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Drug Dissolution from Indomethacin-starch Hybrid Powders Prepared by the Dry Impact Blending Method

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Abstract—Indomethacin was hybridized with potato starch using a dry impact blending method. Resultant hybrid powders were investigated by scanning electron microscopy and X-ray powder diffraction. Amorphous indomethacin spread over the starch surface in a layer immediately after being hybridized, and then gradually reverted to fine crystalline particles adhering firmly to the starch surface. Indomethacin dissolution from the hybrid powder was compared with those from physical mixtures and granules taken from a commercially available capsule. Indomethacin dissolution from powder and capsule dosage forms, even in an acidic medium, was drastically accelerated by the hybridization.

At present, wet processes are mainly used in the manufacture of solid pharmaceuticals. However, as they require supplementary equipment to recover solvents and to dry products, wet processes can be more expensive than dry processes. Incomplete removal of a solvent from the pharmaceutical product may also be a problem, particularly if an organic solvent is used.

It has been reported that an 'ordered mixture' can be produced by a dry process, simple dry mixing of fine and coarse particles (Hersey 1975). When interparticle interactions, such as van der Waals and Coulomb forces, exist between the two types of particles, the fine particle adheres to the surface of the coarse particle; that is, an ordered mixture spontaneously forms. Many investigators have reported on properties of ordered mixtures and their applications in the pharmaceutical field (Staniforth 1987; Crooks & Ho 1976; Thiel et al 1983, 1986). Formation and stability of an ordered unit depends on mixing time (Kulvanich & Stewart 1987), particle size and shape (Thanomkiat & Stewart 1979; Wong & Pilpel 1988), and environmental humidity (Stephenson & Thiel 1980; Kulvanich & Stewart 1988). Moreover, in some cases, ordered units could be disintegrated by applying enough physical force to overcome the interparticle interaction (Staniforth & Rees 1983) or by adding a third component into ordered mixtures (Lai & Hersey 1979).

Dry mixing methods have been developed to modify, coat, or hybridize particles with various materials. There are several reports on their applications in the pharmaceutical field. For example, granules and particles were coated with carnauba wax and magnesium stearate to develop sustained-release products (Koishi & Ishizaka 1988). Dispersibility of titanium dioxide particles into emulsions was improved by adhering them onto the surface of a fine nylon powder (Takashima et al 1986). Drug-diluent hybrid powders in which drugs firmly adhered to the diluent surface were also prepared by the dry-mixing method (Ishizaka et al 1988). As far as durability of a unit is concerned, the hybrid powder seems to be more advantageous than the ordered mixture for the manufacture of solid dosage forms. Dry impact blending with a surface-reforming system is considered the most effective of the dry mixing methods (Koishi et al 1987). The drug-diluent hybrid powder can be obtained by the dry impact blending method in a few minutes (Ishizaka et al 1989).

The purpose of this study was to investigate the effect of the hybridization by the dry impact blending method on indomethacin dissolution.

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Materials and Methods

Materials

Potato starch was used as a core material. A micronized fraction of a sparingly soluble drug, indomethacin (γ-form), was used without further pulverization. Physical mixtures used for comparison with the hybrid powders were prepared by gentle mixing of known quantities of indomethacin and potato starch with a ceramic mortar and pestle for 10 min. Granules taken from a commercially available indomethacin capsule were also used for comparison. Other chemicals used were of analytical grade.

Hybridization of indomethacin with potato starch

The dry impact blending method with a powder surface-reforming system (Nara Hybridization System Model NHS-1, Nara Machinery Co. Ltd, Tokyo, Japan) was used for producing indomethacin-starch hybrid powders. Indomethacin and potato starch were processed under the same conditions as employed in the previous study (Ishizaka et al 1989). The mixture (100 g) was placed in the powder surface-reforming system, and processed for 5 min with the outer edges of the blades rotating at 80 m s^{-1}. To hold the temperature of the atmosphere in the chamber below 60°C, the inner surface of the hybridization chamber was cooled by a jacket through which tap water flowed at a constant rate.

Resultant hybrid powders were kept in sealed containers protected from light.

The resultant powders were observed with a scanning electron microscope (Model S-530, Hitachi, Ltd, Tokyo, Japan). Samples were prepared for observation by sputter-coating with gold.

Evaluation of hybrid powders by X-ray diffractometry

To evaluate hybrid powders, X-ray powder diffraction patterns were obtained using a computer-controlled X-ray diffractometer (Model MXP^3 System, Mac Science Co. Ltd, Tokyo, Japan) with CuKα radiation. Patterns were recorded from 5 to 40° (2θ) in steps of 0·020°.

Dissolution test

In-vitro dissolution studies were carried out using a similar method to the dissolution test described in the JP XI. An automatic test apparatus (TCP System; Toyama Sangyo Co, Ltd, Osaka, Japan) was used for the dissolution test.

The hybrid powder, the physical mixture, or the granule containing about 20 mg indomethacin was accurately weighed and dispersed into 900 mL of a test medium maintained at 37 ± 0·5°C. To attain a homogeneous dispersion of the sample powder, the test medium was agitated with a paddle at a constant speed of 200 rev min^{-1}. When the original indomethacin powder was examined, about 160 mg of the sample was exactly weighed and dispersed into the test medium. Without stopping the agitation, aliquots of the medium were automatically withdrawn at appropriate time intervals through a sampling tube equipped with a filter. Each filtrate was quickly pumped into a UV cell maintained at 37 ± 0·5°C, and then returned to the test vessel by pumping in reverse through the sampling tube. The indomethacin concentration in the filtrate was determined spectrophotometrically from the difference in absorbance at 266 and 320 nm. An acetate buffer (pH 4·7) was used to examine the effect of hybridization on the dissolution of indomethacin, as indomethacin is poorly soluble in an acidic solution. The pH of 4·7 was chosen for the convenience of concentration measurement with the automatic test apparatus. As solubility of indomethacin in the buffer solution was 12·9 mg L^{-1}, sink conditions were not obtained during these tests.

Tests to ascertain supersaturation in the dissolution were carried out as follows. The hybrid powder containing about 70 mg indomethacin was accurately weighed and dispersed into 900 mL of the acetate buffer solution in the vessel. The contents of the covered vessel were maintained at 37 ± 0·5°C and agitation at a constant speed of 200 rev min^{-1} was achieved with the paddle. Ten-millilitre samples were withdrawn with syringes at appropriate time intervals and filtered through 0·22 μm membrane filters (Millipore filter GVWP 02500, Nippon Millipore Ltd, Tokyo, Japan) to remove solid particles. To prevent recrystallization of indomethacin in the filtrates, the syringes, the filters, the filter supports, and the test tubes had been maintained at 37 ± 0·5°C until they were used. Each filtrate was diluted with methanol and was then assayed spectrophotometrically at 320 nm.

Indomethacin dissolution from capsules was examined as follows. The hybrid powder, the physical mixture, or the granule containing 25 mg indomethacin was accurately weighed and filled in No. 1 gelatine capsules. A sinker prescribed in JP XI was used to sink the capsule to the bottom of the vessel. The capsule was placed into the sinker and then dropped into 900 mL of a test medium that was maintained at 37 ± 0·5°C. Agitation was at a constant speed of 100 rev min^{-1} with the paddle started immediately after the capsule was dropped into the test medium. A medium (a mixture of water and a pH 7·2 phosphate buffer solution, 4:1) described in the JP XI for indomethacin capsules and the pH 4·7 buffer were used as test media. Dissolved indomethacin was automatically determined at 320 nm without stopping the agitation, as described above.

Disintegration test of capsules

Disintegration of the capsules was examined in the pH 4·7 buffer solution at room temperature (21°C). The capsule was placed into the sinker and suspended by a wire in an Erlenmeyer flask containing 300 mL of the buffer. Constant agitation at a slow rate was achieved with a magnetic stirrer.

Results and Discussion

Scanning electron-micrographs of an indomethacin-starch hybrid powder are shown in Fig. 1. Drug adhesion as a smooth layer to the core surface was achieved by the hybridization with the powder surface-reforming system. We reported in a previous paper that some drugs which had been attached in a layer to the core surface gradually reverted to fine particles (Ishizaka et al 1989). The finding suggested that mechanochemical phenomena occurred during and after the hybridization. When the mechanical force which is applied to a drug during the hybridization overcomes intermolecular forces holding molecules together in a crystal, it disrupts the three-dimensional structure of the drug crystal lattice; that is, a large part of the drug adhering to the starch surface in the smooth layer is in a metastable state. As the excess energy accumulated in the distorted and disrupted structure is released after the hybridization, the drug is transformed from the amorphous to a crystalline state. The change of the indomethacin on the core surface is clearly indicated in Fig. 1. The smooth indomethacin layer which had been found immediately after preparing the hybrid powder, spontaneously reverted to fine particles adhering firmly to the starch surface. The time required to complete the change seemed to be dependent on the amount of the adhering indomethacin; the more the adhering drug, the more time was required to complete the change. The change in the surface appearance of the hybrid powder containing 1·9% indomethacin appeared to be complete within 4 days.

Fig. 2 shows the effect of the hybridization on indomethacin dissolution. A hybrid powder stored for 237 days (4·1% indomethacin) gave the highest dissolution rate among the samples. Comparisons of dissolved amounts at equivalent times over 10 h gave a rank order for the dissolution of the three samples: the hybrid powder > a physical mixture > the original powder. The slowest dissolution from the original indomethacin powder was thought to have resulted from its poor wettability by the test medium. The improvement in the dissolution by physical mixing of indomethacin with the hydrophilic starch appeared to be due to an increase in the dispersibility of the drug particles, as reported

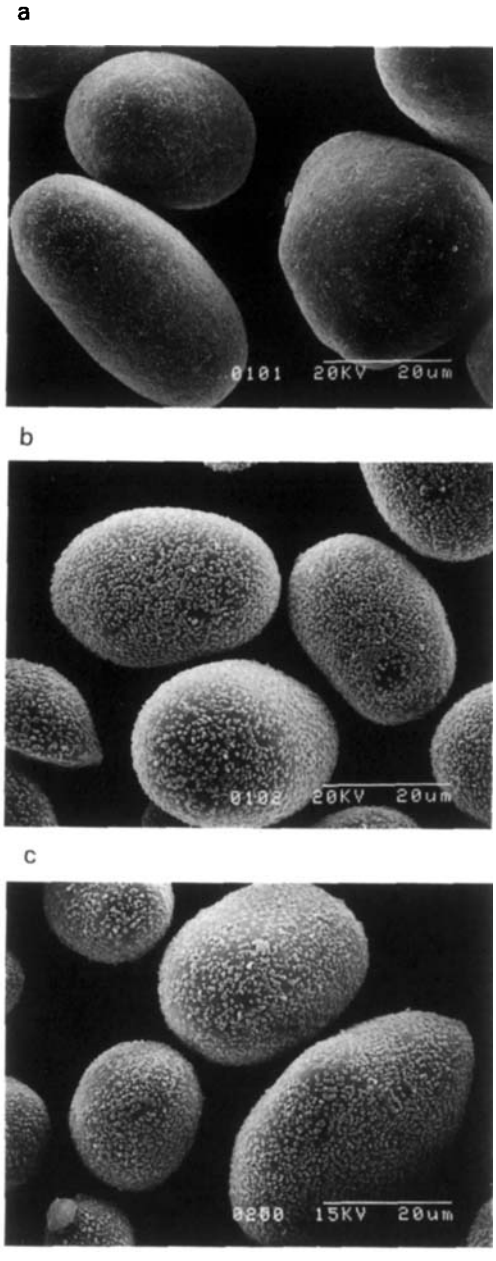

FIG. 1. Change of an indomethacin-potato starch hybrid powder (1·9% indomethacin). a, after 4 h; b, 7 days; c, 37 days. Each bar in a photograph represents 20 μm.

previously (Ishizaka et al 1988). Effects of ordered mixing on drug dissolution have been reported by several investigators (McGinity et al 1985; Nyström & Westerberg 1986; Westerberg et al 1986). Improvement obtained by the formation of ordered mixtures was shown by Nyström & Westerberg (1986) to be caused by increases in the apparent surface area of drug exposed to the dissolution medium and in the dispersibility of drug particles. As the change of indomethacin from a layer to particles was completed, the surface of the hybrid powder used in this test had both hydrophilic parts (exposed parts of the starch surface) and the hydrophobic parts (indomethacin particles), as shown in Fig. 1. It is

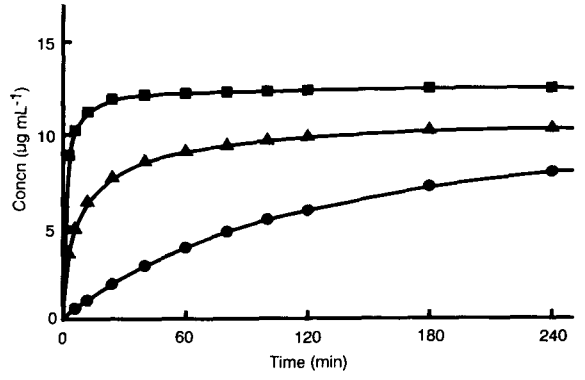

FIG. 2. Dissolution profiles of indomethacin from the powder samples in pH 4·7 buffer. ● original indomethacin powder; ▲ physical mixture (5·0% indomethacin); ■ hybrid powder (4·1% indomethacin) stored for 237 days.

probable that the increases in the wettability and in the apparent surface area also played important roles in the marked improvement of the indomethacin dissolution due to the hybridization. Furthermore, an increase in the true surface area of indomethacin may be an alternative factor responsible for the improvement. The total surface area of the indomethacin fine particles adhering to the starch surface must have been greater than those in the original powder and in the physical mixtures, as the original indomethacin particles having a mean diameter of about 5 μm were changed to fine particles having a mean diameter of about 1 μm by hybridization.

The change of the indomethacin adhering to starch affected the dissolution slightly. Profiles obtained with the hybrid powder containing 1·9% indomethacin are shown in Fig. 3. Indomethacin was quickly dissolved from all samples and the concentrations rose to the saturation concentration within 20 min, irrespective of whether indomethacin was adhering to the starch surface in a layer or as particles.

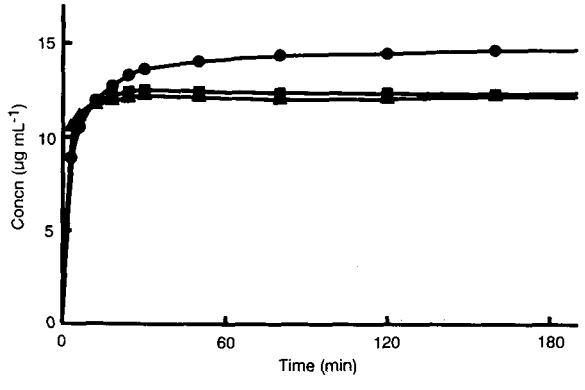

FIG. 3. Change in the indomethacin dissolution from a hybrid powder (1·9% indomethacin) in pH 4·7 buffer. ● after 1 h and 50 min; ▲ after 7 days; ■ after 37 days.

However, a slight difference in the initial dissolution rate and a notable difference in the apparent equilibrium concentration existed between the fresh hybrid powder and the hybrid powders stored for 7 and 37 days. The initial dissolution rate of the fresh hybrid powder was slightly lower than for stored

samples presumably because of the complete covering by the smooth indomethacin layer. The apparent equilibrium concentration obtained for the fresh hybrid powder was above the saturation level. This supersaturation phenomenon was clearly demonstrated by comparing indomethacin dissolution from two hybrid powders containing about 7% indomethacin (Fig. 4). Although supersaturation occurred for both the samples, a maximum concentration for the fresh hybrid powder was greater and was attained faster than that of the 113-day hybrid powder.

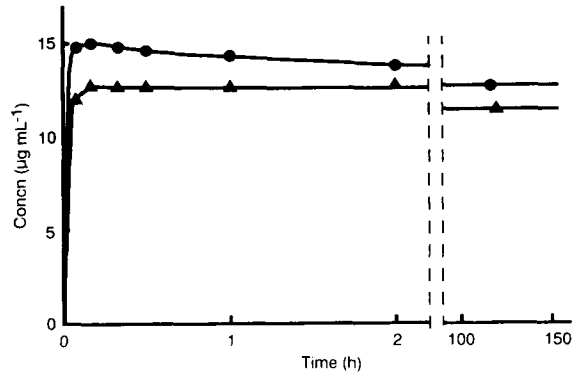

FIG. 4. Dissolution profiles of indomethacin from hybrid powders in pH 4·7 buffer. ● 7·2% after 3·5 h; ▲ 7·1% after 113 days.

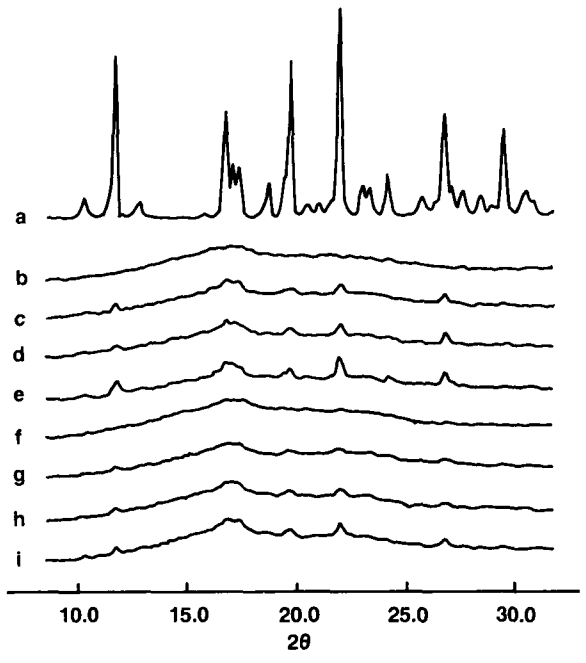

FIG. 5. X-ray powder diffractograms of indomethacin, potato starch, physical mixtures and hybrid powders. a, indomethacin; b, potato starch; c, physical mixture containing 5% indomethacin; d, 7%; e, 10%; f, hybrid powder (7·1% indomethacin) immediately after the hybridization; g, 1 day; h, 7 days; i, 28 days.

Fig. 5 shows typical X-ray powder diffractograms of the original drug powder, potato starch, physical mixtures and a hybrid powder. Though physical mixing with potato starch made it difficult to detect small peaks shown in the X-ray diffractogram of the original powder, peaks at 11·7, 19·7, 21·9, and 26·7° (2θ) could be found in those of the physical mixtures. The intensity of these peaks increased with the increase in the indomethacin content. In the case of the fresh hybrid powder, the diffractogram exhibited no detectable peaks. The diffraction pattern of the hybrid powder changed depending upon the storage time. Small pinnacles appeared at 11·7, 19·7, 21·9, and 26·7° after 1 day, and they then grew into distinct peaks after 7 days. Their growth continued, but the intensities of these peaks of the hybrid powders after 28 days were slightly less than those shown in the diffractogram of the physical mixture containing 7·0% indomethacin. The finding obtained by the X-ray powder diffractometry was closely compatible with that obtained by scanning electron microscopy. This indicated that most of the indomethacin adhering to the starch surface was in an amorphous state immediately after the hybridization and that the ratio of the amorphous portion gradually decreased. Thus, it seemed that the amorphous portion of the adhering indomethacin caused the supersaturation seen in the dissolution from the fresh hybrid powders.

Hybrid powders were compared with the commerically available pharmaceutical product to evaluate the practical significance of the hybridization on indomethacin dissolution. Dissolution profiles from a hybrid powder stored for 21 days and the granules taken from the commercially available capsules are shown in Fig. 6. Although both the samples showed good dispersibility in the pH 4·7 solution, large differences existed in their dissolution profiles. The hybrid powder yielded an initial fast dissolution and an equilibrium concentration was obtained in 120 min; the granule released indomethacin at a rate slower than the hybrid powder and the concentration did not reach saturation within the 16-h test period.

In-vitro release profiles from capsules in the test medium described in the JP XI for the indomethacin capsule dissolution test are shown in Fig. 7. The release of indomethacin from capsules gave sigmoid profiles, and the release rate from the capsule containing a hybrid powder (7·1%) stored for 55 days was slightly lower than that from the capsule

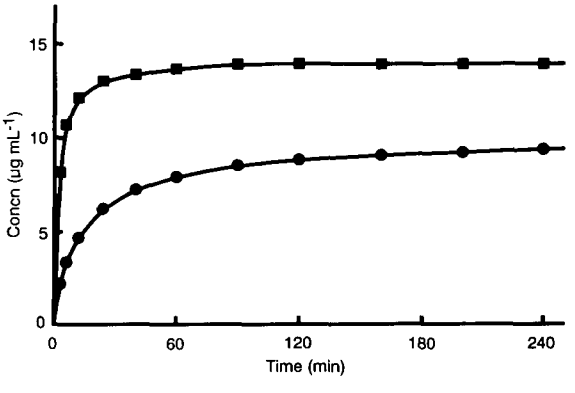

FIG. 6. Comparison of indomethacin dissolution from a hybrid powder and the granule in pH 4·7 buffer. ■ Hybrid powder (7·1%) after 21 days; ● granules taken from a commercially available indomethacin capsule.

filled with the granules, although there was no difference in the capsule disintegration. However, the release from the capsule containing the hybrid powder did not exceed the tolerance, which is described in the JP XI, that not less than 75% of the stated amount of indomethacin is dissolved in 20 min.

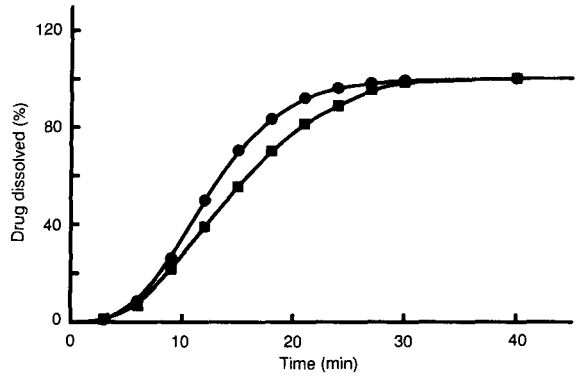

FIG. 7. Comparison of indomethacin dissolution from capsules in the test medium described in the JP XI. ■ Hybrid powder (7·1%) after 55 days; ● granules taken from a commercially available indomethacin capsule.

Indomethacin release from capsules in the pH 4·7 solution was also examined. Profiles are shown in Fig. 8. There were some differences between the release from the capsules containing a hybrid powder (7·1%) stored for 62 days and the granules. The release from the capsule containing the hybrid powder was rapid, and the indomethacin concentration reached a maximum level in 7 h. On the other hand, the release profiles for the capsule containing the granules were biphasic, with an initial rapid release followed by a slower release. Furthermore, the concentration shown in the profile for the granules did not reach equilibrium levels within 22 h. The differences were not related to capsule disintegration, for it was confirmed in the disintegration test that both the capsules gradually disintegrated over a period greater than 60 min, and that the capsules containing the hybrid powder gave a disintegration time slightly longer than that given by the capsules containing the granules. Therefore, the data shown in Fig. 8 suggested that the meaningful acceleration by the hybridization could influence the release from the capsule.

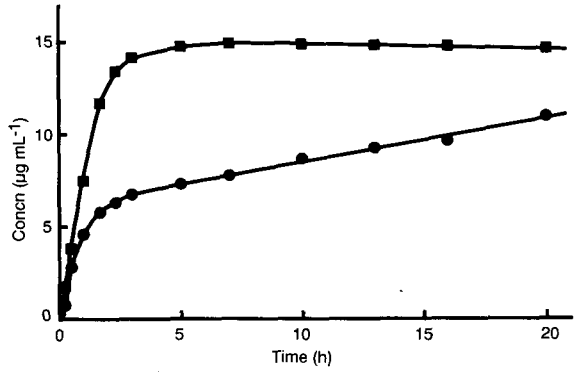

FIG. 8. Comparison of indomethacin dissolution from capsules in pH 4·7 buffer. ■ Hybrid powder (7·1%) after 62 days; ● granules taken from a commercially available indomethacin capsule.

In conclusion, we have shown that the hybrid powder is valuable as an intermediate in the manufacture of pharmaceuticals.

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