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Silymarin Loaded Novel Drug Delivery for Oral and Topical Administration

Gorhe Ankita[a], Kulkarni Abhijeet[b], Kandalkar Pallavi[c], Jagtap Snehal[d]

[a] Department of Pharmaceutical Quality Assurance, Sanjivani College of Pharmaceutical Education and Research, Kopargaon- 423601, Maharashtra, India.

[b] Department of Pharmaceutical Quality Assurance, Sanjivani College of Pharmaceutical Education and Research, Kopargaon- 423601, Maharashtra, India.

[c] Department of Pharmaceutical Quality Assurance, Sanjivani College of Pharmaceutical Education and Research, Kopargaon- 423601, Maharashtra, India.

[d] Department of Pharmaceutical Quality Assurance, Sanjivani College of Pharmaceutical Education and Research, Kopargaon- 423601, Maharashtra, India.

ABSTRACT

Silymarin is polyphenolic flavonoid obtained from the seeds of silybum marianum plant. It has various pharmacological properties such as hepatoprotective, anti-inflammatory, antioxidant, anti-carcinogenic, hypolipidemic properties. Silymarin has recently reported to be neuroprotective agent against neurodegenerative disease such as Alzheimer, Parkinson's and cerebral ischemia. It contains eight active components, among which silibinin is the most active component. However, silymarin is BCS class II drug which having poor bio availability due to extensive phase II metabolism, poor aqueous solubility, low permeability across intestinal epithelial cells and rapid excretion in bile and urine. Therefore, it is necessary to understand all formulations and analytical aspects including all possible future prospects. In this review a potential approach to enhance solubility, bioavailability and to develop a robust formulation is studied. The number of studies describes novel drug delivery system (NDDS) based formulations have been significantly increased. The raise in novel drug delivery exploitation is essentially due to defeated barriers within technological process of lipid based nanoparticles formulations and increased knowledge of underlying mechanisms of transport of NDDS via different route of administration. This review focuses on pharmacological properties of silymarin, challenges, benefits and application of novel drug delivery system. To reduce the adverse effects and toxicities novel drug delivery will be an attractive approach of current therapies.

Keywords: Silymarin, route of administration, novel drug delivery, bioavailability, solubility

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***Address for Correspondence:**

Dr. Abhijeet Kulkarni, Department of Quality Assurance Techniques, Sanjivani College of Pharmaceutical Education and Research, Kopargaon- 423601, Maharashtra, India

INTRODUCTION:

Silymarin is obtained from the extracts of seeds and fruits of Silybum marianum plant it's common name is milk thistle and it is chemically known as 2-(2,3-dihydro-2-(4-hydroxy-3-methoxyphenyl)-3-(hydroxymethyl)-1,4-benzodioxin-6-yl)-2,3-dihydro-3,5,7-trihydroxy4H-1-benzopyran-4-one[1]. It is one of the oldest and thoroughly researched plants of ancient times used as herbal medicine and food supplement for the treatment of various diseases associated with liver and gallbladder, hepatitis, cirrhosis, jaundice and protection against amanita phalloides mushroom and other toxin poisonings. The silymarin is composed of three isomer flavonolignans: silybin, silydianin, isosilibinin and silychristin[2]. Silybin (silibinin) is the most active component of silymarin[3]. Silybin is the mixture of two diastereomers A and B in approximately 1:1 propoportion containing therapeutic properties such as antioxidant, anti-inflammatory, anti-carcenogenic, neuroprotective, hepatoprotective, cardioprotective properties.

In polar aprotic solvents (eg. acetone, N, N-dimethylformanide, and tetrahydrofuran) silybin is highly soluble, in polar protic solvents (e.g ethanol and methanol) it is poorly soluble and in non-polar solvents (eg. chloroform and petroleum ether) it is insoluble. The pharmacokinetics studies showed that the oral administration of silymarin is only 23-47% absorbed from gastrointestinal tract where it undergoes enterohepatic circulation[4,5]. It is metabolized by CYP450-2C8 to mono and dihydroxy silybin (minor) and o-

demethylated silybin (major) metabolites[6]. During the phase II metabolism multiple conjugation reactions are observed it includes formation of silybin monoglucoronide, silybin diglucoronide, silybin monosulfate, and silybin diglucoronide sulfate[7]. The small amount of absorbed silybin is excreted in kidney and about 18% is excreted in the bile after conjugation with sulfate and glucuronide. The reported clearance half-life of silymarin is 6–8 hours[8]. Poor aqueous solubility, high metabolism, poor penetration across epithelial cells, rapid systemic excretion these are main reasons for limited bioavailability of silybin. To overcome these issues, novel drug delivery has shown great potential using different formulations like liposomes, microspheres, solid dispersion, emulsions, dendrimers, solid lipid nanoparticles, nanosuspension, nanocrystals, inclusion complex, micelles, to improve the aqueous solubility, penetration ability and to enhance bioavailability.

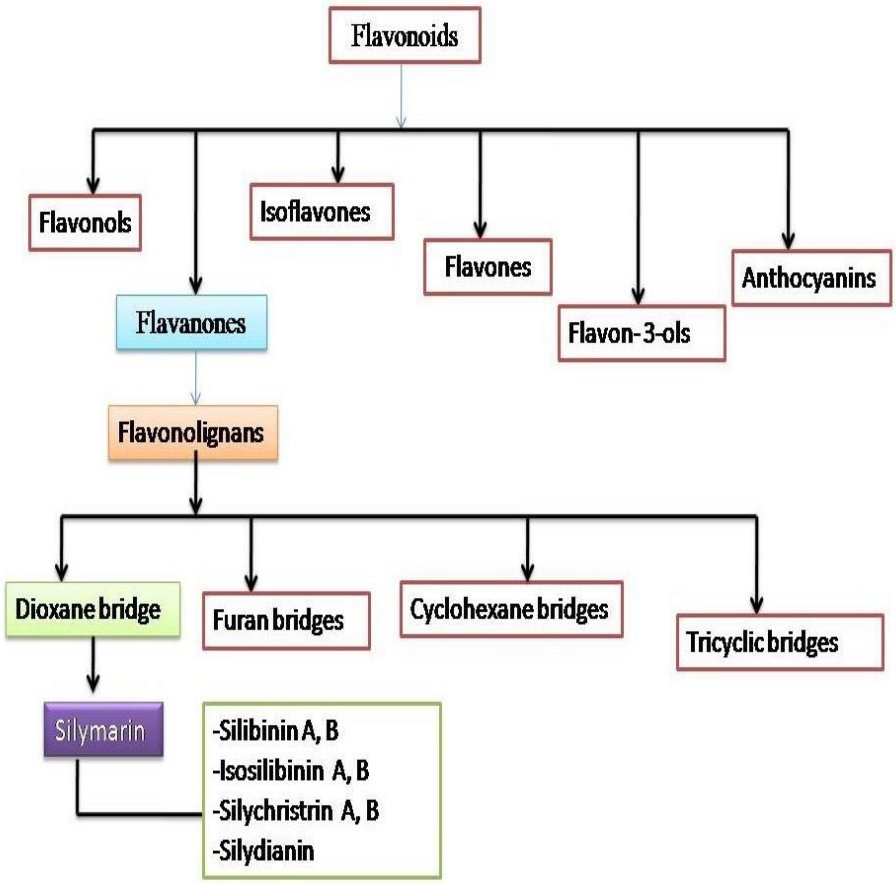

Figure 1: Classification of flavonoids

PHARMACOLOGICAL PROPERTIES:

Silymarin shows antioxidant properties and acts as a free radical scavenger that induces lipid peroxidation and also influences enzyme systems associated with glutathione and superoxide dismutase[9]. In pre-clinical study silymarin and silybin are agents found to be liver protective in mouse and rats against hepatotoxicity induced by different agents such as carbon tetrachloride, ethanol intoxication, cisplatin, acetaminophen, thioacetamide[10]. The silymarin shows action on lung cancer, breast cancer, ovarian cancer, cervical cancer, skin cancer, prostate cancer, liver carcinoma, bladder cancer. Silybin induced MCF7 breast cancer cells to undergo autophagic cell death and observed formation of autophagy related genes i.e Atg12-Atg5, Beclin-1 upregulation and Bcl-2 downregulation[11]. In breast cancer T47 cell line decreases in miR-21, miR-15a and miR-141 while increases in miR-200c expression levels when treated with silibinin[12]. Silybin shows anticancer effect on both androgen-dependent and androgen-independent prostate cancer by inhibiting cell growth, cell invasion and metastasis. The epithelial to-mesenchymal transitions are targeted by silybin in which epithelial characteristics are stimulated and the expressions of mesenchymal markers are inhibited. Silybin treatment for prostate cancer resulted in cytokeratin-18 up regulation and viment down regulation[13]. Silybin shows time and dose dependent apoptotic action on human bladder transitional cell carcinoma (TCC) which is related to cleavage of caspase 3 and poly(ADP-ribose) polymerase[14].

The most active component of silymarin i.e silybin contains anti-inflammatory properties by inhibiting the prostaglandins and leukotrienes from polyunsaturated fatty acids in the liver and enzyme lipoxygenase. The potential of silybin is suggested in the treatment of Alzheimer by inhibiting Hsp 90 which leads to degradation of Hsp 90 protein client. Silybin shows an antifibrotic effect by reducing the transformation of stellate cells into myofibroblasts and down regulates gene expression of extracellular matrix components indispensable for fibrosis. Silybin treatment resulted to decrease in CDK2 and CDK4 levels, the apoptosis of ECV304 cells are induced and angiogenesis inhibited by modulation of caspases, Bcl-2 family and NF-kappaB. The growths of some cancers in rodents are inhibited by dietary silybin and its potential is suggested in treatment of cancer.

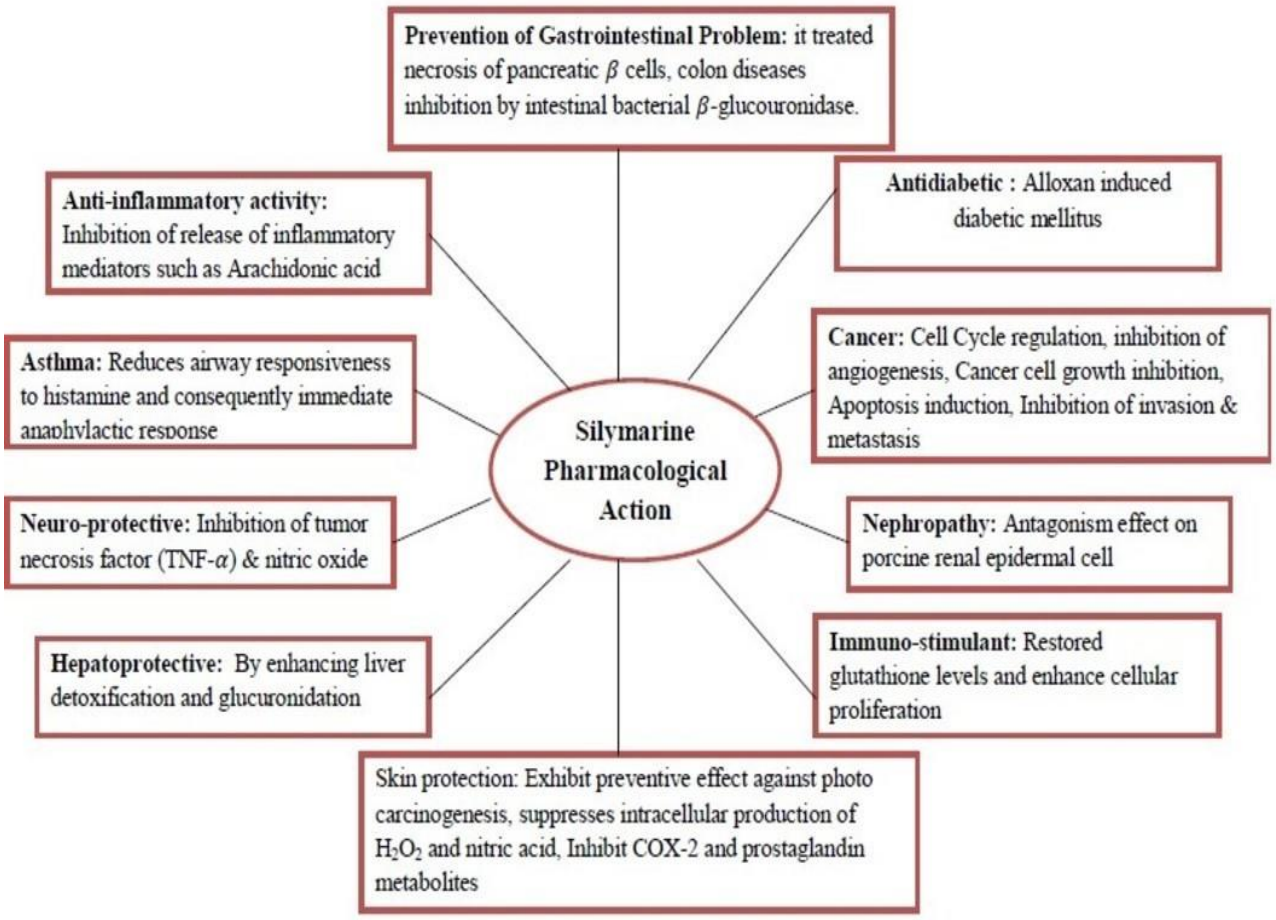

Figure 2: Pharmacological action of silymarin

APPLICATIONS BY DIFFERENT ROUTE OF ADMINISTRATION

Oral route

Oral route of drug administration has been known for decades and widely accepted method for drug delivery because of its simple, convenient, noninvasive, safest, and most economical aspect. The challenging problems in oral drug delivery includes, difficulty in swallowing pill, irritant and unpalatable drugs being not suitable for administration by this route, poor stability in the gastric environment, low solubility and poor bioavailability, slow onset of action, less or no control over drug release, nonspecific delivery site and systemic side effects. The Silymarin is BCS class II drug having poor bioavailability due to extensive phase II metabolism, poor aqueous solubility, low permeability across intestinal epithelial cells and rapid excretion in bile and urine. To overcome this problems the different types of silymarin nanoparticles (NPs), such as liposomes, nano- or micro- emulsions, polymeric NPs and solid lipid NPs, polymer conjugates, nanocrystals, polymeric micelles, mixed micelles inclusion complex, continue to be developed in order to improve the stability and bioavailability of Silymarin.

Table 1: Oral drug delivery of silymarin

Formulation	Composition	Preparation method	Purpose	Ref
		TABLETS		
Floating Tablet	Hydroxypropyl methyl cellulose, microcrystalline cellulose, crospovidone	Wet granulation	Prolong gastric residence time	15
Erodible matrix tablets	Glyceryl monostearate, Polyethylene glycol 6000, Poloxamer188	Melt Fusion	Controlled release of SLM	16
Solid dispersion tablet	Hydroxy propyl-β -cylcodextrine (HP-β-CD)	Direct compression	Enhance dissolution and oral bioavailability	17
Osmotic tablets	Cellulose acetate	Melt fusion	Controlled release of SLM	18
Fast dissolving	Cross povidone,	Dry granulation	Fast dissolving with improve patient compliance and	19

Formulation	Composition	Preparation method	Purpose	Ref
tablet	Microcrystalline Cellulose, Croscarmellose sodium, Aerosil		convenience	
Microporous osmotic pump tablet	Dibutyl phthalate, soyabean lecithin, Sodium chloride, lactose, mannitol	Phytosome complex method	Sustained and controlled-release drug delivery	20
Nanosuspension tablet	Polyvinyl alcohol, Tween 80, mannitol	Lyophilization	Immediate release	21
		LIPOSOMES		
Liposome	Cholesterol	Ethanol injection	Enhance hepatoprotective and gastroprotective effect	22
Liposome	Lecithin, cholesterol, stearyl amine, tween-80	Reverse evaporation technique	Enhance hepatoprotective effect	23
Liposome	ρ- amino phenyl- β-D-Galactopyranoside	Reverse evaporation technique	Targeting to hepatocyte	24
Liposome	Lecithin, Cholesterol	Lipid film hydration method	Targeting to hepatocyte and to improve oral bioavailability	25
Liposome	Soybean phosphatidylcholine, sodium glycocholate	supercritical fluid technology	improve the dissolution and bioavailability of silymarin	26
Proliposomes	Soy-lecithin, D-Galactosamine, Superoxide dismutase (SOD), malondialdehyde (MDA), glutathione peroxidase (GSH-PX)	simple dissolving process	improve bioavailability and hepaptoprotective effects	27
Proliposomes	Phospholipid and mannitol	Film deposition	Enhanced bioavilability	28
Proliposomes	soybean phospholipids, cholesterol, isopropyl myristate and sodium cholate	Film dispersion-freeze drying method	Improve oral bioavailability	29
Bilosomes	Soybean lecithin phosphatidylcholine, cholesterol, Sodium deoxycholate, Sodium taurocholate, Carbon tetrachloride	Film hydration technique	Increase the hepatoprotective activity of the drug	30
		SOLID- LIPID NANOPARTICLE		
Solid lipid nanoparticle	_	High pressure homogenization	Enhanced biodistribution	31
Solid lipid nanoparticle	ATO 5, lecithin, tween 80	High pressure homogenization	Improve oral bioavailability	32
Solid lipid nanoparticle	Compritol 888 ATO, soyabean lecithin, Poloxamer-188	Hot and cold homogenization	Enhanced biodistribution and bioavailability	33
Solid lipid nanoparticle	Campritol 888 ATO	Homogenization	Enhance oral bioavailability	34
		SOLID DISPERSION		
Solid Dispersion	Polyethylene glycol 6000	Fusion method	Enhanced dissolution rate and oral bioavailability	35,36
Solid Dispersion	Hydroxypropyl methyl cellulose E 15LV,	spray drying and co-precipitation methods	Enhance silymarin dissolution	37
Solid Dispersion	Polyvinylpyrrolidone	Fluid bed technique	Enhance dissolution rate	38
Solid dispersion	Polyvinylpyrrolidone	Fluid bed techniques	Enhance oral bioavailability	39
Solid Dispersion	Polyvinylpyrrolidone K30,	supercritical fluids	improve the dissolution and	40

Formulation	Composition	Preparation method	Purpose	Ref
	Hydroxypropyl methyl cellulose K4M and hydroxypropyl methyl cellulose K15M, Carbon dioxide	method	bioavailability	
Solid Dispersion	Hydroxypropyl methylcellulose (HPMC)	Kneading, spray drying, coprecipitation	Enhance dissolution rate	41
Solid dispersion	Tween 80, polyvinylpyrolidone	Spray drying method	Enhance oral bioavailability and dissolution rate	42
		EMULSION		
Emulsion	Poly(lactic-co-glycolic acid) (PLGA), Polycaprolactone (PCL), Sodium Alginate, Chitosan, poly(Llactide) (PLLA), Eudragit,	Membrane emulsification	Improve encapsulation efficiency and drug loading.	43
Nanoemulsion	Sefsol-218, tween-80, ethanol	Spontaneous emulsification	Enhance bioavailability and hepatoprotective activity	44
Nanoemulsion	Sefsol- 218, polyoxyethylene sorbitan monooleate	Titration method	Enhanced oral bioavailability	45,46
Nanoemulsion	Sefsol- 218, Kolliphor RH40, polyethylene glycol 400	Aqueous titration method	efficient carrier for oral delivery of silymarin against human hepatocellular carcinoma without damaging normal	47
Nanoemulsion	Labrasol ECH, Capryol 90, Transcutol HP, Labrafil, oleic acid, Cremophor EL, Triacetin	Aqueous titration method	Improve solubility and oral absorption of silymarin	48
Nanoemulsion	Capryol 90, Solutol HS 15, Transcutol HP	High pressure homogenization	Enhance oral bioavailability	49
SNEDDS	Campul GMO, Tween 20, Crehmophore RH40, Transcutol HP	Phase titration method	improve the dissolution, permeability, and oral bioavailability	50
SNEDDS	PEG 200, PEG 400, glyceryl monooleate, polysorbate 20 and polyoxyethy- lene-50-hydrogenated castor oil (HCO-50), Transcutol	Phase titration method	Enhance bioavailability and dissolution rate	51
		MICROPARTICLES		
Microparticles	Lecithin, tween-20, tween-80, span-20, propylene glycol	Low energy emulsification techniques	Enhanced dissolution, therapeutic efficiency and bioavailability	52,53
Microparticles	Phospholipid, ethanol, sodium cholate, disodium hydrogen phosphate, polyvinylpyrrolidone K30	Freez drying	Improve oral bioavailability	54
Floating microsphere	Hydroxypropyl methyl cellulose, microcrystalline cellulose, crosspovidone	Wet granulation	Prolong gastric residence time	55
		NANO STRUCTURED LIPID CARRIER		
Nanostructured lipid carrier	Glycerol, monostearate, oleic acid, tween 80, caprylic acid, cetyl palmitate, stearic acid	Emulsification and ultrasonication method	Improve solubility, stability and oral bioavailability	56
Nanostructure lipid carrier	Stearic acid, capryol 90, Brij S20,	Emulsion evaporation method	Improve solubility and absorption of silymarin	57
Binary lipids-based nanostructured lipid Carriers	Oleic acid, Tween-80, Precirol ATO 5, egg phosphatidylcholine	Hot high- pressure homogenization	improve the oral bioavailability of silymarin	58
Nanostructured	Capryol 90, Lauroglycol 90, oleic acid,	Emulsion evaporation	Improve solubility and enhance intestinal	59

Formulation	Composition	Preparation method	Purpose	Ref
lipid carrier	precirol ATO 5, cetyl palmitate	method	permeability	
		NANOCRYSTALS		
Nanocrystals	Hydroxypropyl-β-CyD	high pressure crystallization	enhanced dissolution rate and absorbability	60
Nanocrystals	acetone, acetonitrile, ethanol and methanol	Precipitation method	enhance oral bioavailability, and improve solubility	61
		NANOPARTICLES		
Eudragit loaded nanoparticles	Eudragit RL100, Polyvinyl alcohol, Hydroxypropyl methyl cellulose	nanoprecipitation technique	Improve the poor bioavailability of silymarin through buccal delivery.	62
porous silica nanoparticles	Octylphenol polyoxyethylene, cyclohexane, a-naphthol	microemulsion and ultrasonic corrosion methods	improve oral bioavailability	63
Nanoparticles	Hydroxypropyl methyl cellulose, hydroxy propyl- β -cyclodextrin (HP- β-CD), ethanol	Freez drying method	Improve solubility and bioavailability	64
Nanoparticles	Transcutol HP, polysorbate 80 (Tween 80), castor oil, and polyvinylpyrrolidone (PVP K30)	Spray drying techniques	enhanced oral bioavailability and provide excellent hepatic protection	65
Nanoparticles	Poloxamer 188, mannitol	Emulsion solvent evaporation and freez drying method	Improve poor aqueous solubility	66
		INCLUSION COMPLEX		
Inclusion complex	β- cyclodextrine	Kneading method	Enhanced dissolution and bioavailability	67
Inclusion complex	β- cyclodextrine	Kneading, co-precipitation and solvent evaporation	Enhanced dissolution and solubility	68
Inclusion complex	Fulvic acid	Physical mixing and kneading methods	improve the solubility and dissolution profile	69
		NANOMICELLES		
Nanomicelles	Soluplus	Thin film method	Improve the solubility and oral absorption	59
Nanomicelles	Soluplus, d-α-tocopherol, polyethylene glycol 1000 succinate	Thin film method	Improve the solubility and oral absorption	59

Topical route:

The topical route has attracted attention due to its ability to deliver drug substance more selectively to a specific site, avoidance of gastric irritation, avoiding drug levels fluctuations, prevents metabolism of drug, improved compliance, and an enhanced suitability for self-medication. The topical route of administration provides the delivery of drug for both local and systemic effects. The major obstacle for topical delivery is stratum corneum and barrier to the penetration of many drug substances. The topical application of silymarin has received attention because of its pharmacological properties such as antioxidant, anti-inflammatory, and immunomodulatory properties which may prevent UV-induced skin disorders like skin cancer, erythema, and photoaging. The one of the most challenging aspect of drug development is poor aqueous solubility of silymarin (3.2 mg/100 ml). To overcome this issues nanogel, gels, creams, lotions, microemulsion, dendrimer are developed in order to improve solubility, stability and to enhance penetration ability of silymarin.

Table 2: Topical drug delivery of silymarin

Formulation	Composition	Preparation Method	Purpose	Ref
		DENDRIMER		
Dendrimer	Glycine, proline, lysine, Dimethylformamide, dichloromethane, trifluoroacetic acid	Co-precipitation	Enhance skin penetration and deposition	70
Dendrimer	Polyamidoamine (PAMAM-G4) , polyethylene glycol, folic acid	Solvent evaporation	Deliver the poorly soluble drug silybin	71
		GEL		
Organogel	Lecithin, Pluronic F127, isopropyl myristate		Enhance skin penetration	72
		LIPOSOME		
Nanoliposomes	Egg lecithin, cholesterol, chloroform, methanol	Extrusion method	Enhance penetration	73
		SOLID LIPID NANOPARTICLES		
SLN's	Glyceryl monostearate, Tween 80, chloroform and methanol	Micro- emulsion method	Improve stability and enhance permeation	74
SLN's	Glyceryl monostearate, tween 80, solutol HS and loturol F68	Homogenization	Sustain release	75
		MICROEMULSION		
Microemulsion	Labrasol, Transcutol Glyceryl monooleate, ethyl oleate, oleic acid, isopropyl myristate	Phase titration method	Enhance solubility, stability and penetration	76
		NANOSTRUCTURED LIPID CARRIER		
Nanostructured lipid carriers	Compritol ATO 888, Pluronic F-68	Hot high- pressure homogenization process	Increase permeation and reduced toxicity	77
Topical nanostructured lipid carrier	Glycerolmomstearate, oleic acid, carbopol 980	Hot high pressure homogenization process	enhanced solubility, stability and permeation	78

CONCLUSION:

Silymarin is active phytomedicine obtained from silymarium plant containing therapeutic efficacy against various diseases. The major concern of silymarin is poor bioavailability, low aqueous solubility, high metabolism, rapid excretion. The other obstacle is route of administration (oral and topical route) which hindered potential of silymarin. The challenging problems in route of administration are low solubility, poor stability in the gastric environment, poor bioavalability, less penetration. To overcome these issues the review focuses on several novel drug delivery strategies such as liposomes, solid lipid nanoparticles, nano or micro-emulsions, microspheres, nanogels, solid dispersions, nanocrystals, nano structured lipid carrier, inclusion complex, dendrimer, micelles have been described to enhance bioavailability, increase solubility and delivery of silymarin. There are still many challenges that need to be resolved such as safety of nanoparticles for long-time, interaction with biological systems and patient-friendly delivery system.

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