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

V. Mohylyuk [1], T. Pauly [2], O. Dobrovolnyi [3], N. Scott [4], D.S. Jones [1], G.P. Andrews [1]

[1] Pharmaceutical Engineering Group, School of Pharmacy, Queen's University Belfast, Belfast BT9 7BL, UK.

[2] Grace Europe Holding GmbH, In der Hollerhecke 1, 67547 Worms, Germany.

[3] Phytochemical laboratory, Borshchahivskiy Chemical-Pharmaceutical Plant, 17 Myru St, 03134 Kyiv, Ukraine.

[4] School of Biomedical Sciences, Ulster University, Coleraine BT52 1SA, UK.

PURPOSE

- **Silybin** (the active component of **Silymarin**) is a **weak acid** (pKa 5.7) 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**.
- There are a few well-known **strategies for improving oral bioavailability:**
  - increasing intestinal flux by increasing drug concentration at the absorption site,
  - bypassing of first-pass effect by lymphatic transport,
  - inhibition of gut wall efflux mechanisms.

OBJECTIVE(S)

- 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 as function of carrier type (Avicel® PH-102 vs. Syloid®XDP3150) and Tween® 80 concentration.

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 (**Table 1**).
- 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 with HPLC-quantification.
- Powder X-ray diffraction (**PXRD**), thermogravimetric analysis (**TGA**) and differential scanning calorimetry (**DSC**), scanning electron microscopy (**SEM**), mercury intrusion porosimetry (**MIP**) and their particle size were determined via laser diffraction spectroscopy were used as solid-state characterisation methods.
- **Drug release** from silymarin-loaded formulations and reference products were investigated using a dissolution test (USP II: 1L of phosphate buffer solution pH 7.4; 50rpm) at 35mg dose and compared using **similarity factor (F2)**.

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 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℃ (TGA). Silymarin displayed a melting onset at 146℃ during the first heating cycle (DSC). During the second heating cycle, only one thermal event as Tg with onset at 105℃ 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. 2**).
- 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; **Fig. 3**) of Syloid® XDP 3150 versus Avicel® PH-102.
- Based on the MIP, SEM (**Fig. 4**) and laser diffraction, the faster dissolution rate of Syloid® XDP 3150 (D_{50}186µm) versus Avicel® PH-102 (D_{50}54µm) formulation can be explained with the **specific structure** of carrier particles namely high **intra-particle porosity** and **specific surface area**.
- The **addition of Tween®** 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 (**Fig. 3**).
- 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.

CONCLUSIONS

- **Formulation strategy:** Silybin'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 without changing on the drug release profile.**

QUEEN'S UNIVERSITY BELFAST | SCHOOL OF PHARMACY

aaps PharmSci 360 — ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

"… This circumstance is opening the opportunity to modulate silymarin bioavailability by Tween® 80 without changing on the drug release profile."

aaps PharmSci 360 — ADVANCING PHARMACEUTICAL SCIENCES, CAREERS, AND COMMUNITY

Table 1. *Silymarin loaded formulations.*

Composition	Formulations, mg per 35 mg dose of silybin					
	A0	A1	A2	S0	S1	S2
Silymarin	58.3	58.3	58.3	58.3	58.3	58.3
Avicel® PH102	116.7	116.7	116.7	-	-	-
Syloid® XDP 3150	-	-	-	116.7	116.7	116.7
Tween® 80	-	0.6	2.9	-	0.6	2.9
Sum	175.0	175.6	177.9	175.0	175.6	177.9
Composition	Formulations, % (w/w)					
	A0	A1	A2	S0	S1	S2
Silymarin	33.3	33.2	32.8	33.3	33.2	32.8
Avicel® PH102	66.7	66.5	65.6	-	-	-
Syloid® XDP 3150	-	-	-	66.7	66.5	65.6
Tween® 80	-	0.3	1.6	-	0.3	1.6

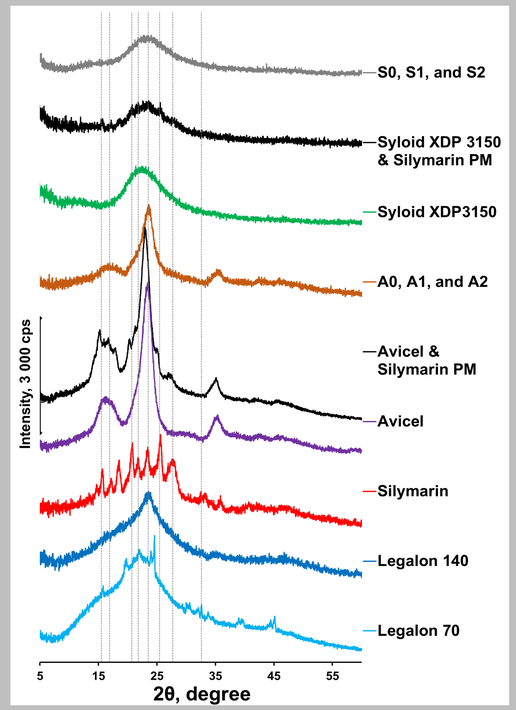
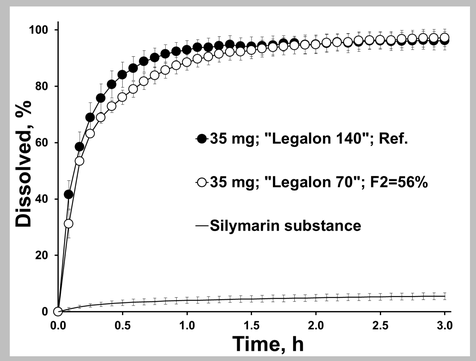
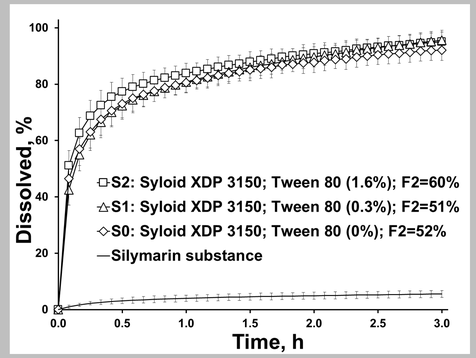


Fig. 1. *X-ray diffractograms of silymarin substance, initial carriers, silymarin-loaded formulations, and reference products.*





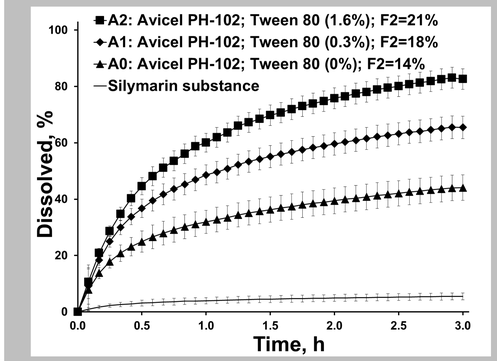
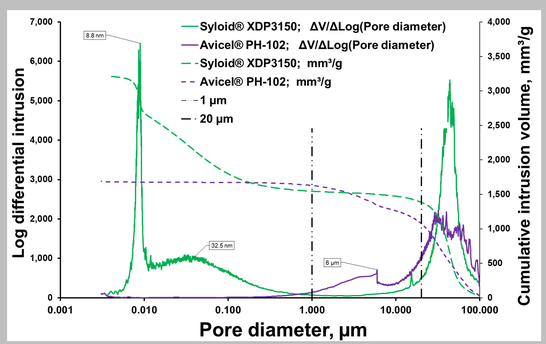


Fig. 2 *Drug release profiles of silymarin at the dose of 35mg from reference formulations (upper), Syloid®XDP 3150 based (middle), and Avicel®PH-102 based formulations (the lower).*



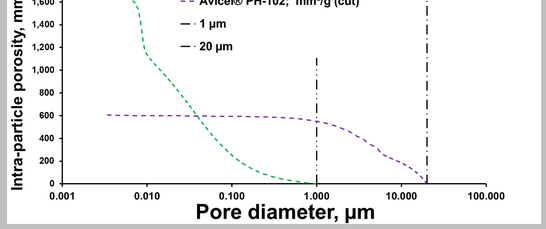


Fig. 3. *Pore size distribution (upper) and assumed intra-particle porosity (the lower) of Avicel® PH-102 and Syloid® XDP 3150 determined with mercury intrusion porosimetry.*

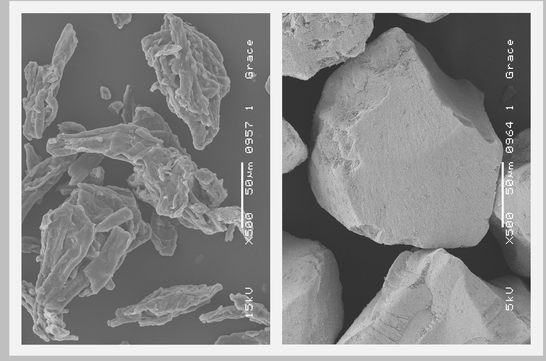


Fig. 4. *SEM pictures: Avicel® PH-102 (left) and Syloid®XDP3150 (right)*