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Self-micellizing solid dispersions enhance the properties and therapeutic potential of fenofibrate: Advantages, profiles and mechanisms

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ABSTRACT

The goal of this work was to compare fenofibrate (FEN)-containing self-micellizing solid dispersion (SmSD) and non-self-micellizing solid dispersion (NsSD) systems. Exploration of underlying mechanisms to improve FEN dissolution/solubility profiles was conducted to understand the enhanced therapeutic potential. SmSD and NsSD of FEN systems (SmSD/FEN and NsSD/FEN) were fabricated using a fuse-quench cooling method. The self-micellizing Soluplus® cloud point was then determined experimentally and FEN phase solubility was measured in solutions containing self-micellizing Soluplus® or non-self-micellizing polymers. Physicochemical characteristics of SmSD/FEN and NsSD/FEN were evaluated using microscopic morphology, amorphous state, thermal performance, dissolution and solubility profiles. FEN exhibited an amorphous state in SmSD/FEN but was not completely amorphous in NsSD/FEN. The dissolution and solubility profile of SmSD/FEN achieved about 1.2- to 2-fold improvement over that of NsSD/FEN. Consequently, relatively enhanced hypolipidemic efficacy *in vivo* was observed in SmSD/FEN *vs* NsSD/FEN, as measured by serum levels of total cholesterol (TC), total triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL). Compared with non-self-micellizing polymers, self-micellizing Soluplus® significantly inhibited FEN crystal growth from a supersaturated state. However, no obvious difference in intermolecular interactions was observed between SmSD/FEN and NsSD/FEN systems. Overall, the SmSD approach exhibited as trengthened dissolution effect, enhancing FEN hyperlipidemic disease therapy efficacy.

1. Introduction

In the pharmaceutical industry, drug formulations often exhibit low aqueous solubility that limits dissolution rates, resulting in poor oral bioavailability and poor pharmacological activity. Moreover, up to 75% of new active pharmaceutical ingredients (APIs) possess low solubility with subsequent low activity toward important therapeutic targets. Overcoming this challenge would improve viability of APIs as candidates for pharmaceutical development (Adler et al., 2017; Baghel et al., 2016).

Meanwhile, cardiovascular disease is a major contributor to morbidity and mortality in modern society, especially in the elderly (Yang et al., 2015). Therefore, effective cardiovascular disease prevention and treatment are vital in order to decrease health care costs and improve quality of life. Fenofibrate (FEN) is an orally active, lipid-regulating drug currently used to control cardiovascular disease by effectively lowering levels of total triglycerides (TG), triglyceride-rich lipoprotein, low-density lipoprotein (LDL), high-density lipoprotein (HDL), apolipoprotein B and total cholesterol (TC) (Chapman, 2003; Fazio and Linton, 2004;

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Vakkilainen et al., 2003). FEN is also a therapeutic agent used for the treatment of hyperlipemia (Guay, 1999; Genest et al., 2000). As a Biopharmaceutical Class System (BCS) II drug (low solubility and high permeability), FEN is a highly lipophilic entity (logP = 5.24, where logP represents lipophilicity) (Griffin et al., 2014; Munoz et al., 1994) and is practically insoluble in aqueous gastrointestinal fluids. Such poor aqueous solubility weakens FEN oral absorption, resulting in low bioavailability and high variability in systemic exposure after oral administration (Guay 2002; Guivarc'h et al., 2004). Ultimately, enhanced efficacy of FEN *in vivo* will require improvement of its solubility and dissolution behaviors.

Numerous approaches have been well documented toward improvement of dissolution and *in vivo* performance of insoluble APIs. These approaches involve nanonization using solid lipid nanoparticles, nanocrystals or nanosuspensions (Serrano et al., 2015), the use of cyclodextrin inclusion complexes (Ye et al., 2015), the addition of organic or inorganic surfactants (Lee et al., 2015), self-emulsification (Inugala et al., 2015), ordered mesoporous silica (Tang et al., 2012), polymeric micelles (Cote et al., 2015), prodrugs (Liu et al., 2016) and solid dispersion techniques (Van Duong and Van den Mooter, 2016). Particularly, the application of solid dispersions (SDs) has resulted in successful creation of several commercial preparations (Bikiaris, 2011a, b). Moreover, Shi and co-workers have reported improvement of insoluble drug properties using SD strategies (Shi et al., 2013, 2014, 2017).

Recently, the use of amphiphilic polymers, including SD carriers, has attracted much attention due to their potential for increasing dissolution rate and absorption of water-insoluble APIs. Because such polymers contain both a hydrophilic portion and a hydrophobic portion, they tend to yield a nano- or micro-sized micelle via self-emulsification upon contact with an aqueous solution. Using this strategy, the Onoue lab has developed a self-micellizing solid dispersion (SmSD) system that incorporates an amphiphilic polymer to enhance oral absorption of insoluble drug candidates (Onoue et al., 2013, 2014; Kojo et al., 2017). The fabrication of SmSDs requires amphiphilic self-micellizing polymer carriers that generate micellar structures during the release process. Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (PLC-PVAc-PEG, 57%vinyl caprolactam-30% vinyl acetate-13% PEG 6000), also designated Soluplus®, is a promising carrier for development of solid dispersions and other nanocarrier systems exhibiting both improved dissolution profiles and bioavailability (Liu et al., 2017; Shi et al., 2017). Moreover, Soluplus® tends to self-assemble into a micellar structure to reduce free energy, allowing precipitation to occur at a lower critical solution temperature. However, challenges must be addressed before Soluplus® replaces conventional therapies. For example, the environmental conditions within the gastrointestinal tract probably alter Soluplus® solubility, as observed for conventional non-ionic polymers with similar cloud points. Furthermore, compared to typical polymer-based non-self-micellizing solid dispersion systems (NsSDs), the mechanism underlying the success of the Soluplus®-based SmSD approach for use with poorly soluble hypolipidemic drugs (e.g., FEN) is far less understood. Therefore, the therapeutic potency of SmSD relative to NsSD formulations must still be evaluated to assess the value of the SmSDs approach. Due to rapid developments that have demonstrated the advantages of SmSDs, SmSDs hold promise as the next generation of SD formulations.

A goal of the current work was to evaluate a self-micellizing solid dispersion (SmSD) system incorporating FEN for improvement of FEN dissolution/solubility profiles and enhancement of therapeutic potential. Comparisons of relevant properties between the SmSD system to non-self-micellizing solid dispersion (NsSD) systems, with exploration of underlying mechanisms, are investigated in this study. Polyethylene-polypropylene glycol 188 (poloxamer188), polyethylene glycol 6000 (PEG6000) and polyvinylpyrrolidone VA64 (copovidone) were selected as representative NsSD system carriers, due to their widespread use and their dissolution/solubility profiles, and compared toa Soluplus®-based

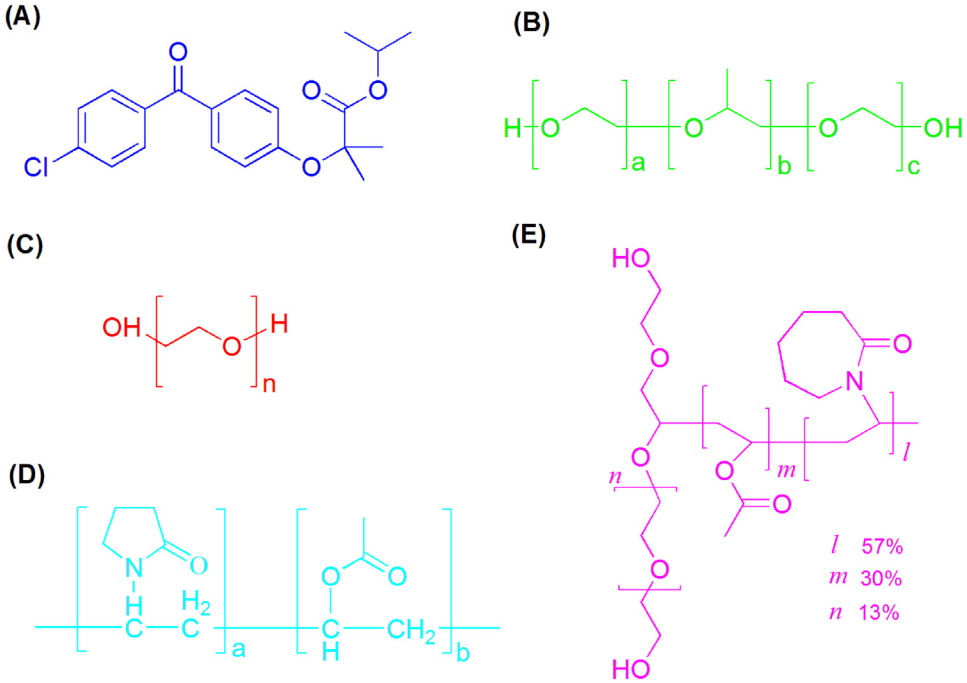

Fig. 1. Molecular structures of FEN (A), non-self-micellizing polymers including poloxamer188 (B), PEG6000 (C) and copovidone (D) and self-micellizing polymer Soluplus® (E).