolution of KCA-098 from the co-ground mixture with PVP K30 reduced the solubility of the hydrate form. The crystal form in the PVP K30 co-ground mixture system after 60 min was found to be a hydrate crystal by the powder X-ray pattern, resulting in rapid recrystallization from an amorphous state to a hydrate, whereas no polymorphic transition was observed up to 60 min in either physical mixture with PVP K30 or HPC-SL. The drug particles were maintained in crystal form II. Because the solubility of the hydrate of KCA-098 was low compared with that of form II, KCA-098 dissolved from the co-ground mixture with PVP K30 decreased with increasing time, and was apparently less than that from the physical mixture at 60 min after the start of the dissolution test. However, the co-ground mixture with HPC-SL exhibited a significantly rapid initial dissolution rate and high solubility, to supersaturation, up to 60 min after the start of the dissolution test, compared with KCA-098 alone or its physical mixture with the polymer. The difference in dissolution behavior between PVP K30 and HPC-SL co-ground mixtures might be based on the difference in particle size. Stabilization of the dispersion of fine particles of KCA-098 by HPC-SL might induce rapid dissolution and the maintenance of high supersaturating solubility, although the fine particle will finally be converted to the hydrate form and show low solubility similar to the physical mixture. In practice, however, the crystal form would be a mixture of amor-

phous and hydrate crystal at 60 min after dissolution because the intensity of the powder X-ray diffraction peaks obtained from a co-ground mixture with HPC-SL was markedly weak compared with that from a co-ground mixture with PVP K30. There are two possible explanations for the maintenance of the high solubility of KCA-098 by HPC-SL. One is a stabilization of the amorphous state fine particles of the drug by inhibition of aggregation due to an interaction between the drug and carrier in the supersaturated suspending solution.[14] The other is a suppressing effect on its crystallization from an amorphous state to the hydrate in the dissolution media influenced by the viscosity due to the polymer.

In conclusion, we have demonstrated that the co-grinding technique with water-soluble polymers is effective for increasing the dissolution rate and the maintenance of high solubility of a poorly water-soluble drug such as KCA-098 by increasing the available particles surface area and portion in the amorphous state.

References

1) Kojima M., Tsutsumi N., Nagata H., Itoh F., Ujiie A., Kawashima K., Endo H., Ozaki M., *Biol. Pharm. Bull.*, **17**, 504—508 (1994).
2) Tsutsumi N., Kawashima K., Arai N., Nagata H., Kojima M., Ujiie A., Endo H., *Bone Miner.*, **24**, 201—209 (1994).
3) Tsutsumi N., Kawashima K., Nagata H., Itoh F., Arai N., Kojima M., Ujiie A., Endo H., *Jpn. J. Pharmacol.*, **65**, 343—349 (1994).
4) Yamada T., Ikegami K., Toda M., Saito N., Iizuka K., Otagiri M., *Yakugaku Zasshi*, **115**, 978—984 (1995).
5) Yamamoto K., Nakano M., Arita T., Nakai Y., *J. Pharm. Biopharm.*, **2**, 487—493 (1974).
6) Yamamoto K., Nakano M., Arita T., Takayama Y., Nakai Y., *J. Pharm. Sci.*, **65**, 1484—1488 (1976).
7) Martini A., Torrice C., Ponti R. D., *Int. J. Pharm.*, **75**, 141—146 (1991).
8) Sugimoto M., Okagaki T., Narisawa S., Koida Y., Nakajima K., *Int. J. Pharm.*, **160**, 11—19 (1998).
9) Yamada I., Kawata M., Shibata T., Ogawa K., Yokobe T., *Yakugaku Zasshi*, **109**, 932—937 (1989).
10) Otsuka M., Matsuda Y., *J. Pharm. Sci.*, **84**, 1434—1437 (1995).
11) Calri F., Colomco I., *Acta Pharm. Jug.*, **38**, 361—371 (1988).
12) Griffiths D. W., Bender M. L., *Advances in Catalysis*, **23**, 209 (1973).
13) Nakai Y., Nakajima S., Yamamoto K., Konno T., *Chem. Pharm. Bull.*, **26**, 3419—3425 (1978).
14) Ikekawa A., *J. Sco. Powder Technol.*, **29**, 365—368 (1992).