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Effect of carrier type and surfactant concentration on the silymarin release

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INTRODUCTION
Silymarin, being the flavonoid complex isolated from Silybum marianum fruits is widely used and has new prospects to be used in medicine. Silybin (also known as silibinin) is main component of silymarin with attributed therapeutically properties. Silymarin behave as weak acid, can be considered as a Class II drug and has slow dissolution kinetics at pH 7.4 and low bioavailability (1). The inhibition of gut wall efflux with additional formulation components, the bypassing the gut wall efflux by lymphatic transport and the increasing intestinal flux by increasing of drug concentration in the place of absorption are well-known strategies for the improvement of bioavailability. The main objective of this study was to justify the chosen formulation strategy and to investigate the drug release of silymarin as function of carrier type (Avicel® PH-102 vs. Syloid® XDP 3150) and surface-active substance (Tween® 80) concentration.

MATERIALS AND METHODS
The sample of Silybum marianum dry extract (silymarin, batch No.: 20160301BT) obtained with acetone extraction (manufactured by and purchased from Liverd Pharma Co., Ltd., China) has met formal requirements EP 8.0. The HPLC-deminished silymarin assay was represented as silybin (= silibinin or silybinin) content equal to 61.8% (w/w) of which sum of silidianin and silicristin, sum of silybin A and B, and sum of isosilibinin A and B were equal to 24.7, 62.3 and 13.0 % of total silybin, correspondently. Reference products (manufactured by MADAUS GmbH, Germany) Legalon® 70 and Legalon® 140 contained Silybum marianum dry extract obtained with ethyl acetate extraction. The sample of mesoporous silica (Syloid® XDP 3150 manufactured by Grace GmbH, Germany) was kindly provided by Grace Engineered Materials UK Sales office. The sample of microcrystalline cellulose (Avicel® PH-102 manufactured by FMC BioPolymer, USA) was kindly provided by IMCD UK Ltd. Analytical grades of polysorbate 80 (Tween® 80) and acetone were purchased from Sigma-Aldrich (UK).

The full experimental design has been conducted for two carriers and three levels of Tween® 80 concentration (0%, 0.3% and 1.6% based on the dry composition weight). The organic solvent evaporation method was used to obtain silymarin-loaded powder formulotions. Silymarin substance, prepared formulotions and widely available silymarin formulotions (Legalon® 70 and Legalon® 140) were characterised using PXRD, TGA and DSC method. Apparent pKa of silymarin substance was determined using the alkaline titration method. Log P was determined using the slow-stirring method (2) with HPLC-quantification. Silymarin-loaded powder formulotions, Legalon® 70 and Legalon® 140 were investigated using a dissolution test (USP Apparatus II: 1 L of phosphate buffer solution pH 7.4; 50 rpm) and compared with similarity factor. Avicel® PH-102 and Syloid XDP® 3150 were additionally investigated with SEM, mercury intrusion porosimetry and their particle size was determined with laser diffraction spectroscopy method.

RESULTS
One of the ways to avoid gut wall efflux is using appropriate excipients-vehicles to reach the lymphatic system. The usual limitation for this approch is drugs lipophilicity, typically logP values should be >5 that leads to their incorporation into the process of intestinal lipoprotein assembly and transport into the intestinal lymphatics. As far as silybin Log P is 1.6 (±0.14) is lower than threshold for this formulation strategy. Silybin is expressing weak acid properties due to ionization of O-H groups, considering that in the intestine environment (pH 5.5-7.4) the Log D of silybin will even lower than Log P.

The thermal degradation of Silymarin was observed at a temperature higher than 228°C (TGA). Silymarin as a mixture of extracted components was demonstrating Tg onset at 85°C and melting onset at 146°C during the first heating cycle and only one Tg with onset at 105°C during the second cycle (DSC). The disappearing of two thermal
events observed during the first heating cycle and substituting them by one thermal event at the intermediate temperature is suggesting about dissolving of chemically similar components in each other. The presence of crystal fraction in silymarin substance (with melting onset at 146°C) has been additionally confirmed with PXRD, clear crystal-related peaks were observed at the range of 15 and 40 degree (Figure 1).

After loading onto the carrier, silymarin lost crystallinity. The drug release kinetics was faster for any drug-loaded carrier versus silymarin substance, and for Syloid® XDP 3150 formulations comparing to Avicel® PH-102 formulations. Adding of Tween 80 and increasing the concentration from 0.3 to 1.6% (w/w) have significantly increased the drug release kinetics of Avicel® PH-102 formulations but almost has not the effect on Syloid® XDP 3150 formulations (Figure 2).

CONCLUSION

The investigation of physicochemical properties of silymarin allowed to justify the increase of drug concentration in the place of absorption as the best formulation strategy.

Figure 1. X-ray diffractograms of silymarin substance, initial Avicel® PH-102 and Syloid® XDP3150 carriers, silymarin-loaded Avicel® PH-102 (A0, A1 and A2) and Syloid® XDP3150 (S0, S1 and S2), and reference products.

Figure 2. Drug release profiles of reference formulations (A), Syloid®XDP 3150 based formulations (B), and Avicel®PH-102 based (C) formulations of silymarin at the dose of 35 mg.

The effect of the carrier (Syloid® XDP 3150 versus Avicel® PH-102) and Tween® 80 concentration on the silymarin dissolution kinetics at pH 7.4 was established. The effect of carrier type was explained with properties of carriers.

REFERENCES
