Oral bioavailability of silymarin formulated as a novel 3-day delivery system based on porous silica nanoparticles

Xia Cao¹, Min Fu¹, Liang Wang¹, Hongfei Liu¹, Wenwen Deng, Rui Qu, Weiyan Su, Yawei Wei, Ximing Xu*, Jiangnan Yu*

Department of Pharmaceutics, School of Pharmacy, and Center for Drug/Gene Delivery and Tissue Engineering, Jiangsu University, 301 Xuefu Road, Jinghou District, Zhenjiang 212001, People’s Republic of China

1. Introduction

Silymarin, an antihepatotoxic polyphenolic substance extracted from fruit seeds of the milk thistle plant (Silybum marianum Gaertn), has been widely used to treat a variety of liver disorders including acute and chronic viral hepatitis [1–3], alcoholic liver disease [4], toxin- and drug-induced hepatitis and cirrhosis, fatty liver radiation, and toxicity. It is mainly composed of four flavonolignans, silybin, isosilybin, silydianin and silychristin, of which silybin is the most biologically active component, representing approximately 60–70% [3–5]. However, the therapeutic effects of silymarin are restricted due to its poor water solubility, resulting in poor oral absorption and low bioavailability after oral administration [6–8]. Xiao and co-workers reported that after oral administration of pure silybin, it was not detected in plasma [9]. In addition, Wu and co-workers reported that absolute oral bioavailability of silybin in rats was approximately 0.95% due to the poor solubility and extensive pre-systemic metabolism of the drug [10]. It was also reported that only 20–50% of silymarin was absorbed from the gastrointestinal tract after oral administration [6]. Furthermore, silymarin’s poor water solubility and poor absorption may be attributed to its poor permeation across intestinal epithelial cells [11,12]. Therefore, developing strategies to overcome these difficulties and to enhance the oral bioavailability of silymarin are highly desirable.

In recent times, different strategies have been investigated to improve the dissolution and bioavailability of silymarin. These strategies included silymarin/polyvinylpyrrolidone solid dispersion (SD pellets) [13], a silybin or dehydroxy silymarin proliposome [9,14,15], a silymarin self-microemulsifying drug delivery system (SMEDDS) [16], a silybin–phospholipid complex [17], silybin-loaded povidone–sodium cholate–phospholipid mixed micelles [18] and silymarin liposomes [19]. Again, Xiao and co-workers reported that a silymarin proliposome improved the oral bioavailability of silymarin in beagle dogs and enhanced gastrointestinal absorption. The relative bioavailability of silymarin SMEDDS is superior to that of silymarin PEG 400 solution and its suspension. Although the oral administration of these drug delivery systems in previous studies showed improved bioavailability, only few of these formulations that displayed sustained release of silymarin for more than 16 h in vivo have been reported. Thus improvement in bioavailability has been limited.

Over the past few decades, the application of mesoporous silica nanoparticles (MSNs) as a drug delivery system has attracted considerable attention [20–22]. It was reported that ordered mesoporous silica materials could be developed into a broad-spectrum...