[S2-3] [10/10/2003(Fri) 10:25-10:50/ Grand Ballroom 103]

Strategy on the Development of Acetal® Capsule Containing Poorly Water-soluble Aceclofenac

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Introduction

Aceclofenac (AFC) as a model has poor solubility in water, resulting in lower dissolution rate and bioavailability. A solid dispersion (SD) is one of effective methods to enhance the solubility or dissolution rate of various poorly water-soluble drugs. Polyvinylpyrrolidone (PVP) that is a nontoxic, water-soluble and generally applicable pharmaceutical excipient has been widely used as a carrier in the preparation of solid dispersions. In addition to, various additives such as fatty acid and surfactants can be also utilized to improve the solubility of poorly water-soluble drugs in the PVP-based solid dispersions. These formulation approaches are highly motivated for the enhanced dissolution and bioavailability of aceclofenac.

Purpose

The object of this study was to design and evaluate polyvinylpyrrolidone (PVP)-based solid dispersion (SD) system that can enhance the dissolution and bioavailability of aceclofenac (AFC), a practically insoluble in water and acidic solution. Thereafter, dissolution characteristics, stability at various storage conditions, and in vivo pharmacokinetic behaviors in rats and human volunteers were widely evaluated. Finally, bioequivalence of the novel Acetal® capsule approved by KFDA containing AFC were compared with commercial Airtal® tablet.

Experimental Methods

The solid dispersions consisted of AFC, oleic acid, surfactants and PVP. They were dissolved in semi-aqueous solution and then powdered by spray dryer. The powders were filled in hard capsules after the mixing with lubricant. The release study of AFC capsules was performed using USP dissolution method II in the simulated gastric fluid (pH 1.2). The

photo-image was also obtained using digital camera during dissolution test. The stability of SDs was also studied during storage at 40°C/75% for 6 months. To evaluate bioavailability of the capsules containing AFC solid dispersion, the Acetal® capsules (AFC 70mg) and commercial tablets (Airtal® AFC 100mg) were orally given to human volunteers with 240ml water for pharmacokinetic comparisons in a 2x2 cross over design. Plasma concentrations of AFC were monitored by reverse phase HPLC system with UV detector over 12 h after a single oral administration. The AUC was calculated by the trapezoidal method and Cmax and Tmax were directly read from the plasma concentration-time data.

Results and Discussion

The PVP-based SD containing AFC was a fine powder form with low bulk density but had some hygroscopic property. The PVP-based SD containing various solubilizing compositions showed higher dissolution rate in low pH of the gastric fluid than the commercial tablets (<2%) (Figure 1). The SDs showed more rapid and increased dissolution rate than commercial product in gastric fluid. The Acetal® capsule containing PVP-based SD showed good dissolution rate by forming nanoemulsion when dispersed in gastric fluid (Figure 2). The dissolution rate of AFC in gastric fluid was dependent on the amount and the type of solubilizing excipients.

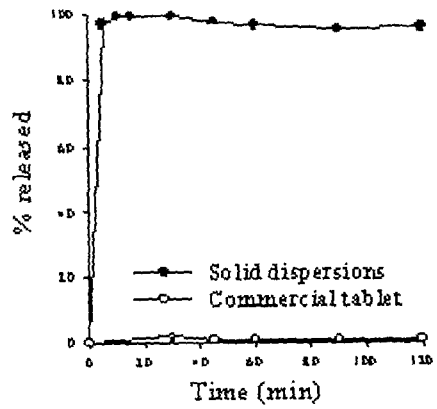

Figure 1. Comparison of release profiles of AFC solid dispersion and commercial Airtal® tablet

The PVP-based SD prepared by an oven drying was higher bulk density than other methods. Drying time and amount of solvents used together with powder property must be also

considered to decide drying methods. The dissolution profiles of PVP-based SDs were dependent on the sources of AFC raw materials. The large scale-up production of PVP-based SD might be possible because there was no difference in dissolution when scaled-up.

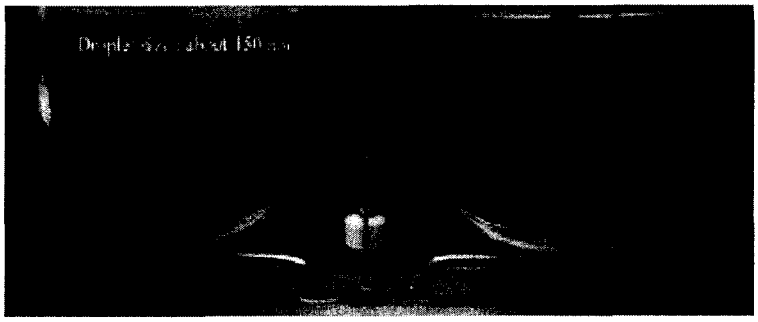

Figure 2. Comparison of photo-image of Acetal® capsule and Airtal® tablet during dissolution in simulated gastric fluid.

The contents and release profiles of Acetal® capsule was stable when stored in the condition of room and 40°C /75% during 6months. An antioxidant increased stability of PVP-based AFC SD by protecting oxidation of fatty acids, and reducing incompatibility of the excipients used. Because the PVP-based SD was also affected by moisture, the dampproofing package would recommend keeping the stability of PVP-based SD.

Plasma concentration-time curves of the Acetal® capsule [70mg AFC] containing solid dispersion and commercial tablet [100mg AFC] were compared in Figure 3. The Acetal® capsule containing PVP-based SD powders with surfactant and fatty oil showed the same Cmax and AUC as commercial Airtal tablets in spite of 70% reduced doses of AFC. The statistical ANOVA test of the logarithmically transformed or untransformed AUC and Cmax clearly indicated that no significant difference between the two preparations was observed, indicating the bioequivalence of Acetal® capsule containing 70 mg of AFC with Airtal® tablet containing 100 mg of AFC.

Conclusions

The solid dispersions were easily prepared by spray dryer and the products were easy to handle. The dissolution and bioavailability of AFC in PVP-based SD were highly enhanced due to the formation of nanoemulsion when dispersed in gastric fluid. The optimal

formulation originally approved as Acetal® capsule is very economical and stable during storage condition. The Acetal® capsule has unique advantage such as reduced gastric irritation, rapid onset time and unique dosage form. Due to the enhanced bioavailability, the capsules filled AFC solid dispersions were bioequivalent to the commercial tablets in lower content of drug. The novel 70 mg Acetal® capsule may also provide an alternative to commercial 100mg Airtal® tablet based on BE test.

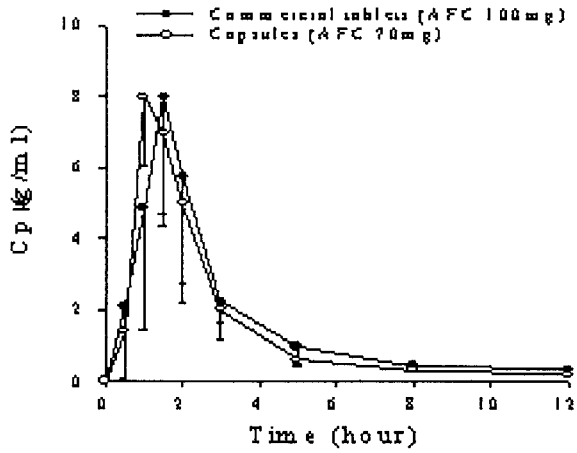

Figure 3. Comparison of in vivo bioavailability of AFC capsule containing solid dispersion and commercial tablet in human volunteers (n=6).

Acknowledgment

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