Effect of precipitation/re-dissolution processes from the supersaturated solution on the intestinal absorption of poorly water-soluble drugs

Haruki Higashino*, Keiko Minami, Makoto Kataoka, Shinji Yamashita
Faculty of Pharmaceutical Sciences, Setsunan University, Nagao toge-cho 45-1 Hirakata, Osaka 573-0101, Japan

ARTICLE INFO

Article history:
Available online 23 November 2015

Keywords:
Supersaturation
Oral absorption
Precipitation
Re-dissolution
HPMC

As one of the possible technologies to improve the oral absorption of poorly water-soluble drugs, supersaturable formulation, which enables to dissolve the drug to the higher concentration than their equilibrium solubility, is now attracting the attention [1]. This include salt-formation, solid-dispersion, co-crystallization or the use of amorphous form. Since supersaturation is a thermodynamically metastable state, supersaturated solution has a high potential to precipitate. Some pharmaceutical excipients, such as hydroxypropyl methylcel-lulose (HPMC), are used as precipitation inhibitors to stabilize the supersaturated state of drugs in the GI tract [2]. In addition, re-dissolution process of the precipitated drug might play an important role to improve the oral absorption even though there is little evidence to support it. In this study, for better understanding the in vivo performance of supersaturable formulations, precipitation/re-dissolution processes of BCS class 2 drug from a supersaturated solution were investigated in the presence or absence of HPMC. The contribution of re-dissolution process on the total drug absorption was also evaluated.

Danazol was used as a model drug of BCS class 2 and its supersaturated solution was prepared by solvent shift method [3]. Briefly, danazol was completely dissolved in DMSO as a stock solution, then the stock solution was diluted with fasted state simulated intestinal fluid (FaSSIF, pH = 6.5) to obtain a supersaturated solution. As a control, danazol was directly dispersed in FaSSIF. Dissolved concentration of the drug was observed in vitro during 4 h, reflecting a transit time in human GI tract. As an in vitro index of the dissolved amount of drug, area under the dissolved concentration–time curve (AUC_{dissolved}) was calculated. Further, the precipitation from the supersaturated
solution was collected to analyze the particle size. In vivo drug absorption was evaluated by intra-intestinal administration experiment in rat. Under the anesthesia, a supersaturated solution was injected into the small intestine, then plasma drug concentration–time profile was observed.

Dissolved concentration of danazol in the supersaturated solution was about 15% at 1 min after the dilution regardless of the presence/absence of HPMC. Supersaturation disappeared within 30 min in the absence of HPMC, while the addition of HPMC greatly stabilized the supersaturated state, keeping the higher dissolved concentration than that in the control for 4 hours (Fig. 1). The ratio of $\text{AUC}_{\text{dissolved}}$ to that in the control was 1.7-fold in the absence of HPMC and 11-fold in the presence. However, in the in vivo experiment, addition of HPMC failed to improve the oral absorption of danazol and no significant differences were observed in their plasma concentrations. Since danazol is a highly permeable drug, it was considered that the initial dissolved fraction in the supersaturated solution was absorbed quickly from the upper intestine in vivo, then the effect of prolonged supersaturation by HPMC was not observed. Interestingly, the fraction of absorbed from the supersaturated solution was estimated to be 60%, whereas the initial dissolved fraction was only 15% regardless of the presence/absence of HPMC. Since it was found that the particle size of precipitated danazol was much smaller than the original material, it was suggested that the increase in the re-dissolution rate from the precipitate contributed to the improved absorption of danazol. This study indicated the importance of the re-dissolution process after precipitation from the supersaturated solution for improving the oral absorption of poorly soluble drugs.

REFERENCES