Preparation of Solid Dispersion of Dronedarone Hydrochloride with Soluplus® by Hot Melt Extrusion Technique for Enhanced Drug Release

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In order to enhance the dissolution rate of dronedarone hydrochloride (DRN), a novel soluplus® (polyethylene glycol–polyvinyl caprolactam–polyvinyl acetate grafted copolymer)-based solid dispersion (SD) was formulated using a hot melt extrusion technique. The physical characteristics determined using scanning electron microscopy and X-ray powder diffraction, revealed that the active compound was molecularly dispersed in the amorphophlic polymer in a stable amorphous form. The dissolution rate of DRN from the tablet dosage form of SD extrudate consisted of the drug and Soluplus® in a weight ratio of 1:1, and was obviously more rapid and higher than that of the intact drug and marketed product (Multaq®, Sanofi, U.S.A.) at pH 1.2, 4.0 and 6.8. This suggests that Soluplus®-based SD formula can be a promising approach for enhancing the dissolution and oral absorption of DRN with a simple preparation process.

Key words dronedarone hydrochloride; Soluplus®; hot melt extrusion; dissolution

Dronedarone hydrochloride (Fig. 1, DRN), an antiarrhythmic agent, has been recently prescribed to reduce the risk of cardiovascular hospitalization in patients with paroxysmal or persistent atrial fibrillation or atrial flutter.1,2 In a clinical study, DRN effectively reduced hospitalization due to cardiovascular events or death due to any cause by 24.2% when compared to the placebo group.2 However, the oral absorption of DRN is quite challenging owing to its pH-dependent aqueous solubility; solubility in a weak acidic environment (pH 3 to 5) is about 1 to 2 mg/mL, but the solubility is remarkably decreased to one hundredth of a point in gastric fluid (pH 1.2) and/or intestinal fluid (pH 6.8).3 To improve oral absorption of the antiarrhythmic agent, the originator (Sanofi, U.S.A.) formulated an oral dosage form (Multaq® tablet, 400 mg as base) based on the solid dispersion (SD) system using conventional solvent method, with a triblock copolymer of polypropylene glycol and polyethylene glycol.3 In the SD formula, the drug may be dispersed within the hydrophilic carrier at a molecular level and it provided perfect wettability of the antiarrhythmic agent, the originator (Sanofi, U.S.A.) for the dissolution and oral absorption of DRN with a simple preparation process.

In the present study, we attempted to increase the amount of drug released throughout the gastrointestinal tract in the pH range of 1.2 to 6.8, by fabrication of Soluplus®-based SD using HME technique. Physicochemical properties of SDs were characterized with an emphasis on drug content, surface morphology, and crystallinity. Dissolution profiles of DRN from the SD system were investigated under various pH conditions in comparison with those of an intact drug alone and marketed product (Multaq®, Sanofi, U.S.A.).

Fig. 1. Chemical Structure of DRN

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Results and Discussion
Preparation and Physicochemical Characteristics of SDs of DRN  HME is a continuous process of transforming a drug compound and polymeric materials into a homogeneous SD by forcing it through a die under high temperature and pressure, thereby making extrude solids resistant to shear forces.8) Thus, the commonly used HME materials are thermoplastic polymers that are stable at the processing temperature.16) In our study, to increase dissolution rate of DRN via preparation of SD formulation using HME technique, a novel thermoplastic polymer, Soluplus®, was exploited. This polymer was demonstrated that it as a HME matrix but also as a solubilizer, thus effectively improving the solubility of Biopharmaceutical Classification System (BCS) II drugs. Furthermore, it is amorphous and due to its low glass transition temperature (about 70°C), is it easily extrudable with good flowability without the use of plasticizers.11–13) In our study, the HME process was performed at 150°C, which is around the melting point of DRN. The drug content in all Soluplus®-based HME formulations was uniform (98.0 to 102.0%) within the accepted limits and had low values of standard deviation (Table 1). These results indicate that the active compound was stable at the extrusion temperature along with uniform distribution within the SDs.

Figure 2 shows the scanning electron microphotographs (SEM) pictures of the drug powder (Fig. 2a), Soluplus® polymer (Fig. 2b), a physical mixture of drug and the amphiphilic polymer (Fig. 2c), and SD powder (F3) prepared by the HME method at a 1:1 ratio of drug to Soluplus® (Fig. 2d). The drug crystals were rectangular in shape, ranging in the size from 10–100μm (Fig. 2a). DRN crystalline powder was distinctively found from Soluplus® itself (Fig. 2b) in the physical mixture (Fig. 2c), suggesting that the drug itself presented in a crystalline form in the physical mixture. On the other hand, in case of SD, it was difficult to distinguish the existence of drug crystals (Fig. 2d), indicating that the drug crystals appeared to be incorporated into molten mass of the polymeric carrier. The appearance of SDs at different ratios was almost same to that of SD granules at a 1:1 ratio as shown in Fig. 2d (data not shown).

The crystallinity of DRN in Soluplus®-based SD formulations was investigated using X-ray powder diffraction (XRD) (Fig. 3). The diffraction spectrum of DRN powder showed that the drug is a highly crystalline powder and possesses sharp peaks at 2θ equal to 7.3°, 13.5°, 15.4°, 21.1°, 21.3° and 25.7° (Fig. 3a). No diffraction peak was observed in Soluplus® (Fig. 3b). All the principles peaks from DRN were shown in its physical mixture and thus, no interaction could be detected between the drug and the polymer (Fig. 3c). In case of F1, there was a decrease in the intensity of DRN, but major peaks originated from the drug substance still remained at the same positions. On the other hand, powder X-ray diffraction patterns of SDs with higher polymer ratios (F2–F4), were completely different from those of the raw materials and did not show any characteristic diffraction peaks corresponding to DRN. These data confirm that DRN exists in a whole amorphous state in the SD formulations F2, F3, and F4.

Dissolution Test  The dissolution profile of DRN from SD formulations at different drug to Soluplus® ratios was investigated in gastric juices (pH 1.2) on the basis of its limited solubility in acidic medium. Indeed, it can be seen that

Table 1. Compositions and Drug Content of DRN-Loaded SD Formulations

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<thead>
<tr>
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<th>F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
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<tr>
<td>Compositions (mg)</td>
<td></td>
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<tr>
<td>DRN</td>
<td>426.0</td>
<td>426.0</td>
<td>426.0</td>
<td>426.0</td>
</tr>
<tr>
<td>Soluplus®</td>
<td>106.5</td>
<td>213.0</td>
<td>426.0</td>
<td>852.0</td>
</tr>
</tbody>
</table>

Drug content (%) 98.0±1.2 101.0±2.0 102.0±4.7 101.4±2.7

a) Values represent mean±S.D. (n=3).
significantly faster and higher release rates were obtained with SD formulations compared to drug powder. The rate of DRN released within 15 min was all above 70% in all SD formulations, while the result for the drug powder was only about 15%. The dissolution rate at 1:0.25 DRN/Soluplus® ratio was lower other SD formulations, which may be due to the crystalline form of the drug contained at a low drug/polymer ratio as demonstrated by XRD observation. Drug dissolution rates were increased as the proportion of the amphiphilic carrier was increased, and they reached a plateau at a ratio of 1:0.5, where more than 80% of the drug was released within 15 min (Fig. 4). No significant differences in the release of DRN were observed between F2–F4.

When considering the pH-dependent solubility profile of the antiarrhythmic agent, it was very important in improving dissolution of the drug in the gastrointestinal tract, regardless of pH conditions, to increase the oral absorption of the drug. Thus, dissolution studies were further performed for the drug
powder, powder and tablet forms of F3 formula, and the commercially available product using various dissolution mediums (distilled water, pH 1.2, pH 4, and pH 6.8), and the results are shown in Fig. 5. The release patterns of DRN powder was obviously pH-dependent; over 50% of the drug was released after 2 h in pH 4 and distilled water, whereas the cumulative dissolution rates of DRN in pH 1.2 and 6.8 were only 23% and 2%, respectively. Although the marketed product (Multaq®) increased the amount of drug released in distilled water, the cumulative dissolution rates of DRN in pH 1.2 and 6.8 were similar to that of API itself. On the other hand, Soluplus®-based SD formula (F3) significantly increases the amount of DRN released in all mediums, regardless of pH conditions, achieving almost 80% of the drug released in all mediums tested. Especially, the amounts of DRN released from F3 powder in pH 1.2 and 6.8 were noticeably higher than those released from the marketed product, a 3.5-fold and 40-fold higher cumulative dissolution rate, respectively. The tablet dosage form of F3 also exhibited the higher release rate in pH 1.2 and 6.8 mediums compared to drug powder and even the marketed product, providing comparable dissolution rate to the powder dosage form. These results indicate that the incorporation of DRN into the amphiphilic polymer provided the complete wettability and a substantial increase in the saturation solubility of the poorly water-soluble compound. The amphiphilic polymer also might prevent the recrystallization of molecular DRN via interactions between drug and carrier, which result in improved dissolution rates of the active compound.

Conclusion

To increase the dissolution of DRN in the gastrointestinal tract, a novel SD system was prepared by molecularly dispersing the active compound into Soluplus® using the HME technique. The optimized SD system consisted of the drug and the amphiphilic polymer at the weight ratio of 1:1. The tablet form of the optimized SD significantly increased drug release in pH 1.2 and 6.8 mediums compared to that of the intact drug and the commercially available product. It released more than 60% of the drug in pH 1.2 and 6.8, whereas the cumulative dissolution rates of DRN were only 23% and 2% in the marketed product, respectively. On the basis of these results, it suggests that the Soluplus®-based SD formulation is a possible alternative to improve the oral absorption of DRN.

Experimental

Materials DRN was purchased from Bright-Gene (China, purity over 98.0 w/w%). Soluplus® was kindly obtained from BASF Co., Ltd. (Ludwigshafen, Germany). Avicel® PH 102 (microporous cellulose) and magnesium stearate were obtained from Asahi Kasei (Tokyo, Japan) and Taihei Chemical (Kawaguchi, Japan), respectively. Primojel® (sodium starch glycolate) was purchased from DFE Pharma (Nörten-Hardenberg, Germany). All organic solvents were high-pressure liquid chromatography (HPLC) grade and all other chemicals were reagent grade.

Preparation of Hot-Melt Extrudates Composites of the drug and polymer at different ratios were applied to prepare SDs by the Haake Minilab twin-screw extruder with counter rotating screws (Table 1). Physical mixtures were carried forward by the kneading screw set at 60 rpm at 150°C. The homogeneous hot-melt extrudates were collected and allowed to cool down to room temperature for 24 h, and then pulverized to pass through a 60-mesh screen. The powders of DRN-loaded SDs were stored at room temperature for further in vitro physicochemical characterization and dissolution test.

Preparation of Tablet Dosage Form The hot-melt extrudates of DRN obtained were blended with microcrystalline cellulose (Avicel® PH 102) 223.3 mg, sodium starch glycolate (primojel®) 40 mg, and magnesium stearate 4.2 mg, by dry mixing. The formulation containing DRN 400 mg as base was compressed on a single-punch tablet machine (Erweka, Germany) using an 10-mm round shaped flat punch by the direct compression technique. The total weight of the tablets was set to 800 mg. The hardness of the formulated products was between 8–10 kP, which is acceptable physical characteristics.

Physicochemical Characterization of SDs of DRN Drug Content: Each formulation containing 40 mg of the drug was dissolved in 1000 mL of acetonitrile and sonicated for 10 min. The samples were centrifuged at 12000 rpm for 10 min and the supernatants were analyzed by HPLC analysis. The quantitative determination of DRN was performed by HPLC using acetonitrile–water–triethanolamine (900:100:1) as a mobile phase at a flow rate of 1.0 mL/min. The HPLC system consisted of a pump (L-2130), UV detector (L-2400), a data station (LaChrom Elite, Hitachi, Japan), and a 15 cm C18 column (Capcell Pak C18 MG column, Shiseido, Japan). The column eluant was monitored at 245 nm, and the peak of DRN was separated with a retention time of 4.5 min.

Scanning Electron Microscopy (SEM): The SD powders were coated with a thin gold layer by an automatic magnetron sputter coater system (Jeol MSC201, U.S.A.). Then, SEM photographs were taken by a scanning electron microscope (Jeol JSM 6510 SEM, U.S.A.) operated at an acceleration voltage of 15 kV.

XRD: XRD observation of the SD powders was performed at room temperature with an X-ray diffractometer (X’Pert PROMPT PANalytical Co., Lelyweg, the Netherlands). Monochromatic CuKα-radiation (λ=1.5418 Å) was obtained with a Ni-filtration and a system of diverging and receiving slides of 0.5° and 0.1 mm, respectively. The diffraction pattern was measured with a voltage of 40 kV and a current of 30 mA over a 20 range of 3–40° using a step size of 0.02° at a scan speed of 1 s/step.

Dissolution Test Dissolution studies were performed according to the USP XXVIII paddle method using a VK 7000 dissolution testing station and VK 750d heater/circulator (VARIAN Industries, NJ, U.S.A.). The stirring speed was 50 rpm, and the temperature was maintained at 37±0.1°C. Each test was carried out in 900 mL of dissolution media (pH 1.2, pH 4.0, pH 6.8, and distilled water). Gastric juice was prepared with 2 g of sodium chloride and 7 mL of HCl in 1000 mL of distilled water. Each sample containing 400 mg DRN as a base were placed in the dissolution medium. Then, 5 mL aliquots were withdrawn at various time intervals and filtered using a 0.45 μm glass membrane syringe filter (Whatman® GD/X, GE Healthcare, U.S.A.). At each sampling time, an equal volume of the test medium was replaced. Filtered samples were appropriately diluted with acetonitrile, and the drug concentration was assayed by HPLC as described earlier.

Conflict of Interest The authors declare no conflict of interest.
References