Poster abstract: Effect of Carrier Type and Tween® 80 Concentration on the Silymarin Release from the Solid Dispersion

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**SUBMISSION PREVIEW: EFFECT OF CARRIER TYPE AND Tween® 80 CONCENTRATION ON THE SILYMARIN RELEASE FROM THE SOLID DISPERSION**

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Purpose
Silybin (the active component of Silymarin) is a weak acid having low solubility in gastric fluid. The active component also has limited absorption across the gut wall and as such can be considered a Class IV drug. The inhibition or bypassing of gut wall efflux mechanisms by lymphatic transport as well as increasing intestinal flux by increasing drug concentration at the absorption are well-known strategies for improving bioavailability. The main objective of this study was to identify a formulation strategy for this BCS Class IV drug and to examine the drug release properties of a range of carriers containing silybin (Avicel® PH-102 vs. Syloid® XDP 3150) and Tween® 80.

Methods
Silymarin was provided by Liverd Pharma Co., Ltd. (China) whereas Legalon®70 and Legalon®140 used as reference products were provided by MADAUS GmbH (Germany). Mesoporous silica Syloid® XDP 3150 was a generous gift from Grace GmbH (Germany) and microcrystalline cellulose Avicel® PH-102 supplied by FMC BioPolymer (USA), were used as carriers. Analytical grades of polysorbate 80 (Tween® 80) and acetone were purchased from Sigma-Aldrich (UK).

A full experimental design was conducted for two carriers and three concentration levels of Tween® 80 (0%, 0.3% and 1.6% w/w based on the dry composition). The wet impregnation of silymarin solution and Tween® 80 followed by organic solvent evaporation was used to obtain silymarin-loaded powder formulations. Log P was determined using the slow-stirring method with HPLC-quantification. Powder X-ray diffraction (PXRD), thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) were used as solid-state characterisation methods. Drug release from silymarin-loaded formulations and reference products were investigated using a dissolution test (USP Apparatus II: 1L of phosphate buffer solution pH 7.4; 50rpm) at 35mg dose and compared using similarity factor. Carriers were additionally investigated with SEM, mercury intrusion porosimetry (MIP) and their particle size were determined via laser diffraction spectroscopy.

Results
One of the ways to avoid gut wall efflux is to use appropriate excipients to reach the lymphatic system. The usual limitation for this approach is drug lipophilicity, typically log P values should be >5. This formulation strategy was not an option for silybin, due to its low Log P level of 1.6 (±0.14). In this study, we utilised the inclusion of Tween® 80 into the formulation as a means of inhibiting gut wall efflux and increasing drug concentration at the site of absorption.

The crystallinity of raw silymarin was been confirmed using PXRD (Fig.1) and its thermal degradation was observed at a temperature higher than 228°C (TGA). Silymarin displayed a melting onset at 146°C during the first heating cycle (DSC, Fig.2). During the second heating cycle, only one thermal event as Tg with onset at 105°C was observed. The loss of the melting endotherm during the second heat cycle suggests the loss of crystallinity following heating.

The drug release kinetics was faster for any drug-loaded carrier versus silymarin alone, and Syloid® XDP 3150 formulations were considerably more enhanced relative to Avicel® PH-102 formulations (Fig.3). Silymarin dissolution kinetics were faster for Syloid® XDP 3150 versus Avicel® PH-102 that may be explained with approx. three times higher specific pore volume (MIP) of Syloid® XDP 3150 versus Avicel® PH-102. Based on the MIP and laser diffraction, the faster dissolution rate of Syloid® XDP 3150 formulation can be explained with the specific structure of carrier particles namely high intra-particle porosity and specific surface area. The addition of Tween® 80 and increasing the concentration from 0.3 to 1.6% (w/w) significantly increased the drug release kinetics of Avicel® PH-102 formulations but had no effect on Syloid® XDP 3150 formulations. The drug release from Avicel® PH-102 formulations increased with the increase of Tween® 80 concentration, but even at highest Tween® 80 concentration, the Avicel®-based formulation was slower than Syloid® XDP 3150-based formulation without Tween® 80.

**Conclusion**

Silymarin's Log P value means that the approach to reach the lymphatic system should be rejected. Silymarin dissolution kinetics were faster for Syloid® XDP 3150 versus Avicel® PH-102 and explained though carrier properties. The addition of Tween® 80 and increasing the concentration from 0.3 to 1.6% (w/w) significantly increased the drug release kinetics of Avicel® PH-102 formulations but had no effect on Syloid® XDP 3150 formulations. Tween® 80 had minor effects on the silymarin release from Syloid® XDP 3150-based formulations, at the same time its ability to inhibit gut wall efflux is well known. This circumstance is opening the opportunity to modulate silymarin bioavailability by Tween® 80 concentration without changing of the drug release profile.

**References**

**Uploaded File(s)**

**Figures and/or Tables**
Fig. 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.

Fig1.jpg

Fig. 2. DSC-profile of silymarin.

Fig2.jpg
Fig. 3. Drug release profiles of reference formulations (A), Syloid®XDP 3150 based formulations (B), and Avicel®PH-102 based formulations (C) of silymarin at the dose of 35 mg.

Fig3.jpg