Preparation and Evaluation of Ibuprofen Solid Dispersion Systems with Kollidon Particles Using a Pulse Combustion Dryer System

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Solid dispersions (SDs) of ibuprofen (IBU) were prepared with four carriers: Kollidon 25, Kollidon 30, Kollidon VA64, and Kollidon CL, using a newly developed pulse combustion dryer system, HYPULCON. Physicochemical properties of the SDs obtained were investigated by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscope (SEM), and Fourier transformation IR spectroscopy (FT-IR). Powder X-ray diffraction (PXRD) showed that the crystal diffraction peaks of IBU in SDs disappeared completely, and in differential scanning calorimetry (DSC) curves, the endothermic peaks of IBU in SDs were not observed. Fourier transformation IR spectroscopy (FT-IR) proved that interactions between the drug and carrier existed. These findings demonstrated that IBU changed to an amorphous form in the SDs with the four carriers using the pulse combustion dryer system. The dissolution property of IBU in the SDs was markedly enhanced. The dissolution test showed that after 5 min of dissolution, the concentrations of IBU in the SDs with Kollidon CL as the carrier was 43.81 µg/ml, corresponding to 13.0 times that of pure IBU. So, it is demonstrated that the pulse combustion dryer system is very useful for preparing SDs of IBU with Kollidon of different grades as carriers.

Key words ibuprofen; HYPULCON; solid dispersion; Kollidon; pulse combustion dryer system

In recent years, as one of the effective approaches to improve the dissolution property and oral bioavailability of poorly water-soluble drugs, solid dispersion methods have been extensively used and numerous approaches have been reported such as fusion, solvent evaporation, and spray-drying methods. However, these methods involve various problems. Solid dispersions prepared by fusion usually have the shortcoming of being tacky and unstable, and solvent evaporation requires a large amount of organic solvent, which leads to environmental pollution, a high cost, and health concerns. So, it is a matter of some urgency to find new methods to solve the problems which are associated with the above-mentioned methods.

A pulse combustion dryer system, HYPULCON, is a newly developed drying machine using shock wave apparatus. Shock wave drying is one of the applications utilizing the power of shock waves in air. The pulse combustion dryer system has been recognized as a technology of the future since it provides an advantageous superposition of unsteady gas flow and high-intensity sound waves. Such a combination results in enhanced momentum and heat/mass transfer rates in industrial processes such as the field of drying food, inorganic and agricultural products, and heat-sensitive biomaterials such as antibiotics, vitamins, biostepticides, and the like.

Figure 1 shows a schematic diagram of HYPULCON. The system is composed of a pulse combustor and an associated combustion chamber with a pulsating flow of hot gases. A tail pipe is connected to the outlet of the combustion chamber for receiving the pulsating flow of hot gases and a material introduction chamber is connected at the outlet of the tail pipe. A drying chamber is connected at the outlet of the material introduction chamber. Air for combustion and gaseous fuel are drawn into the pulse combustion chamber and form a fuel–air mixture, which is ignited by a pilot and explodes, creating hot and high pressure gases. The hot pulse combustion exhaust gases are cooled to control the temperature of the gases issuing from the outlet of the tail pipe and entering the material introduction chamber. A separate diluent air stream may be employed for contacting with material issuing from the introduction chamber and passing into the drying chamber. This combustion cycle repeats itself at a frequency of about 50 to 1000 Hz to produce consecutive high temperature shock waves. Next, the introduced material is sprayed by the atomizer with high-speed combustor exhaust gases produced by the pulse engine and is dried by the actions of shock waves.

Traditional spray-drying is separate for the atomization and application of heat functions in space and time, and the heat transfer rate is lower, so the drying time is longer and the costs are higher. However, the pulse combustion dryer system can offer important advantages over traditional spray-drying such as instantaneous drying (within 1/100 s), low temperature drying (below 80 °C), high thermal efficiency (40% up to traditional spray drying), and low cost. Furthermore, products have good qualities such as superior particle
surface characteristics, a uniform mean particle size, a large specific surface area, and a narrow particle size distribution. Kollidon systems are used extensively as excipients for the pharmaceutical industry. The systems include two grades: a water-soluble grade and a water-insoluble grade. The water-soluble grades such as Kollidon 25, Kollidon 30, and Kollidon VA64 are used as a dry binder in tablets, as a granulating agent, a retarding agent, and film-forming agent in the pharmaceutical industry. Kollidon CL is the water-insoluble grade, which has hygroscopic properties, swelling properties, and a strong hydration capacity, so it is described as one of the three “superdisintegrants”. It has been reported that SDs were prepared with a water-soluble Kollidon system by different methods.11–13 It also has been reported that SDs of nilvadipine were prepared using crospovidone and methylcellulose as dispersion carriers, and SDs of indomethacin were prepared with crospovidone as a carrier by a hot-melt extrusion process.14,15

Ibuprofen (IBU) is one of the safest and most potent non-steroidal anti-inflammatory drugs, being widely used in the market for 30 years.16 Its low solubility (water, 46.9 μg/ml, 37 °C; 29.1 μg/ml, 25 °C) leads to a potential bioinequivalence problem.17 Pignatello et al.18 reported that SDs of IBU were prepared with Eudragit RL100 as carriers using a co-evaporative method. Shibata et al.19 also reported that solid dispersions of ibuprofen were prepared with PVP by a solvent method. Khan and Jiabi20 reported that solid dispersions of ibuprofen were prepared by a solvent evaporation method using polyethylene glycol 10000 (PEG), talc, and PEG-talc as dispersion carriers. Sekizaki et al.21 reported that the solid-state interaction between ibuprofen and PVP mixed without grinding or shaking at temperatures below the melting point of the drug.

In our research, we use the pulse combustion dryer system—HYPULCON to prepare a solid dispersion of IBU with Kollidon of different grades as carriers with pure water as a solvent, not a conventional organic solvent. Some physico-chemical properties of the SDs and PMs were studied. Also, we compared SDs prepared by hylpulcon and the conventional spray-drying method.

Experimental

Materials IBU as a model drug was obtained from KNOLL Co. Ltd., Germany; Kollidon 25, Kollidon 30, Kollidon VA64, and Kollidon CL as carriers were obtained from BASF AG (Ludwigshafen, Germany). All other chemicals were of analytical or HPLC grade.

Preparation of Solid Dispersions and Physical Mixtures IBU and carriers with a weight ratio of 1:5 were mixed in a polyethylene bag by hand for 10 min to obtain physical mixtures (PMs). PMs with IBU of 2 g and carrier of 10 g were added to pure water of 600 ml to prepare suspensions, which then were dried by HYPULCON (Pultech Corporation, Kyoto, Japan). The operating conditions for HYPULCON and the spray dryer are shown in Tables 1 and 2.

Powder X-Ray Diffraction (PXRD) Powder X-ray diffraction analysis was performed using a linear X-ray diffraction system (RAD-2VC, Rigaku Geiger-Flex diffractometer, Japan) in which CuKα rays (40 kV, 20 mA) were used as X-rays. The degree of diffraction was measured at 5°/min every 0.01° between 5 and 45°.22

Differential Scanning Calorimetry (DSC) DSC analysis was carried out using a differential scanning calorimeter (DSC 60, Shimadzu Co., Japan). Thermograms were obtained by heating the samples at a rate of 10 °C/min in atmospheric air.

Fourier Transormation IR Spectroscopy (FT-IR) Drug–carrier interactions in SDs were determined based on IR spectra measured with a FT-IR spectrometer (JASCO FT/IR-4100) by the KBr method in the 4000—450 cm−1 region at 4 cm−1 resolution at 64 scans per spectrum.

Scanning Electron Microscope (SEM) The morphology of particles was observed with a scanning electron microscope (SEM, JEOL TypeSM-T20).

Results and Discussion

Powder X-Ray Diffraction (PXRD) The powder X-ray diffraction spectrograms for physical mixtures and solid dispersions with Kollidon systems of different grades are shown in Figs. 2 and 3. Pure IBU showed numerous and strong diffraction peaks, which indicated that IBU is present in a highly crystalline state. In all SDs of IBU with Kollidon systems of different grades as carriers using the pulse combustion dryer system, diffraction peaks of IBU were not observed. Meanwhile, in all PMs, the diffraction peaks of IBU were seen clearly. The complete disappearance of diffraction peaks of IBU in SDs demonstrated that in SDs with Kollidon systems as carriers using the pulse combustion dryer system IBU had changed to an amorphous state.

Differential Scanning Calorimetry (DSC) The differential scanning calorimetry curves for physical mixtures and solid dispersions with Kollidon systems of different grades
are shown in Fig. 4. Pure IBU showed a sharp endothermic peak at 80.25 °C (Fig. 4A). In PMs of IBU with Kollidon 30, Kollidon 25, and Kollidon VA64 (Figs. 4B, D, F) as carriers, wide endothermic peaks of IBU were illustrated. In PMs of IBU with Kollidon CL (Fig. 4H) as a carrier, a sharp endothermic peak of IBU was observed at 77.98 °C. But, in all SD systems, the endothermic peak of IBU was not observed. The findings indicated that IBU in SDs with Kollidon systems of different grades as carriers using the pulse combustion dryer system had possibly changed to an amorphous state.

Fourier Transformation IR Spectroscopy (FT-IR) FT-IR spectrograms are shown in Figs. 5 and 6. IBU illustrated the characteristic peak at 1721 cm⁻¹ due to the carboxyl group (–COOH) in the molecular structure of IBU, which was observed in all physical mixture systems regardless of the grade of carrier. In solid dispersion systems, the characteristic peak of the carboxyl group disappeared completely. This can be accounted for by a hydrogen bond being formed between the carboxyl group of IBU and the amide group of Kollidon. Sekizaki et al. and Bogdanova et al. demonstrated that a hydrogen bond could be formed between ibuprofen and polyvinylpyrrolidone and analyzed the detailed action mechanism.

Scanning Electron Microscope (SEM) SEM photographs of the IBU–Kollidon CL and IBU–Kollidon 25 systems are shown in Fig. 7. From Fig. 7, it was observed that...
IBU was present in a crystal form. The Kollidon CL system is an aggregate of massive particles with irregular shapes. The Kollidon 25 system is composed of globular particles with introcession on their surface. It was found that the crystals of IBU were dispersed between the carriers in the IBU–Kollidon CL PM system and IBU–Kollidon 25 PM system, which was not observed in the two SD systems. These findings demonstrated that the drug was changed into an amorphous state.

**Water Vapor Adsorption Test**

The water vapor adsorption isotherms of IBU–Kollidon CL systems are presented in Fig. 8. From the isotherms, it was observed that the amount of adsorbed water increased with the elevation of pressure. The adsorbed amounts of pure IBU, SD and PM at 0.4 relative pressure was 0.04, 64.06 and 75.28 ml/g, respectively. The amount adsorbed on the surface of SD and PM was found to produce a marked increase over pure IBU. Moreover, the amount adsorbed for IBU–Kollidon CL SD system was decreased slightly than the corresponding PM. It showed that the wettability of SD for IBU with Kollidon CL system by the HYPULCON increased, which could contribute to the accelerating dissolution rate of SD.

**Dissolution Test**

The results of the dissolution test for the IBU–Kollidon PM and the IBU–Kollidon SD systems are shown in Figs. 9 and 10. From the dissolution profiles, it was observed that the dissolution rate of IBU from all SD sys-
tems increased markedly, corresponding to PMs and pure IBU. After 5 min of dissolution, the concentrations of IBU from SD systems with Kollidon CL, Kollidon VA64, Kollidon 25 and Kollidon 30 were 43.81, 37.41, 17.08 and 15.1 mg/ml, corresponding to 13.0-, 11.1-, 5.1- and 4.5-fold higher than that of pure IBU, respectively. It could be concluded that after 5 min of dissolution from SDs with Kollidon systems of different grades using the pulse combustion dryer system, the order of the concentration of IBU is as follows: Kollidon CL > Kollidon VA64 > Kollidon 25 > Kollidon 30.

The apparent dissolution rate constants ($K_p$) for different systems are shown in Fig. 11. It indicated that the dissolution rate for IBU was improved markedly by preparing IBU–Kollidon solid dispersion using HYPULCON than pure IBU and physical mixtures. In increasing the dissolution rate of IBU, Kollidon CL is super to the other three carrier systems.

**Contrasting HYPULCON with the Spray Dryer** Table 3 shows the particle size of IBU–Kollidon SD systems prepared by hypulcon and the spray dryer. It was found that SD particles prepared by hypulcon have a smaller particle size and a tighter particle size distribution than those prepared by the spray dryer.

The apparent dissolution rate constants ($K_p$) for SD systems prepared by HYPULCON and the spray dryer are shown in Fig. 12. It can be observed that the dissolution rate for IBU–Kollidon SDs prepared by HYPULCON was improved markedly than that prepared by the spray dryer.

**Stability Test** The results are shown in Fig. 13. It was observed that the amorphous state of IBU in the IBU–Kollidon CL SD system was maintained under 65% RH and 25 °C for three months. Otherwise, it was observed that the IBU–Kollidon CL 5PM system appeared to agglomerate when it was stored under the same conditions after 1 d. Enhancement of the stability of the IBU–Kollidon CL 5SD can

<table>
<thead>
<tr>
<th>Particle size (µm)</th>
<th>IBU</th>
<th>Kollidon CL</th>
<th>Kollidon VA64</th>
<th>Kollidon 25</th>
<th>Kollidon 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_{10}$</td>
<td></td>
<td>13.9</td>
<td>16.1</td>
<td>25.9</td>
<td>1.5</td>
</tr>
<tr>
<td>$D_{50}$</td>
<td></td>
<td>28.1</td>
<td>47.4</td>
<td>75.1</td>
<td>3.1</td>
</tr>
<tr>
<td>$D_{90}$</td>
<td></td>
<td>54.3</td>
<td>119.2</td>
<td>181.1</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Table 3. Particle Size of the IBU–Kollidon SD Systems Prepared by HYPULCON and the Spray Dryer

$\Delta$, IBU; $\blacktriangle$, IBU: Kollidon CL=1:5 SD; $\blacktriangledown$, IBU: Kollidon VA64=1:5 SD; $\blacklozenge$, IBU: Kollidon 30=1:5 SD; $\blacklozenge$, IBU: Kollidon 25=1:5 SD.
be explained via the establishment of hydrogen bonds between IBU and the Kollidon systems.

Conclusions

1. In the evaluation of IBU–Kollidon SD systems, the results of differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), scanning electron microscope (SEM), and Fourier transformation IR spectroscopy (FT-IR) demonstrated that in all SD systems with Kollidon system as carriers prepared by HYPULCON, crystal IBU changed to an amorphous state.

2. From the result of dissolution for IBU–Kollidon SD systems, it can be concluded that for improvement of dissolution characters, IBU–Kollidon systems with the water-insoluble carriers are better than with the water-soluble carriers. So, in future research, we will try to increase the dissolution behavior of SDs with water-soluble carriers such as Kollidon 30 or Kollidon 25 as a carrier using HYPULCON so that the SD systems can achieve a better effect.

3. Kollidon systems are used firstly in preparing IBU solid dispersions using the pulse combustion dryer system with pure water as a solvent. The results demonstrated that the pulse combustion dryer system, HYPULCON is very effective to prepare SDs of IBU with Kollidon systems of different grades as carriers. So, in future we will attempt to prepare SDs with new drugs and carriers using the pulse combustion dryer system.

References