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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** (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)**.

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

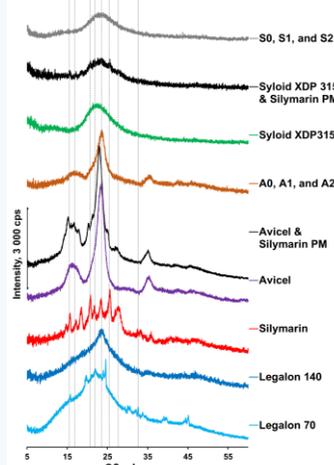


Fig. 1. X-ray diffractograms of silymarin substance, initial carriers, silymarin-loaded formulations, and reference products.

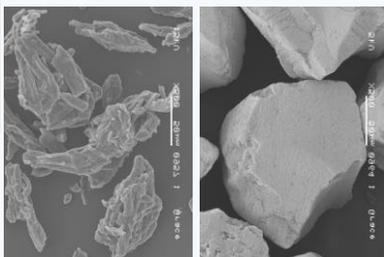


Fig. 4. SEM pictures: Avicel® PH-102 (left) and Syloid®XDP3150 (right)

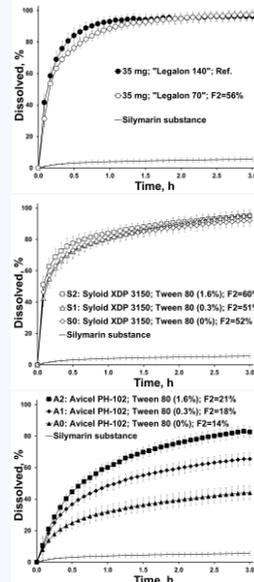


Fig. 2 Drug release profiles of silymarin at the dose of 35mg from reference formulations (upper), Syloid®XDP 3150 based (middle), and Avicel®PH-102 based formulations (the lower).

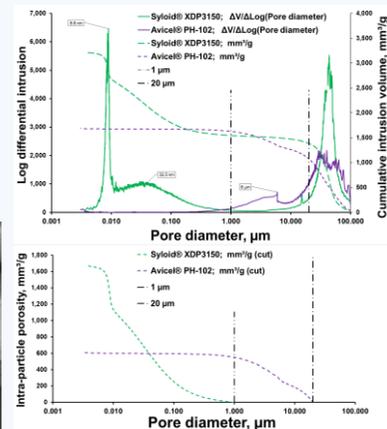


Fig. 3. Pore size distribution (upper) and assumed intra-particle porosity (the lower) of Avicel® PH-102 and Syloid® XDP 3150 determined with mercury intrusion porosimetry.

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 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). During the second heating cycle, only one thermal event at 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. 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.186µm) versus Avicel® PH-102 (D.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® 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 (**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.**

REFERENCE

Mohylyuk V, Pauly T, Dobrovolnyi O, Scott N, Jones DS, Andrews GP. Effect of carrier type and Tween® 80 concentration on the release of silymarin from amorphous solid dispersions. J D Deliv Sci Tec. 2021;63, DOI:10.1016/j.jddst.2021.102416.