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# Development of self-micellizing solid dispersion system employing amphipathic copolymer for the improvement of dissolution and oral bioavailability of cyclosporine A

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The main objective of the present study is to develop a self-micellizing solid dispersion (SMSD) system of cyclosporine A (CsA) using an amphiphilic copolymer, poly[MPC-*co*-BMA] (pMB) to improve the biopharmaceutical properties of CsA (Fig. 1A). Unlike conventional carrier compounds, pMB would perform the bifunctional ability as both polymeric carrier of solid dispersion system and solubilizer derived from a high micellizing property, which could be considered beneficial for the production of highly water soluble formulation of poorly water soluble compound [1]. Improvement in the aqueous solubility has been believed to be a key consideration for acquiring potent pharmacological effects of BCS class II drug like CsA. However, far less is known about its feasibility and applicability of pMB to solid dispersion systems and CsA with its high molecular weight.

pMB-based solid dispersion of CsA with drug loading 15% (w/w) was prepared using a wet-milling system, and its physicochemical properties were characterized with respect to the morphology, particle size distribution, dissolution behavior, crystallinity and stability. Pharmacokinetic studies of orally dosed CsA formulations were also performed to assess the improvement of oral absorption in rats. The cytotoxicity of pMB was assessed in rat intestinal IEC-6 cells, and the pMB was less cytotoxic than polysorbate 80, a non-ionic

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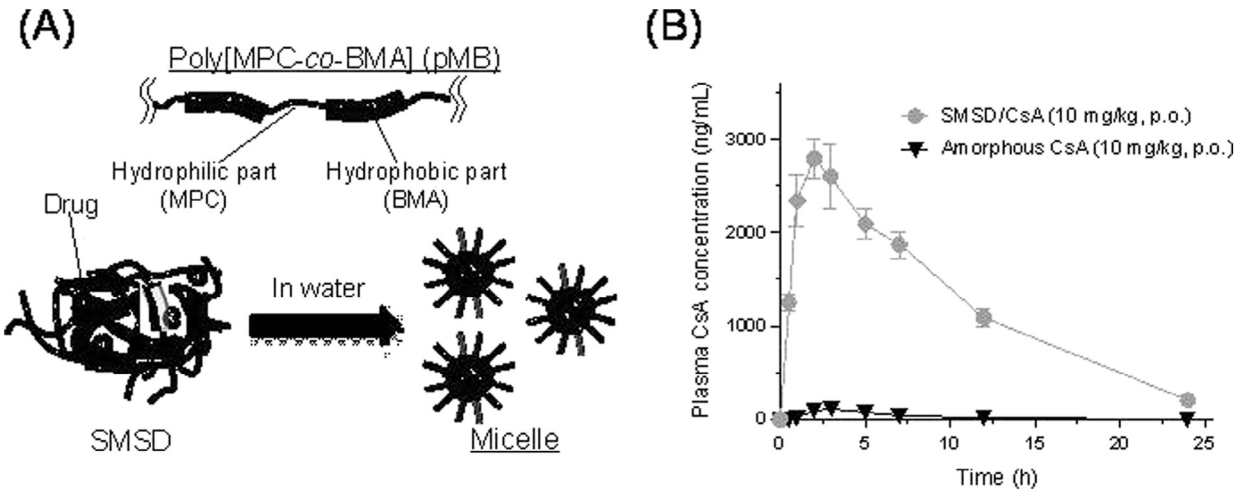


**Fig. 1 – The schematic image (A) and pharmacokinetic study after oral administration (B) of SMSD/CsA.**

surfactant with a wide safety margin. The SMSD/CsA exhibited immediate formation of fine micelles with a mean diameter of ca. 180 nm when introduced into aqueous media. There was marked improvement in the dissolution behavior of the SMSD/CsA compared with amorphous CsA. Even after storage at 40 °C/75% relative humidity, the dissolution behavior of aged SMSD/CsA seemed to be almost identical to that of its freshly prepared equivalent, and CsA in aged SMSD/CsA was still in amorphous form. After oral administration of SMSD/CsA (10 mg CsA/kg) in rats, enhanced CsA exposure was observed with increases of $C_{max}$ and bioavailability by ca. 11- and 42-fold, respectively, compared with those of amorphous CsA (Fig. 1B). From these findings, the pMB-based SMSD system might be an efficacious approach for improvements in oral bioavailability of CsA.

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