Silymarin, a flavonolignan derived from *Silybum marianum*, possesses diverse pharmacological activities, including hepatoprotective, antioxidant, anti-inflammatory, anticancer, and cardioprotective. Although clinical trials have shown silymarin is safe at high doses (>1500 mg/day) in humans, the pharmacokinetic studies over the past three decades related to absorption, distribution, metabolism, and excretion of silymarin have revealed poor absorption, rapid metabolism, and ultimately poor oral bioavailability. For optimum silymarin bioavailability, issues of solubility, permeability, metabolism, and excretion must be addressed. An array of methods have been described in recent years that can improve its bioavailability, including complexation with β-cyclodextrins, solid dispersion method, formation of microparticles and nanoparticles, self-microemulsifying drug delivery systems, micelles, liposomes, and phytosomes. This article critically reviews the recent published literature on various techniques for increasing the bioavailability of silymarin.

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**Introduction**

*Silybum marianum*, commonly known as milk thistle in the family Asteraceae, is one of the oldest and thoroughly researched plants of ancient times for the treatment of liver and gallbladder disorders, including hepatitis, cirrhosis, jaundice, and protection against *Amanita phalloides* mushroom and other toxin poisonings.1 Silymarin, the active component of this plant, is a standardized extract consisting of approximately 70- to 80-percent silymarin flavonolignans (silybin A & B, isosilybin A & B, silydianin, and silychristin) and flavonoids (taxifolin and quercetin), and the remaining 20-30 percent consisting of a chemically undefined fraction comprised of polymeric and oxidized polyphenolic compounds (Figure 1).2

Silymarin possesses a wide range of biological and pharmacological effects, including antioxidant activity,3 stimulation of protein synthesis and cell regeneration (making it useful in the treatment of toxic liver damage, chronic inflammatory liver diseases, and liver cirrhosis),4,5 and impressive anticancer effects against several human carcinoma cell lines.6,7 In addition, antidiabetic activity,8 cardioprotection,9 anti-inflammatory, antifibrotic, hypolipidemic, neurotrophic, neuroprotective, and immune modulation effects are well documented.10

**Physicochemical and Pharmacokinetic Properties of Silymarin**

**Dosage**

All clinical trials of milk thistle conducted in the past have demonstrated safety and efficacy of silymarin at doses of 1,200-1,500 mg/day.1 The typical oral adult dose of silymarin is 240-800 mg/day in two or three divided doses.11

**Solubility**

Low water solubility (0.04 mg/mL) of silymarin is reported. Solubility of silymarin in various other solvents like transcutol, ethanol, polysorbate 20, and glyceryl monooleate is 350.1 mg/mL, 225.2 mg/mL, 131.3 mg/mL, and 33.2 mg/mL, respectively.12 Silymarin possesses no lipophilic properties, even though its water solubility is poor.12

**Bioavailability**

Silybin is the primary and most active component of the silymarin complex. All pharmacokinetic parameters of silymarin are referred to, and standardized as, silybin. Orally administered silymarin (silybin) is rapidly absorbed with a t<sub>max</sub> (2-4 hours) and t<sub>1/2</sub> (6 hours). Only 20-50 percent of oral silymarin is absorbed from the gastrointestinal tract where it undergoes extensive enterohepatic circulation. Therefore, absorption of silymarin from the gastrointestinal tract is low, making
bioavailability poor. Wu et al reported 0.73-percent oral bioavailability of silymarin (standardized as silybin) in rat plasma.

### Tissue Distribution
Zhao and Agarwal performed a tissue distribution experiment in mice and concluded that silybin (50 mg/kg), both in free and conjugated form (e.g., glucuronide and sulfate conjugated forms), is quickly absorbed after oral administration and has a good tissue distribution profile in various tissues examined.

### Metabolism
Silymarin (standardized as silybin) undergoes phase I and phase II biotransformation in the liver. It is metabolized by CYP450-2C8 in vitro into o-demethylated silybin (major) and mono- and dihydroxy- silybin (minor) metabolites. During phase II, multiple conjugation reactions have been observed that include the formation of silybin monoglucuronide, silybin diglucuronide, silybin monosulfate, and silybin diglucuronide sulfate (Figure 2).

### Excretion
Silybin in humans and rats demonstrates rapid elimination of both free and conjugate forms. Wen et al, through pharmacokinetic analysis, discovered that silymarin flavonolignans were rapidly eliminated with short half-lives (1-3 and 3-8 hours for free and conjugated forms, respectively). Studies in humans and rodents suggest that biliary excretion of glucuronide and sulfate conjugates is the major route for silymarin’s elimination.

### Summary of Causes for Limited Silymarin Bioavailability
The four major causes of limited silymarin bioavailability are extensive phase II metabolism, low permeability across intestinal epithelial cells, low aqueous solubility, and rapid excretion in bile and urine (Figure 3). These factors necessitate the incorporation of silymarin into a form that can augment its bioavailability. Table 1 illustrates the various methods used to enhance silymarin’s bioavailability.

### Methods to Augment Silymarin Bioavailability
#### Complexation with Phospholipids
From standardized silymarin, silybin can be isolated and combined on a molecular level with phosphatidylcholine. The formulation, initially named IdB 1016 (from Indena; Italy), is patented as Siliphos® and also referred to as silipide or silybin phytosome. It is provided as one part silybin and two parts phosphatidylcholine. Major advantages include increased absorption, lower therapeutic dose, and better stability profile.
Barzaghi et al assessed the Siliphos pharmacokinetic profile in humans. Siliphos bioavailability was found to be significantly greater than that of non-complexed silymarin, probably because complexation with phosphatidylcholine facilitating its passage across the gastrointestinal mucosa.\textsuperscript{21}

Morazzoni et al found silybin complexation with phosphatidylcholine was 10 times more bioavailable than silybin alone.\textsuperscript{22,23}

Schandalik et al administered silipide to patients with cholestasis secondary to biliary extrahepatic obstruction. On average, the area under the curve (AUC) for total silybin was more than 40-fold greater than the AUC for free silybin.\textsuperscript{24}

Skottová et al administered radio-labeled silybin and their complexes 1:1 with phosphatidylcholine concurrently with unlabeled silybin in a comparative study of bioavailability in the rat. The superior bioavailability of radio-labeled silybin was observed with increased radioactivity in liver, kidney, spleen, and heart.\textsuperscript{25}

Yanyu et al compared the oral pharmacokinetic characteristics and bioavailability of silybin-phospholipid complexes to silybin-methylglucamine in rats. Pharmacokinetic parameters were found to be $T_{\text{max}}$, 10 minutes and 5 minutes; $C_{\text{max}}$, 126.72 ng/mL and 104.29 ng/mL, AUC\textsubscript{0-∞}, 1,020.33 ng/mL/hour and 235.81 ng/mL/hour, respectively. Silybin bioavailability in rats increased remarkably after oral administration of silybin-phospholipid complex compared to silybin-methylglucamine, primarily due to improvement of the lipophilic property of the complex.\textsuperscript{26}

Filburn et al, studying the bioavailability of a phytosome complex in dogs, found $C_{\text{max}}$, $T_{\text{max}}$, and AUC\textsubscript{0-24}. Values for total silybin were 1,310±880 ng/mL, 2.87±2.23 hours, and 11,200±6,520 ng/mL per hour, respectively. Corresponding values for a standardized silymarin extract were 472±383 ng/mL, 4.75±2.82 hours, and 3,720±4,970 ng/mL/hour, respectively, showing the phytosome complex markedly enhances bioavailability in dogs.\textsuperscript{27}
Verschoyle et al advanced silipide to the stage of clinical investigation in prostate cancer. Silipide is silybin combined with phospholipids to increase the oral bioavailability and biological activity of silybin.

**Liposomes**

The aim of this technique is to engage silymarin into liposomal structures to make it more effective, safe, and targeted to liver cells. Liposomes are spherical, self-enclosed structures with a lipid bilayer (ranging from some nanometers to several micrometers) that possess a unique amphiphilic character.

Maheshwari et al prepared liposomal vesicles of silybin by the ethanol injection method. The results of the *in vivo* studies for hepatoprotective activity in mice against carbon tetrachloride induced hepatotoxicity and gastroprotective activity using the pyloric ligation method indicated 55-percent hepatoprotection by silymarin liposomes compared to 33-and 24 percent by non-liposomal silymarin and liposomes without silymarin, respectively. Liposomes, even without silymarin, can convey some hepatoprotective effects because of their liver supportive phospholipid content.

Xiao et al studied physicochemical properties, pharmacokinetic characteristics, and bioavailability of silymarin proliposomes in rats after oral administration. Proliposomes are defined as dry, free flowing particles that immediately form liposomal suspension on contact with water. By this technique the stability problem of liposomes can be resolved without influencing their intrinsic characteristics. The encapsulation efficiency (amount of drug that goes into the liposomal core/total amount of drug incorporated) of silymarin liposomes is up to 90 percent, with an average particle size of about 238.8 nm and achievement of good stability.

Yanyu et al compared the pharmacokinetic characteristics and bioavailability of silymarin proliposome with pure silymarin after oral administration to beagle dogs. Pharmacokinetic parameters of silymarin proliposome and silymarin were both 30 minutes; $C_{\text{max}}$ 472.62 and 89.78 ng/mL; and AUC$_{\text{0-31}}$ 2,606.21 and 697 ng/mL/hour, respectively. This study demonstrated the high bioavailability and enhanced gastrointestinal absorption of silymarin proliposome compared to pure silymarin.

El-Samaligy et al demonstrated increased bioavailability of silymarin using a buccal liposomal delivery system. In a subsequent study, these silymarin liposomes were evaluated for hepatoprotective activity against carbon tetrachloride-induced oxidative stress in albino rats. The liposomal formulation significantly reduced serum glutamic pyruvic transaminase (SGPT) level compared to a silymarin suspension.

Dube et al primed galactosylated liposomes for silybin delivery and targeting lectin receptors present on hepatocytes by covalently attaching them with p-aminophenyl β-d-galactopyranoside. A positive hepatoprotective effect demonstrated galactosylated liposomes were more effective than non-galactosylated liposomes and suitable for targeted delivery of silybin to hepatocytes.

**Inclusion Complex with β-Cyclodextrins**

Complexation is also an approach to increase the solubility of a compound. Cyclodextrin is known to enhance solubility of a variety of compounds by forming what are called inclusion complexes.

Arcari et al demonstrated a dramatic increase in dissolution rate of a silybin and β-cyclodextrin complex (>90% within five minutes) compared to non-complexed silybin that is almost insoluble. After administration of the silybin complex *in vivo*, the silybin concentration in rat bile was nearly 20-times greater than after administration of silybin in its traditional form.

Voinovich et al prepared and optimized the physicochemical properties of a

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**Table 1. Methods of Silymarin Bioavailability Augmentation**

<table>
<thead>
<tr>
<th>Conventional Methods</th>
<th>Novel Methods</th>
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<td>Soft gel capsule technology</td>
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<td>Micronization up to 5-20 microns</td>
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silybin-β-cyclodextrin complex by XRD, DRIFT, and Raman spectroscopy. The activated systems significantly enhanced the in vitro drug dissolution kinetics with subsequent improved oral bioavailability. Furthermore, in vivo studies on rats revealed a 6.6-fold increased bioavailability compared to S. marianum (Italian commercial product Silirex® 200 mg capsules).³⁹

**Incorporation in Solid Dispersions**

Solid dispersions appear to be a viable technique for overcoming the bioavailability problem of poorly water-soluble substances.⁴⁰ This section addresses various solid dispersion formulations of silymarin that can lead to a highly bioavailable product.

Li et al discovered that the dissolution rate of silymarin considerably increased when formulated in solid dispersion of polyethylene glycol 6000 (PEG 6,000) compared to pure silymarin; the increased dissolution rate might favorably impact oral absorption.⁴¹,⁴²

Zhang et al formulated a water-soluble polyethylene glycol prodrug of silybin and characterized it by proton NMR, FT-IR, and TOF-MS. The drug loading capability was found to be 6.65 percent and the solubility was 800 mg/mL, indicating significantly higher solubility of the prodrug in comparison with silybin alone.⁴³

Qiu et al prepared dripping pills of silymarin and PEG 6,000 in a 1:4 ratio by the traditional fusion method. The dissolution rates of silymarin dripping pills were higher than the rates of marketed silymarin preparations, including Viganling film-coated tablets (China), Yiganling sugar-coated tablets (China), and Legalon capsules (Germany).⁴⁴

Nakhat et al formulated silymarin-β-cyclodextrin solid dispersion tablets by a direct compression technique using superdisintegrants such as croscarmellose sodium, sodium starch glycolate, and polyplasdone in different concentrations. All the formulations showed improved dissolution over marketed formulations, reflecting a vital role of β-cyclodextrin in promotion of silymarin oral bioavailability.⁴⁵

Sun et al enhanced the dissolution of silymarin/polyvinylpyrrolidone solid dispersion pellets after preparation by a one-step fluid-bed coating technique, which increased the relative bioavailability of silybin solid dispersion pellets about five-fold compared to a silybin suspension, confirming enhanced oral bioavailability.⁴⁶,⁴⁷

**Formation of Derivatives: Salt, Prodrug, and Glycosides**

Formation of water-soluble derivatives, salts, and glycosides has helped increase the bioavailability of silymarin. Glycosylation often improves the solubility of various drugs without affecting their activity. Respective glycosides may also act as prodrugs. Moreover, β-galactosylation can improve hepatic cell uptake, known to contain high concentrations of β-galactoside receptors.⁴⁸ A salt of silybin is available as silybin dihemisuccinate, which is given in emergency cases of Amanita phalloides poisoning.⁴⁹,⁵⁰

Pifferi et al synthesized silybin 11-o-phosphate-3 by selective phosphorylation of silybin with POCl₃. The pharmacological activity was evaluated in the rat by using the praseodymium poisoning test. Results showed that the compound possessed hepatoprotective activity, possibly with lower potency compared to the reference drug silybin hemisuccinate.⁵¹

Kren et al isolated two silybin diastereoisomers in the form of acetylated monoglycosides. They were between four and 30 times more water soluble and their hepatoprotecitivity was equal to the parent compound silybin.⁵²

Kosina et al prepared four β-glycosides of silybin (silybin β-galactoside, silybin β-glucoside, silybin β-maltoside, silybin β-lactoside) in order to improve silybin water solubility and bioavailability.⁵³,⁵⁴

Gazak et al synthesized a silybin derivative (2,3-dehydrosilybin). This compound demonstrated improved water solubility by selective oxidation of the parent compound silybin. Although the antioxidative property of dehydrosilybin was superior to silybin by one order, its water solubility was too low for application in an aqueous milieu. On the other hand 2,3-dehydrosilybinic acid was found to be fairly soluble, with better anti-lipoxidation and other antioxidant properties than that of silybin.⁵⁴ Dzubak et al prepared a series of α-alkyl derivatives (methyl and benzyl) of silybin that demonstrated enhanced cytotoxic and p-glycoprotein modulatory activity.⁵⁵

Zhang et al increased the solubility of silybin in aqueous polyvinylpyrrolidone (PVP k30) solution at the temperature range from 293.15 to 313.15 K by a solid = liquid equilibrium method. Experimental results reveal that the solubility of silybin increased with the increase both in PVP concentration and temperature.⁵⁶
Bai et al increased the solubility of silybin in aqueous dextran solution and aqueous poly (ethylene glycol) 6000 solution by a solid liquid equilibrium method at temperatures ranging from 293.15 to 313.15 K. Experimental results reveal that the solubility of silybin increased in both solvents with the increase both in concentration and temperature.\textsuperscript{57,58}

Bai et al increased the solubility of silybin in aqueous hydrochloric acid solution at temperatures ranging from 293.15 to 313.15 K. Experimental results also revealed that the solubility increased with the increase of both temperature and pH value.\textsuperscript{59}

**Floating Tablets**

Garg and Gupta formulated floating effervescent tablets of silymarin to prolong gastric time and compared to silybin in hard shell capsules. In the softgel, silybin was complexed in 1:2 ratio with phosphatidylcholine. The pharmacokinetic parameters demonstrated that the mean values of both $C_{\text{max}}$ and $AUC_{0-1}$ increased dramatically when the patented soft gelatin capsule formulations were administered ($C_{\text{max}}$ more than three-fold and $AUC_{0-1}$ more than two-fold) in comparison to pure silybin.\textsuperscript{61} Since the silybin was complexed with phosphatidylcholine in the softgel but provided as straight silybin in the hard shell capsule, it is impossible to determine whether the capsule type made a significant difference.

**Softgel Technology**

A cross-over, randomized study on silybin bioavailability in softgel capsules was conducted by Savio et al and compared to silybin in hard shell capsules. In the softgel, silybin was complexed in a 1:2 ratio with phosphatidylcholine. The pharmacokinetic parameters demonstrated that the mean values of both $C_{\text{max}}$ and $AUC_{0-1}$ increased dramatically when the patented soft gelatin capsule formulations were administered ($C_{\text{max}}$ more than three-fold and $AUC_{0-1}$ more than two-fold) in comparison to pure silybin.\textsuperscript{61} Since the silybin was complexed with phosphatidylcholine in the softgel but provided as straight silybin in the hard shell capsule, it is impossible to determine whether the capsule type made a significant difference.

**Micronization and Nanonization**

More than 40 percent of compounds identified through combination screening programs are poorly water soluble. These molecules are difficult to formulate using conventional approaches and are associated with innumerable formulation-related performance issues. Micronization and nanonization are newer techniques for increasing drug bioavailability. Micronization is the process of reducing the particle size of a solid to 2-5 µm; whereas, in nanonization, particle size is reduced to 5-300 nm to increase its surface area, leading to an improvement in the dissolution rate.\textsuperscript{62}

Di Pierro et al reported on the clinical efficacy, safety, and tolerability of micronized silymarin as BIO-C®. Used as a galactagogue, consumption resulted in an 85-percent increase in daily breast milk production in healthy women after delivery, without affecting milk quality.\textsuperscript{63} Similarly, Capasso et al evaluated the effect of a micronized standardized extract of *S. marianum* on serum levels of prolactin in female rats. A 14-day treatment with silymarin (25-200 mg/kg, given orally) increased serum prolactin levels in a dose-dependent manner due to increased bioavailability.\textsuperscript{64}

Zhang et al effectively prepared micronized silybin particles by an emulsion solvent diffusion method using sodium dodecyl sulfate concentration (0.1 wt %) at 30°C and 15°C. Dissolution tests demonstrated that micronized silybin exhibited a significantly enhanced dissolution rate when compared to commercial, non-micronized silybin powder.\textsuperscript{65}

**Controlled Delivery Systems**

**Transdermal Delivery Systems**

Delivery of silymarin via the skin has, until recently, been virtually unexplored. In 2010, Hung et al studied the transdermal absorption of silymarin components (silybin, silydianin, and silychristin) and concluded that the lipophilicity increased in the order of silychristin < silydianin < silybin. Greater lipophilicity conferred higher skin deposition, but had a minor effect on permeation across the skin in the less-ionized form (pH 8). It is apparent that compounds in the less-ionized form showed higher skin uptake compared to the more-ionized form.\textsuperscript{66}

**Sustained Release Systems**

Sustained delivery systems for herbal medicines are difficult because of their complex composition. Lu et al generalized the concept of synchronized release of silymarin from erodible matrix systems based on glyceryl monostearate and polyethylene glycol 6000 or poloxamer 188 by a melt fusion method to perform strict control on synchronized release of the five active components of silymarin (i.e., taxifolin, silychristin, silydianin, isosilybin, and silybin). The release was sustained up to 12 hours with erosion-controlled release mechanisms.\textsuperscript{67}
Targeted Delivery Systems

Microspheres
Abrol et al formulated silymarin-loaded lipid microspheres with constituents, including an internal oily core, a surfactant such as soybean lecithin, and cosurfactants such as span 20 (sorbitan laurate), tween 20 (polyoxyethylene 20 sorbitan monolaurate), tween 80 (polyoxyethylene 80 sorbitan monooleate), and propylene glycol in different concentrations to optimize the final formulation for globule size range, structural integrity, sustainability, and percent drug-holding capacity. When compared to a silymarin solution in propylene glycol, the mean percent release from silymarin-loaded lipid microspheres was 56 percent after 36 hours, compared to 18 percent with the silymarin solution.68,69

Nanocarriers
Nanocarriers, such as nanoparticles, niosomes, solid lipid nanoparticles, polymeric micelles, and dendrimers, are colloidal particulate systems with a size range of 10-1,000 nm. They have been successfully utilized in the diagnosis, treatment, and monitoring of various diseases because of their bioavailability-enhancing ability.70

Ibrahim et al prepared and characterized sodium alginate-based, pH-responsive, hydrogel microspheres encapsulating poly (d, l-lactic-co-glycolic acid) (PLGA) nanoparticles. This preparation technique is ideal for encapsulation of hydrophobic ingredients such as silymarin. Also, the encapsulation of the water-insoluble silymarin into nanosized particles would enhance the dissolution and consequently the bioavailability of silymarin.71

Parveen et al prepared a nanocarrier formulation of silymarin to increase its oral bioavailability. The pharmacokinetic parameters AUC and $C_{\text{max}}$ of nanoemulsion after oral administration were four-fold and six-fold higher than those of a silymarin drug suspension.72

Jun et al prepared silymarin-solid lipid nanoparticles (SLNs) by lyophilization and investigated the effect of particle size on oral absorption of various sized nanoparticles (150 nm, 500 nm, and 1,000 nm). The oral bioavailability of 150-nm SLNs in rats was significantly higher than the other two SLN sizes (AUC of 150 nm was 2.08-fold and 2.54-fold that of 500-nm and 1,000-nm SLNs, respectively).73 In a body distribution study of silymarin-SLNs after oral administration, the relative bioavailability was 2.79-fold higher compared to the silymarin suspension (milled silymarin powder). These results indicated preparing silymarin as SLNs can improve the oral bioavailability.74

Xu et al formulated silybin lipid nanoparticles by a thin film emulsion high pressure homogenization technique and studied the biodistribution in mice. This method resulted in increased distribution of silybin in blood and liver compared with the preparations on the market. The drug targeting index (DTI; Drug Targeting Index = $\frac{\text{AUC}_{\text{liver}}}{\text{AUC}_{\text{blood}}}$) of SLN compared to the market preparation was 1.81, leading the authors to conclude that SLN can increase the uptake of silybin in liver after oral administration, which could be of benefit in the treatment of hepatitis.75 Note: The DTI was calculated based on AUC at a target (liver) and systemic site (venous blood) following administration into and sampling from both sites. The closer a compound’s DTI is to 1, the less targeting it has. The liver DTI of SLN compared to the market preparation was 1.81, indicating that SLN was more effective than the market preparation in liver targeting.76,77

Zhang et al developed stealth solid lipid nanoparticles (size in the nanometer range) for silybin. Stearic acid was used as a biodegradable lipid and Brij-78 as surfactant. A very slow release of silybin was reported from SLNs.78

Jia et al prepared silybin-loaded nanostructured lipid carriers (NLC) with various liquid lipid contents by the method of emulsion evaporation at a high temperature and solidification at a low temperature. The size and morphology of nanoparticles were significantly influenced by the liquid lipid content. Compared with solid lipid nanoparticles, NLC provided improved drug-loading capacity that increased with increasing liquid lipid content. The drug in vitro release behavior from NLC displayed a biphasic pattern with burst release at the initial stage and prolonged release afterwards; successful controlled release rate was achieved by controlling the liquid lipid content.79

Self Micro-Emulsifying Drug Delivery Systems (SMEDDS)
SMEDDS are isotropic mixtures of oils, surfactants, and/or co-solvents used in the oral delivery of poorly water-soluble drugs. They improve oral bioavailability via enhancement of gastrointestinal solubilization. Other advantages are potential reduction in dose, selective targeting of the substance toward specific absorption windows in the gastrointestinal tract, and protection of the substance from a hostile gut environment like acids and enzymatic degradation.80
Yuan et al investigated the absorption of silymarin microemulsion in rat intestine and found it to be well absorbed at the middle and lower segments of the intestine. The absorption was a first-order process with a passive diffusion mechanism.81

Relative bioavailability of silymarin was dramatically enhanced an average of 1.88- and 48.82-fold that of silymarin-polyethylene glycol 400 solution and suspension, respectively, concluding enhanced bioavailability of silymarin by SMEDDS.82

Woo et al formulated SMEDDS of silymarin, and upon its oral administration to rats the bioavailability of the drug from the SMEDDS was found to be 3.6-times higher than the reference dosage form (i.e., Legalon capsules).12

Liu et al developed SMEDDS of silymarin and compared them with commercial capsules (Legalon, Germany) and tablets (Yiganling, China). The SMEDDS formulation proved to be a suitable alternative for improving the oral absorption of silymarin.83

Polymeric Micelles
Polymeric micelles are nano-sized particles composed of polymer and copolymer chains. They wrap a hydrophobic substance into their hydrophobic cores and significantly increase drug delivery by preventing its degradation by the body. They can survive reticuloendothelial system identification and capture because the polymer is non-toxic, biocompatible, and non-immunogenic. This extends its retention time and improves its bioavailability.

Wu et al prepared silymarin-loaded amphiphilic chitosan micelles and performed an in situ silymarin absorption investigation in rat intestine. The absorption of silymarin micelles at different segments of rat intestine was significantly higher than that of silymarin suspension.84

Li et al found micelles significantly increased the amount of silybin in the liver.85

A summary of the techniques to enhance silymarin bioavailability is found in Table 2.

Table 2. Summary of Techniques for Enhancement of Silymarin Bioavailability

<table>
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<th>Bioavailability Augmentation Methods</th>
<th>Improvement in Bioavailability</th>
<th>Reference</th>
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<tr>
<td>Complexation with phospholipids</td>
<td>Siliphos 10 times more bioavailable than silybin alone</td>
<td>Morazzoni P et al; 1992, 1993</td>
</tr>
<tr>
<td>Inclusion complexes with β-cyclodextrins</td>
<td>Silybin cyclodextrin complex 20 times more bioavailable than silybin alone</td>
<td>Arcari M et al; 1992</td>
</tr>
<tr>
<td>Incorporation in solid dispersions</td>
<td>Solid dispersion form of silybin is five-fold more bioavailable than the silybin suspension</td>
<td>Sun N, Wei X et al; 2008</td>
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<tr>
<td>Glycoside formation</td>
<td>Silybin glycosides 4-30 times more water-soluble than pure silybin</td>
<td>Kren V et al; 1997</td>
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<tr>
<td>Floating tablets</td>
<td>Prolonged the drug release for 24 h, thereby improving the bioavailability</td>
<td>Garg R, Gupta GD; 2009</td>
</tr>
<tr>
<td>Soft gel capsule technology</td>
<td>Increase in Cmax more than three-fold and AUC0-1 more than two-fold</td>
<td>Savio D et al; 1998</td>
</tr>
<tr>
<td>Controlled drug delivery systems</td>
<td>Prolonged and sustained release is achieved</td>
<td>Lu C et al; 2007</td>
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<tr>
<td>Microparticles</td>
<td>The mean percent release of 56.70 ± 2.03% was observed in 36 h from silymarin microparticles, compared to 18.67 ± 0.192% with silymarin solution</td>
<td>Abrol S et al; 2004</td>
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<td>Nanoparticles</td>
<td>The relative bioavailability was 2.79-fold higher compared to the silymarin suspension</td>
<td>Jun H et al; 2007</td>
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<tr>
<td>Liposomes</td>
<td>Tmax, Cmax and AUC0-1 of silymarin proliposome in beagle dogs were much higher than pure silymarin, concluding high bioavailability profile</td>
<td>Yanyu X et al; 2006</td>
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<tr>
<td>Self microemulsifying drug delivery systems (SMEDDS)</td>
<td>Upon oral administration in rats the bioavailability of silymarin from the SMEDDS was found 3.6-fold higher than the Legalon capsules</td>
<td>Woo JS et al; 2007</td>
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Liu et al developed SMEDDS of silymarin and compared them with commercial capsules (Legalon, Germany) and tablets (Yiganling, China). The SMEDDS formulation proved to be a suitable alternative for improving the oral absorption of silymarin.83
Future Directions

Although milk thistle demonstrates significant clinical efficacy, its utility is limited by poor oral bioavailability. A number of approaches for increasing the oral bioavailability of silymarin have been extensively studied, including solubilization, cosolvency, complexation with β-cyclodextrins, and solid dispersion. More targeted delivery systems are currently being explored – a transdermal delivery of silymarin for various skin-related disorders like skin cancers, for example. Another possible approach to improve bioavailability is to reduce the particle to nano size by methods like pearl milling, high pressure homogenization, emulsification, and precipitation, which can lead to superior in vivo drug performance.

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