Research Article

Resveratrol Oral Delivery Using Nanocarriers: Formulation Approaches, Pharmacokinetics, and Translational Challenges

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Abstract

Resveratrol is a polyphenolic compound that occurs naturally and has a variety of pharmacological effects; yet its use as a therapeutic agent after being given by mouth is greatly limited because of its poor solubility in water, photosensitivity, chemical instability, tendency to undergo auto-oxidation, and rapid and extensive presystemic metabolism, which in turn leads to low systemic bioavailability . Nanocarrier-based drug delivery systems have therefore become promising methods for enhancing the solubility, stability, gastrointestinal absorption, bioavailability, and pharmacokinetic properties of resveratrol . The present review deals with the various formulation strategies that make use of different nanocarriers, such as polymeric nanoparticles, liposomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions and self-nano-emulsifying systems, as well as other newly emerging nanoscale delivery platforms . Special attention is given to the way in which the design of the nanocarrier affects drug protection, dissolution, intestinal permeability, absorption, controlled release, biodistribution, and systemic exposure. In vivo studies reported in the literature show that various nanocarrier systems can improve pharmacokinetic parameters such as the maximum plasma concentration (Cmax), the area under the concentration-time curve (AUC), absorption rate, mean residence time (MRT), and plasma half-life when compared to free resveratrol or conventional formulations . For instance, in animal studies, orally administered PLGA nanoparticles, polymeric systems, nanoemulsions and SLNs have all shown an increase in resveratrol exposure and bioavailability . The literature also shows that both formulation stability and nanocarrier characteristics are important factors in determining performance, although further in vivo evaluation is needed in order to confirm safety, reproducibility, and translational potential . In summary, nanocarrier-based formulations offer a logical approach for overcoming the biopharmaceutical drawbacks of resveratrol and for improving its prospects for effective oral delivery. [1,2]

Keywords: Resveratrol; nanocarriers; oral bioavailability; polymeric nanoparticles; liposomes; solid lipid nanoparticles; nanostructured lipid carriers; nanoemulsions; pharmacokinetics.

1. Introduction

Resveratrol (RES; 3,5,4′-trihydroxystilbene) is a stilbene polyphenol which occurs naturally in substances such as grape skins, berries and peanuts. Because of its wide range of pharmacological effects it has become a major focus of research in the field of pharmaceutical and nutraceutical sciences. The effects that have been reported include antioxidant, anti-inflammatory, cardioprotective, antitumor and chemosensitising ones. The literature also mentions effects involving the modulation of oxidative stress, inflammatory signalling, apoptosis, cellular proliferation and other pathwaPys linked to diseases. Although there is this pharmacological potential, it is difficult to convert free RES into an effective oral therapy. The compound has low solubility in water and is susceptible to environmental instability. It is mainly found as trans- and cis-isomers, light causing a photoisomerisation from trans to cis; its stability is also affected by pH and temperature.

Moreover, RES is liable to oxidation and is subject to extensive metabolism in the intestine and liver, especially through glucuronidation and sulfation, leading to low levels of unchanged RES in the blood and a short duration of effective systemic exposure. Therefore, the problems associated with oral RES are not due to one particular formulation issue but result from the combined impact of poor aqueous solubility, light-induced isomerisation and degradation,

oxidation and rapid presystemic metabolism.

These limitations offer a solid basis for using nanocarrier-based drug delivery systems. Instead of simply increasing the dose, an appropriately designed nanocarrier can deal with the various obstacles in the oral delivery process by improving apparent solubility and dissolution, providing physical protection for RES against degradation, altering its interaction with the fluids of the gastrointestinal tract and with the intestinal membranes, enhancing its absorption and controlling the release of the drug.

There are examples in the literature that support this approach which is aimed at overcoming the barriers. Polymeric nanoparticles such as PLGA systems have been found to enhance intestinal absorption and increase systemic exposure; galactosylated PLGA nanoparticles have furthermore improved intestinal permeability and transcellular uptake. Self-nano-emulsifying systems have been studied in order to increase both the rate and the extent of RES absorption, while lipid-based systems such as solid lipid nanoparticles have caused significant changes in the pharmacokinetic parameters after oral administration. [1,3]

It is important to note that one cannot regard different nanocarriers as being interchangeable since the methods used to formulate them are designed to overcome different delivery obstacles. While lipid-based systems can offer a lipid-compatible environment for a compound that is poorly soluble in water and thus help with its dispersion and absorption, polymeric nanoparticles can provide physical protection and control the rate of release while also affecting intestinal transport. SLNs and other lipid nanocarriers have the advantage of incorporating the drug into a lipid matrix together with the ability to provide a sustained release, whereas nanoemulsifying systems produce fine dispersions that enhance the apparent solubilization and absorption of lipophilic RES. This relationship between formulation and delivery barrier is especially relevant since the improvements in pharmacokinetics that have been reported depend on the composition of the carrier, its surface characteristics, its particle properties, and the route of administration. [1,3]

Many reviews have already highlighted the significance of nanotechnology in the delivery of resveratrol (RES), although they place different emphases on various aspects. Santos et al. concentrated on the in vivo bioavailability and bioactivity of RES after it had been encapsulated or conjugated in nanotechnology-based carriers, with a special focus on the pharmacokinetic results. Li et al. gave a more comprehensive recent review of nanotechnology-based drug carriers used for the delivery of resveratrol, discussing various types of carriers and the roles they play in enhancing delivery performance. In view of this, the current review uses a barrier-to-carrier framework instead of merely listing nanocarriers according to their material type.

Each major carrier system is evaluated in relation to the main problem it is designed to solve—for instance, solubility and dissolution limitations, chemical or photochemical instability, gastrointestinal degradation, insufficient intestinal permeability, rapid presystemic metabolism, or the requirement for controlled and sustained systemic exposure. The aim of this approach is to link formulation design with the underlying pharmacokinetic limitation and to allow for a more mechanistic comparison of SLNs, NLCs, liposomes, SNEDDS/nanoemulsions, polymeric nanoparticles, and other relevant nanocarrier systems. This approach is in line with the literature, which states that the composition of nanocarriers, their physicochemical characteristics, and their surface properties affect the bioavailability and biological performance of RES. [1,2,3]

Aim of the review: The aim of this review is to critically examine nanocarrier-based strategies for overcoming the major barriers responsible for the poor oral bioavailability of resveratrol and to relate the physicochemical and formulation characteristics of each carrier platform to its effects on solubility, stability, intestinal absorption, pharmacokinetics, and systemic exposure.

2. Physicochemical and pharmacokinetic barriers

2.1 Solubility, BCS classification, and trans-to-cis isomerisation and oxidation

Resveratrol (RES) presents a combination of physicochemical and pharmacokinetic characteristics that substantially restrict its oral bioavailability. The most prominent limitation is its low aqueous solubility despite relatively high membrane permeability. RES is therefore categorised as a Biopharmaceutical Classification System (BCS) Class II compound, in which low solubility is the principal biopharmaceutical limitation.

One of the provided studies reports an aqueous solubility of approximately 30 mg/L and a log P of about 3.1, consistent with the high lipophilicity and high membrane permeability of the molecule. Because dissolution is limited, increasing

the apparent solubility of RES is an important strategy for improving the amount of drug available for absorption.

Formulation approaches such as lipophilic vehicles, cyclodextrin complexation, nanopreparations, and micellar solubilization have consequently been investigated to overcome this limitation. [4]

The relationship between solubility and oral absorption is particularly relevant for RES because BCS Class II compounds are characterised by adequate membrane permeability but inadequate aqueous dissolution. The BCS framework classifies drugs according to their solubility and permeability into four categories: Class I (high solubility/high permeability), Class II (low solubility/high permeability), Class III (high solubility/low permeability), and Class IV (low solubility/low permeability). In the supplied BCS review, resveratrol is specifically classified as Class II, with low water solubility and high lipophilicity. Thus, the delivery problem for RES is primarily associated with dissolution and the availability of dissolved drug for intestinal absorption rather than an intrinsically poor ability to cross biological membranes. [4]

Experimental evidence from the supplied formulation studies demonstrates the importance of this dissolution barrier. Spogli et al. reported that RES alone showed a maximum solubility of approximately 13 mg/L, whereas RES incorporated into a magnesium dihydroxide solid dispersion reached approximately 40.8 mg/L, with a substantially faster dissolution rate. The authors also observed that reducing the particle size alone modified dissolution kinetics but did not increase the maximum solubility, suggesting that improved dissolution cannot always be attributed simply to particle-size reduction. Similarly, Almeida et al. described RES as a BCS Class II compound and showed that formulation into a third-generation solid dispersion increased RES solubilization by approximately 8-, 12-, and 8-fold at pH 1.2, 4.5, and 6.8, respectively, compared with pure RES. The formulation also produced higher intestinal permeability, illustrating that improving the dissolution environment can influence subsequent absorption. [5,6]

A second important physicochemical barrier is the photosensitivity of RES and its trans-to-cis isomerisation. RES exists as geometric trans and cis isomers, and the two forms differ in chemical stability and their interactions with intestinal transport systems. The supplied BCS review notes that RES absorption involves both isomers and that their different chemical stabilities and transporter interactions contribute to its highly permeable character. Exposure to ultraviolet radiation can drive the conversion of trans-RES into cis-RES. The supplied 2024 experimental study further illustrates the sequential photochemical transformation of trans-resveratrol under UV-A exposure: trans-resveratrol is rapidly converted to cis-resveratrol, followed by formation of an additional oxidation product identified as 2,4,6-phenanthrenetriol. The corresponding experimental figures demonstrate the time-dependent decrease of trans-resveratrol and appearance of the photoproducts during UV-A exposure. [4,7]

In addition to photoisomerisation, oxidative instability represents another barrier to maintaining RES in its biologically active form. The supplied BCS review reports that glycosylation of resveratrol can protect the molecule against enzymatic oxidation, indicating that its free phenolic structure is susceptible to oxidative transformation. The rapid phase-II metabolism of RES further compounds this problem. Its free hydroxyl groups undergo rapid glucuronidation and sulfation in intestinal and hepatic tissues, while the literature supplied for this section also identifies rapid metabolism as a major cause of the low bioavailability of orally administered RES. Almeida et al. similarly emphasised that RES is extensively metabolised and rapidly eliminated and that strategies capable of protecting RES from gastrointestinal and hepatic metabolism can increase its systemic exposure. [4,9]

Taken together, the available evidence indicates that the oral delivery of RES is constrained by a multifactorial barrier profile: low aqueous solubility and dissolution, high lipophilicity, light-induced trans-to-cis isomerisation, oxidative degradation, and extensive presystemic metabolism. These features provide a clear formulation rationale for delivery systems capable of increasing apparent solubility, protecting RES from environmental and chemical degradation, maintaining the active form, and reducing premature metabolism. In this context, nanocarrier-based systems are particularly relevant because their composition and architecture can be selected to address one or more of these barriers simultaneously. [4,7,8,9]

2.2 Absorption versus first-pass metabolism: glucuronidation and sulfation in gut and liver.

trans-Resveratrol exhibits relatively efficient intestinal absorption but very low systemic bioavailability of the unchanged parent compound. Human studies summarised in the supplied literature indicate that approximately 75% of an orally administered dose can be absorbed, with absorption occurring mainly through trans-epithelial diffusion.

However, only a small fraction of the absorbed compound remains as unchanged resveratrol in the systemic circulation because extensive presystemic metabolism occurs in the intestine and liver.

Following a 25 mg oral dose, circulating unchanged resveratrol was reported at less than 5–10 ng/mL, whereas the concentration of resveratrol together with its metabolites was considerably higher, demonstrating the large contribution of biotransformation to the observed pharmacokinetic profile. [8,9]

The major metabolic pathways of *trans*-resveratrol are glucuronidation and sulfation. Resveratrol undergoes phase II conjugation in intestinal epithelial cells and hepatocytes, producing metabolites such as resveratrol-3-O-glucuronide, resveratrol-4′-O-glucuronide, resveratrol-3-O-sulfate, and resveratrol-4′-O-sulfate. In the intestinal epithelial model provided, sulfate conjugation was the predominant metabolic route for *trans*-resveratrol, whereas glucuronidation also occurred to a significant extent. These conjugated metabolites are more water-soluble than the parent compound and can subsequently be eliminated through urine or undergo further intestinal processing. [9]

The supplied Caco-2 study provides useful insight into the disposition of *trans*-resveratrol during intestinal passage. From an initial concentration of 20 µM, approximately 57.2% of *trans*-resveratrol was transported unchanged to the basolateral compartment, whereas about 20.3**%** was metabolised or transformed and approximately 22.1**%** remained in or was returned to the apical compartment. In contrast, cis-resveratrol showed substantially greater metabolic transformation. The findings therefore indicate that the trans isomer has a different metabolic fate from its cis counterpart and that intestinal transport cannot be considered solely a passive diffusion process. [9]

Another important factor limiting systemic exposure is bidirectional intestinal transport and efflux. Resveratrol and its conjugated metabolites can be transported back toward the intestinal lumen through ATP-binding cassette transport systems, including multidrug resistance-associated protein 2 (MRP2) and breast cancer resistance protein (BCRP). This process can reduce the fraction of absorbed compound reaching the systemic circulation. In the intestinal model, approximately 22% of unchanged *trans*-resveratrol was recovered from the apical compartment after incubation, supporting the contribution of efflux to its disposition. [9]

In addition to phase II metabolism in the intestine and liver, colonic microbial metabolism represents another important component of resveratrol disposition. Resveratrol reaching the colon can be transformed by intestinal microbiota into metabolites including dihydroresveratrol and related stilbenoid metabolites. These microbial metabolites may subsequently undergo absorption and further conjugation. The supplied review reports that bacterial metabolites can contribute substantially to the recovered resveratrol-derived products, suggesting that the systemic pharmacological profile of orally administered resveratrol cannot be explained solely by the concentration of unchanged parent resveratrol in plasma. [1,9]

The distinction between low parent-drug bioavailability and the biological activity of metabolites is particularly important. The supplied literature describes the so-called “resveratrol paradox,” in which substantial biological effects have been reported despite very low circulating concentrations of unchanged resveratrol. One explanation is that resveratrol metabolites may retain biological activity or may function as reversible reservoirs from which resveratrol can be regenerated. In addition, tissue exposure may not always correspond directly to plasma concentrations. The Walle review reports evidence of tissue accumulation of resveratrol and emphasises that concentrations at cellular sites of action may provide information that is not apparent from plasma measurements alone. [1,8]

Dose escalation studies further indicate that increasing the oral dose does not necessarily produce a proportional increase in systemic exposure to unchanged resveratrol. The supplied review describes an approximately linear increase in peak plasma resveratrol concentrations across single oral doses ranging from 25 to 5000 mg, but even at the highest dose the measured plasma concentrations remained relatively low. The low circulating levels were considered to reflect limitations including solubility and extensive metabolism. Repeated or chronic administration may alter tissue exposure, but the available data remain insufficient to fully characterise the relationship between long-term dosing, parent resveratrol, and its metabolites. [8]

Overall, the oral bioavailability of *trans*-resveratrol is determined by the interaction of intestinal absorption, phase II conjugation, microbial metabolism, efflux transport, hepatic metabolism, and tissue distribution.
Although a substantial proportion of the oral dose can be absorbed, extensive conversion to glucuronide and sulfate conjugates means that systemic exposure to unchanged *trans*-resveratrol remains low. This metabolic profile represents a major target for formulation development, because an effective oral nanocarrier should ideally not only improve dissolution and intestinal absorption but also protect resveratrol from premature metabolism and efflux while maintaining an appropriate release profile. [8,9]

3. Nanocarrier-Based Strategies for Improving Oral Bioavailability

3.1 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are submicron lipid-based carriers in which the drug is incorporated within a solid lipid matrix. Their application to oral resveratrol delivery is supported by the drug's lipophilicity, poor aqueous solubility, chemical instability, and extensive presystemic metabolism. The supplied studies investigated SLNs primarily as protective and controlled-release systems capable of maintaining resveratrol in an incorporated state during gastrointestinal transit and facilitating intestinal absorption. [10,11,12]

3.1.1 Formulation design and composition

The oral SLNs described in the supplied studies were prepared using cetyl palmitate or Precirol ATO 5 as the solid lipid, with polysorbate or Tween surfactants used to stabilise the aqueous dispersion. In the first formulation study, cetyl palmitate was selected as the lipid matrix and polysorbate 60 as the stabiliser. Resveratrol was incorporated into the melted lipid phase, followed by dispersion in a hot aqueous medium and high-shear homogenization and ultrasonication. The method avoided organic solvents and was considered suitable for scale-up. [10]

The formulation design in the 2013 study varied the amount of resveratrol while maintaining the lipid and surfactant concentrations. The SLN formulations contained 500 mg total cetyl palmitate, 100 mg polysorbate 60, and 4.4 mL water, with resveratrol concentrations of 2, 5, 10, or 15 mg. Increasing the resveratrol concentration resulted in progressively lower entrapment efficiency, while particle size and polydispersity remained within the nanoscale range. [10]

Table 1. Composition of resveratrol-loaded SLNs reported in the supplied study [10]

Formulation	Resveratrol (mg)	Cetyl palmitate (mg)	Polysorbate 60 (mg)	Water (mL)	Ref.
SLN-placebo	0	500	100	4.4	[10]
SLN-1	2	498	100	4.4	[10]
SLN-2	5	495	100	4.4	[10]
SLN-3	10	490	100	4.4	[10]
SLN-4	15	485	100	4.4	[10]

The formulation was produced by melting the lipid phase containing resveratrol, dispersing it in an aqueous surfactant solution at the same temperature, followed by high-speed homogenization and sonication. [10]

3.1.2 Particle size, polydispersity and surface charge

Cryo-scanning electron microscopy showed that resveratrol-loaded SLNs were predominantly spherical and relatively uniform, with smooth surfaces and no visible aggregation. The microscopic particle diameter was approximately 100–200 nm, while dynamic light scattering provided larger hydrodynamic diameters because measurements were performed in the hydrated state. [10]

The detailed physicochemical characterisation showed that the SLN particle size remained approximately 165–195 nm across the tested resveratrol concentrations. The polydispersity index remained close to 0.20, indicating a relatively

narrow size distribution. The zeta potential remained negative, ranging from approximately −25 to −35 mV. These parameters remained statistically unchanged during 2 months of storage at room temperature. [10]

Table 2. Physicochemical characteristics of resveratrol-loaded SLNs [10]

Formulation	Entrapment efficiency (%)	Z-average (nm)	PDI	Zeta potential (mV)	Ref.
SLN-placebo	—	184.9 ± 20.6	0.204 ± 0.031	−34.3 ± 7.2	[10]
SLN-1	88.5 ± 5.1	164.7 ± 15.7	0.209 ± 0.035	−34.6 ± 6.7	[10]
SLN-2	79.2 ± 2.4	164.1 ± 20.6	0.211 ± 0.029	−33.5 ± 7.1	[10]
SLN-3	67.8 ± 4.2	187.3 ± 18.8	0.196 ± 0.037	−26.8 ± 6.9	[10]
SLN-4	64.2 ± 9.7	194.5 ± 18.3	0.212 ± 0.035	−25.4 ± 6.6	[10]

The supplied data indicate that increasing the amount of resveratrol from 2 to 15 mg reduced entrapment efficiency from approximately 88.5% to 64.2%, whereas no consistent increase in particle size or PDI was observed. [10]

3.1.3 Entrapment of resveratrol within the lipid matrix

The lipophilic character of resveratrol favours its partitioning into the lipid matrix of SLNs rather than remaining in the aqueous continuous phase. The supplied study reported an average entrapment efficiency of approximately 70% across the tested SLN formulations, with no statistically significant difference between the SLNs and NLCs studied. [10]

The second supplied study reported an entrapment efficiency of approximately 80% for resveratrol-loaded SLNs, with particle sizes between 160 and 190 nm and a zeta potential of approximately −30 mV. Thus, the two supplied studies consistently demonstrate efficient incorporation of resveratrol within SLNs, although the absolute entrapment value varies with formulation composition and preparation conditions. [11]

3.1.4 Physical stability and lipid-state characteristics

Physical stability is an important consideration for SLNs because changes in the crystalline lipid matrix can cause drug expulsion during storage. In the supplied 2013 study, particle size, PDI, and zeta potential remained essentially unchanged during 2 months of storage at room temperature. The negative surface charge and presence of polysorbate 60 were associated with maintenance of dispersion stability. [10]

Differential scanning calorimetry confirmed that the lipid matrix remained in the solid state at both room and body temperatures. Incorporation of resveratrol altered the organisation of the lipid crystal structure and reduced the degree of crystallinity, suggesting increased structural disorder within the carrier. This alteration was associated with improved drug accommodation within the lipid matrix. [10]

3.1.5 Controlled release and gastrointestinal protection

For oral administration, retention of resveratrol within the SLN matrix during gastrointestinal transit is particularly important because premature drug release would expose resveratrol to degradation and metabolism before intestinal absorption. In the supplied release experiments, negligible resveratrol release was observed from SLNs during storage in an aqueous medium. [10]

When the formulation was sequentially exposed to simulated gastric fluid followed by simulated intestinal fluid, resveratrol remained predominantly associated with the lipid nanoparticles. The findings indicate that the SLN matrix can provide physical protection to resveratrol during simulated gastrointestinal transit and delay its release until after exposure to the gastrointestinal environment. [10]

The second SLN study also demonstrated that lipid encapsulation protected resveratrol against premature release and degradation during gastrointestinal conditions. These findings support the role of SLNs as protective oral carriers rather than simply solubilising systems. [10]

3.1.6 Photoprotection of trans-resveratrol

Protection against photoisomerization is another relevant function of the SLN system. Free trans-resveratrol exposed to UV radiation showed a decrease in absorbance at 306 nm together with a shift toward the spectral characteristics of cis-resveratrol. Approximately 50% conversion of trans-resveratrol to the cis form occurred after 4 h of UV exposure in aqueous solution. In contrast, incorporation within SLNs reduced the extent of photodegradation/isomerization to less than 10%. [11]

This result demonstrates that incorporation into the solid lipid matrix can physically shield resveratrol from UV exposure and maintain a greater proportion of the trans isomer. Therefore, SLN encapsulation addresses not only the aqueous solubility and gastrointestinal stability limitations of resveratrol but also its photochemical instability. [11]

3.1.7 Intestinal biocompatibility and permeability

The effect of resveratrol-loaded SLNs on intestinal epithelial cells was assessed using Caco-2 monolayers. At the concentration selected for permeability studies, approximately 10 μM, neither free resveratrol nor resveratrol-loaded SLNs produced a significant cytotoxic effect after 4 h of incubation. Significant reduction in metabolic activity was observed only at concentrations above 50 μM. [11]

The Caco-2 permeability experiments showed that SLNs did not significantly increase resveratrol permeability compared with free resveratrol. The apparent permeability coefficient for SLN-loaded resveratrol was $1.9 \pm 0.2 \times 10^{-5}$ cm/s in HBSS, compared with $1.6 \pm 0.4 \times 10^{-5}$ cm/s for free resveratrol. In fasted-state simulated intestinal fluid, the corresponding values were 3.0 ± 0.1 and $2.7 \pm 0.2 \times 10^{-5}$ cm/s, while in fed-state medium they were 3.8 ± 0.1 and $3.5 \pm 0.4 \times 10^{-5}$ cm/s, respectively. The differences for SLNs were not statistically significant. [11]

Table 3. Apparent permeability of resveratrol-loaded SLNs across Caco-2 monolayers [11]

Formulation	HBSS	FaSSIF	FeSSIF	Ref.
Free resveratrol	1.6 ± 0.4	2.7 ± 0.2	3.5 ± 0.4	[11]
SLN-resveratrol	1.9 ± 0.2	3.0 ± 0.1	3.8 ± 0.1	[11]

Values represent Papp × 10^{-5} cm/s.

Although SLNs did not significantly increase apparent permeability, they maintained resveratrol absorption while protecting against degradation. The study therefore indicates that the principal contribution of SLNs may be protection and maintenance of drug availability rather than a direct increase in epithelial permeability. [11]

3.1.8 Surface-modified SLNs for improved oral delivery

A limitation identified in the supplied literature is the potential instability of conventional SLNs in the acidic gastric environment. Surface modification was therefore investigated using N-trimethyl chitosan grafted with palmitic acid (TMC-g-PA**)**. The polymer was applied to resveratrol-loaded SLNs prepared using Precirol ATO 5, palmitic acid, Gelucire 50/13, Tween 80, and resveratrol. TMC is water-soluble over a broad pH range and possesses mucoadhesive and absorption-enhancing properties. [12]

Surface modification increased the particle size of the SLNs from approximately 100 nm to 258 nm and changed the surface potential from approximately **−**19 mV to +21 mV, while maintaining an entrapment efficiency of approximately 95%. The positive surface charge following TMC-g-PA modification was consistent with the deposition of the cationic

polymer on the nanoparticle surface. [12]

Table 4. Physicochemical and pharmacokinetic characteristics of conventional and TMC-g-PA-modified SLNs [12]

Parameter	Resveratrol suspension	Resveratrol-loaded SLNs	TMC-g-PA SLNs	Ref.
Tmax (h)	0.19	0.50	1.00	[12]
Cmax	0.39 ± 0.02	0.40 ± 0.08	0.62 ± 0.08	[12]
$AUC_{0–8}h$	0.37 ± 0.10	0.81 ± 0.06	1.39 ± 0.08	[12]
$AUC_{0–\infty}$	0.74 ± 0.08	2.01 ± 0.03	5.22 ± 0.49	[12]
MRT (h)	2.21	3.37	3.62	[12]
Relative bioavailability	1.0	2.1	3.8	[12]

Pharmacokinetic values were obtained after a single oral dose of 25 mg/kg in mice. The relative bioavailability was calculated using the AUC of the resveratrol suspension as reference. [12]

3.1.9 Pharmacokinetic enhancement

The surface-modified SLN system produced a clear improvement in systemic exposure. Following oral administration of 25 mg/kg in mice, the resveratrol suspension produced an $AUC_{0–8}h$ of 0.37 ± 0.10, whereas conventional SLNs increased the value to 0.81 ± 0.06. The relative bioavailability therefore increased approximately 2.1-fold with conventional SLNs. [12]

TMC-g-PA modification further increased the $AUC_{0–8}h$ to 1.39 ± 0.08 and the $AUC_{0–\infty}$ to 5.22 ± 0.49, corresponding to a relative bioavailability of 3.8-fold compared with the resveratrol suspension. The Tmax was delayed from 0.19 h for the suspension to 0.50 h for conventional SLNs and 1 h for TMC-g-PA SLNs, indicating a slower and more sustained absorption profile. The modified system also increased mean residence time. [12]

The release data provide a formulation-based explanation for this pharmacokinetic improvement. TMC-g-PA SLNs showed negligible release in simulated gastric fluid and sustained release in simulated intestinal fluid. The delayed plasma peak and increased systemic exposure were therefore associated with protection of resveratrol under gastric conditions, mucoadhesive behaviour of the surface polymer, enhanced absorption, and prolonged gastrointestinal residence. [12]

Table 5. Major findings of SLN-based resveratrol delivery in the supplied studies [10,11,12]

Study	SLN composition/approach	Main findings relevant to oral delivery	Ref.
2013 lipid nanoparticle study	Cetyl palmitate + polysorbate 60	~70% mean EE; 150–250 nm; PDI ~0.2; zeta potential ~−30 mV; stable for 2 months; negligible release during storage; resveratrol remained associated during simulated GI transit	[10]
2016 intestinal delivery study	Cetyl palmitate + polysorbate 60	160–190 nm; ~80% EE; ~−30 mV; strong photoprotection; no significant impairment	[11]

		of Caco-2 absorption; Papp 1.9×10^{-5} cm/s in HBSS	
2016 surface-modified SLN study	Precirol ATO 5-based SLN + TMC-g-PA coating	~95% EE; controlled gastric release; sustained intestinal release; relative oral bioavailability 3.8-fold versus suspension	[12]
Overall evidence	Conventional and surface-modified SLNs	Protection of trans-resveratrol, controlled gastrointestinal release, maintenance of absorption, and increased systemic exposure	[10–12]

The supplied studies therefore support **SLNs primarily as protective and controlled-release carriers for oral resveratrol**. Conventional SLNs maintained high drug entrapment, physical stability, photoprotection, and gastrointestinal retention, but did not significantly increase Caco-2 permeability. Surface modification with TMC-g-PA provided an additional strategy to overcome gastric instability and increase systemic exposure, producing a 3.8-fold relative bioavailability compared with resveratrol suspension. [10,11,12]

3.2 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) are lipid-based systems composed of a mixture of solid and liquid lipids. In the supplied studies, the incorporation of liquid lipid into the solid lipid matrix produced a less ordered structure with lattice defects, providing space for resveratrol incorporation and reducing drug leakage. The investigated NLC systems were primarily evaluated for dermal delivery, cellular delivery, and protection of resveratrol under oxidative or cryopreservation conditions. None of the four supplied studies directly evaluated oral administration or oral pharmacokinetic bioavailability of resveratrol; therefore, oral bioavailability conclusions cannot be derived from these studies alone. [13,14,15,16]

3.2.1 NLC composition and formulation

Gokce et al. prepared resveratrol-loaded NLCs using Compritol 888 ATO as the solid lipid and Miglyol 812 as the liquid lipid, with Poloxamer 188 and Tween 80 as surfactants. The lipid and aqueous phases were heated to 85 °C separately and subsequently combined under high-shear homogenization at 24,000 rpm. Different proportions of liquid lipid were investigated, corresponding to 5%, 15%, 30%, and 45% of the lipid phase. The optimised NLC contained **15% Miglyol 812**, corresponding to 255 mg Compritol 888 ATO and 45 mg Miglyol 812. [13]

Najafi et al. prepared resveratrol-loaded NLCs using Precirol as the solid lipid, Miglyol as the liquid lipid, and Poloxamer 407 as the surfactant. Resveratrol was dissolved in 20 mg Miglyol and incorporated into 80 mg melted Precirol at a resveratrol-to-carrier ratio of 1:100. The heated surfactant solution containing 75 mg Poloxamer 407 in 10 mL water was incorporated under homogenization at 20,000 rpm for 15 min, followed by cooling to 24 °C to allow lipid recrystallisation and NLC formation. The mean encapsulation efficiency was **94%**. [16]

In the study by Liu et al., the NLC consisted of shea butter as the solid lipid and capric triglyceride as the liquid lipid. Resveratrol was incorporated with capric triglyceride, shea butter, Olivem 1000, Olivem 800, vitamin E, and red myrrh. The resulting NLC was subsequently incorporated into a hydrogel containing sodium hyaluronate and carboxymethyl cellulose. [14]

Table 6 NLC formulations reported in the supplied studies [13,14,15,16]

Study	Solid lipid	Liquid lipid	Main surfactant/emulsifier	Additional formulation	Ref.
Gokce et al.	Compritol 888 ATO	Miglyol 812	Poloxamer 188, Tween 80	Optimised at 15% liquid lipid	[13]
Liu et al.	Shea butter	Capric triglyceride	Olivem 1000, Olivem 800	Incorporated into hydrogel	[14]
Barbosa et al.	Solid/liquid lipid NLC system	Miglyol-containing NLC system	—	Resveratrol-loaded NLC for dendritic-cell delivery	[15]
Najafi et al.	Precirol	Miglyol	Poloxamer 407	NLC incorporated into semen extender	[16]

The formulations differed according to the intended application, and the supplied studies did not use a single standardised NLC composition. [13,14,15,16]

3.2.2 Particle size, PDI, zeta potential and entrapment efficiency

The Gokce et al. study demonstrated that incorporation of liquid lipid substantially influenced the physical characteristics of the NLCs. The optimised resveratrol-loaded formulation, RN2, contained 15% Miglyol 812 and showed a particle size of 110.5 ± 1.3 nm, PDI of 0.259 ± 0.01, zeta potential of −13.8 ± 0.1 mV, and an entrapment efficiency of **91%**. The particle sizes of the resveratrol-loaded formulations ranged from approximately 91 to 149 nm, with entrapment efficiencies of 72–91%. [13]

Table 7 Physicochemical characteristics of resveratrol-loaded NLCs in Gokce et al. [13]

NLC formulation	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)	Ref.
RN1	90.58 ± 1.7	0.280 ± 0.06	−16.1 ± 0.1	82	[13]
RN2	110.5 ± 1.3	0.259 ± 0.01	−13.8 ± 0.1	91	[13]
RN3	117.3 ± 1.6	0.224 ± 0.03	−15.2 ± 0.6	72	[13]
RN4	148.7 ± 1.5	0.213 ± 0.01	−16.3 ± 0.08	78	[13]

The RN2 formulation containing 15% liquid lipid was identified as the most promising formulation in the study. [13]

Liu et al. reported a particle size of 175.6 ± 11.2 nm, PDI of 0.179 ± 0.007, zeta potential of −54.3 ± 3.2 mV, and an encapsulation efficiency of 97.76% for RES-NLC-gel. TEM demonstrated a spherical morphology. The resveratrol content remained unchanged during 14 days, indicating limited drug leakage from the NLC. [14]

Barbosa et al. reported NLCs with a mean diameter below 200 nm, PDI between 0.1 and 0.2, and highly negative zeta potential approaching −30 mV. The resveratrol entrapment efficiency was greater than 80%, and no reduction in resveratrol incorporation was observed during 3 months of storage. [15]

Najafi et al. reported an encapsulation efficiency of 94% for the resveratrol-loaded NLC prepared from Precirol, Miglyol, and Poloxamer 407. Particle size and zeta potential were not reported in the supplied paper. [16]

Table 8. Physicochemical characteristics of NLC systems from the supplied papers [13,14,15,16]

Study	Particle size	PDI	Zeta potential	Entrapment efficiency	Ref.
Gokce et al.	90.58–148.7 nm	0.213–0.280	−13.8 to −16.3 mV	72–91%	[13]
Liu et al.	175.6 ± 11.2 nm	0.179 ± 0.007	−54.3 ± 3.2 mV	97.76%	[14]
Barbosa et al.	<200 nm	0.1–0.2	Up to approximately −30 mV	>80%	[15]
Najafi et al.	NR	NR	NR	94%	[16]

NR: not reported in the supplied paper.

3.2.3 Structural characteristics of NLCs

The formation of lattice defects resulting from the incorporation of liquid lipid was a recurrent characteristic of the NLC systems. In the Gokce study, DSC analysis showed a slightly lower lipid melting point for the NLC system compared with the corresponding SLN system. The less ordered lipid structure was associated with increased accommodation of resveratrol. The authors selected the formulation containing 15% liquid lipid as the optimised NLC formulation. [13]

Barbosa et al. also attributed the high stability of their NLC formulation to its disordered lipid matrix. The liquid lipid reduced the crystallinity of the lipid core and generated lattice defects that allowed better accommodation of resveratrol and reduced premature release or loss of incorporated material during storage. [15]

3.2.4 Stability and protection of resveratrol

The NLC systems demonstrated retention of resveratrol during the storage periods investigated. Barbosa et al. observed no significant changes in particle size, PDI, or zeta potential for 3 months when the NLCs were stored at room temperature and protected from light. Resveratrol entrapment also remained above 80% without a decrease over the storage period. [15]

Liu et al. observed no significant decrease in resveratrol content after 3 h of UVA or UVB irradiation when resveratrol was incorporated into NLC-gel. In contrast, free resveratrol content decreased to 86.0% after UVA exposure and 75.4% after UVB exposure for 3 h. The NLC-gel therefore provided substantial protection against UV-associated degradation. Resveratrol also showed no significant leakage from the NLC during 14 days of observation. [14]

Table 9 Stability-related findings from the supplied NLC studies [14,15]

Study	Stability/protection finding	Ref.
Gokce et al.	Optimised NLC contained 15% liquid lipid; NLC matrix showed reduced lipid crystallinity.	[13]
Liu et al.	No significant RES loss after 3 h UVA or UVB exposure; no significant leakage for 14 days	[14]
Barbosa et al.	Size, PDI and zeta potential remained stable for 3 months; EE remained >80%	[15]
Najafi et al.	NLC stored at 4 °C; EE was 94%	[16]

3.2.5 NLC-mediated skin deposition and antioxidant activity

Gokce et al. evaluated NLCs for dermal delivery. Resveratrol-loaded NLCs showed greater skin penetration and accumulation than the corresponding SLNs. After 24 h, no resveratrol was detected in the receptor phase of the Franz diffusion system, indicating that the drug did not cross the complete skin membrane under the experimental conditions. Instead, resveratrol accumulated within the skin. The total amount extracted from nanoparticle-treated skin was approximately 1.55 ± 0.13 μg/cm² for SLNs and 1.99 ± 0.17 μg/cm² for NLCs. NLCs showed greater dermal accumulation, whereas SLNs showed greater epidermal accumulation. [13]

The optimised NLC formulation also produced antioxidant activity in human dermal fibroblasts. Concentrations below 50 μM were considered suitable based on cell viability. At 50 μM, resveratrol-loaded NLCs decreased intracellular ROS accumulation. The mean fluorescence intensity percentage for NLC-loaded resveratrol was 30.69 compared with 32.06 for SLN-loaded resveratrol and 31.17 for free resveratrol, although the difference between the formulations was not statistically significant. [13]

Liu et al. similarly reported that RES-NLC-gel accumulated predominantly in the epidermis following topical administration. Compared with free resveratrol and resveratrol gel, the NLC-gel produced lower cumulative transdermal transport but greater drug accumulation within skin tissue. Confocal imaging showed stronger epidermal fluorescence with NLC-gel than with conventional hydrogel. [14]

3.2.6 NLC-mediated cellular uptake

Barbosa et al. investigated NLC internalisation in primary human dendritic cells. NLCs remained below 200 nm with a PDI of approximately 0.1–0.2 and a highly negative surface potential. Imaging flow cytometry demonstrated efficient internalisation of NLCs by dendritic cells. At the highest tested nanoparticle volume, nearly 100% of cells contained internalised NLCs. Both immature and TNF-α-stimulated dendritic cells internalized the nanoparticles, and no significant cytotoxic effect was observed. [15]

Resveratrol-loaded NLCs also showed biological activity after cellular uptake. At **5 μM**, rsv-NLC significantly decreased the activation marker CD83 and inhibited NF-κB phosphorylation and IL-12/23 production. For comparable inhibition of these inflammatory responses, a higher concentration of free resveratrol was required. [15]

3.2.7 NLCs in cryopreservation

Najafi et al. applied resveratrol-loaded NLCs to rooster semen cryopreservation rather than drug delivery in vivo. The NLC contained resveratrol at a 1:100 resveratrol-to-carrier ratio and exhibited 94% encapsulation efficiency. Resveratrol-loaded NLC was incorporated into the semen extender at 20, 40, and 60 μM. [16]

The 40 μM resveratrol-loaded NLC treatment produced higher total and progressive motility, greater sperm viability and membrane functionality, greater mitochondrial activity, and reduced early apoptosis compared with the control and several higher-dose groups. The same treatment reduced MDA, increased GPx activity, and increased total antioxidant capacity. Fertility and hatchability were also increased in the 40 μM resveratrol-loaded NLC group. [16]

Table 10 Biological effects of resveratrol-loaded NLCs in the supplied studies [13,14,15,16]

Study	Experimental model	Main NLC findings	Ref.
Gokce et al.	Human dermal fibroblasts and rat skin	Reduced ROS accumulation; increased skin accumulation compared with SLN	[13]
Liu et al.	HaCaT cells, rabbits and mice	Improved UV protection, reduced oxidative damage, increased epidermal accumulation	[14]
Barbosa et al.	Human dendritic cells	Efficient cellular internalisation; reduced inflammatory activation at lower resveratrol concentration	[15]
Najafi et al.	Cryopreserved rooster sperm	Improved motility, viability, mitochondrial activity, antioxidant status, fertility and hatchability at 40 μM	[16]

3.3 Liposomes

Liposomes are vesicular carriers composed of phospholipid bilayers surrounding an aqueous core and can accommodate lipophilic compounds within the lipid bilayer. The supplied studies investigated conventional, PEGylated, deformable, ultradeformable, and pH-driven nanoliposomes for resveratrol delivery. Their reported effects include improved drug encapsulation, protection against chemical degradation, controlled release, enhanced cellular transport, and increased localisation of resveratrol within target tissues. [17,18,19,20]

3.3.1 pH-driven nanoliposomes

A pH-driven loading method was investigated for resveratrol using sunflower lecithin nanoliposomes. Nanoliposomes were prepared by high-pressure homogenization and subsequently loaded with resveratrol after dissolving the drug in an alkaline NaOH solution, followed by rapid adjustment to pH 6.5. The method exploits the increased aqueous solubility of ionised resveratrol at alkaline pH and its subsequent partitioning into the hydrophobic regions of the liposomes after acidification. [17]

The main limitation of this approach was the alkaline instability of resveratrol. Resveratrol remained stable for 1 h at pH 7 but underwent progressive degradation with increasing pH and was completely degraded after 1 h at pH 12. The degradation was associated with ionisation of the phenolic hydroxyl groups and increased susceptibility of the resulting phenate species to oxidation. [17]

Despite this limitation, rapid alkaline exposure allowed efficient encapsulation. Resveratrol showed a retention rate of **93.8%** after the pH-driven loading process. Encapsulation efficiency remained approximately 90**%** at initial resveratrol concentrations of 0.3–0.5 mg/mL and decreased to 81.3% at 0.6 mg/mL. The maximum reported solubility of resveratrol in the liposomal system was approximately 4.8 mg/mL. [17]

The study demonstrated that preparation time at high pH was critical. Although 73% of resveratrol degraded after 30 min at pH 12, dissolution in 100 mM NaOH for only 2 min followed by rapid liposome preparation produced an encapsulation efficiency of approximately 90%. [17]

Table 11 Resveratrol encapsulation using the pH-driven nanoliposome method [17]

Parameter	Reported finding	Ref.
Lipid	Sunflower lecithin	[17]
Liposome preparation	High-pressure homogenization	[17]
Loading method	pH-driven	[17]
Loading pH	Alkaline NaOH followed by adjustment to pH 6.5	[17]
Resveratrol concentration tested	0.3–0.6 mg/mL	[17]
Retention rate	93.8%	[17]
EE at 0.3–0.5 mg/mL	~90%	[17]
EE at 0.6 mg/mL	81.3%	[17]
Maximum reported solubility	~4.8 mg/mL	[17]
Major limitation	Alkaline degradation of resveratrol	[17]

3.3.2 Nanoliposomal resveratrol: physicochemical characteristics

A separate study prepared resveratrol-loaded multilamellar liposomes using dipalmitoylphosphatidylcholine (DPPC) and cholesterol at a 1:1 molar ratio by thin-film hydration. A PEGylated formulation was produced by incorporating 5 mol% DSPE-PEG2000 into the liposomal suspension. [18]

Both formulations exhibited nanoscale dimensions and high resveratrol encapsulation. The conventional resveratrol liposomes had a particle size of 215 ± 4 nm, PDI of 0.077 ± 0.037, zeta potential of −45.3 ± 2.1 mV, and EE of 85.5 ± 2.7%. PEGylation produced a slightly larger particle size of 226 ± 7 nm, PDI of 0.099 ± 0.023, zeta potential of −44.5 ± 2.4 mV, and EE of 84.2 ± 2.1%. [18]

Table 12 Physicochemical characteristics of resveratrol nanoliposomes [18]

Formulation	Size (nm)	PDI	Zeta potential (mV)	EE (%)	Ref.
RSV-LP	215 ± 4	0.077 ± 0.037	−45.3 ± 2.1	85.5 ± 2.7	[18]
RSV-P-LP	226 ± 7	0.099 ± 0.023	−44.5 ± 2.4	84.2 ± 2.1	[18]

The conventional liposomes were physically stable at 4 °C for 3 months, with no significant increase in particle size or decrease in zeta potential. At 25 °C, particle size increased, and zeta potential decreased during storage. The calculated shelf lives of encapsulated resveratrol were 25 days at 4 °C and 21 days at 25 °C for RSV-LP, and 23 and 20 days, respectively, for PEGylated RSV-P-LP. [18]

3.3.3 Release and cellular transport

In vitro release from the conventional and PEGylated liposomes was evaluated for 24 h at pH 7.4. Cumulative release reached 92.6% for RSV-LP and 87.2% for RSV-P-LP, compared with 97.4% for the resveratrol solution. Both liposomal formulations therefore showed slower release than free resveratrol under the tested conditions. [18]

Transport across pancreatic β-TC cell monolayers was also investigated. At the end of the experiment, transported resveratrol was 53.3% from solution, 49.8% from RSV-LP, and 44.9% from RSV-P-LP. The corresponding permeability values were 0.079 ± 0.070, 0.107 ± 0.058, and 0.105 ± 0.089 log k, respectively. TEER values after transport were 72 ± 1.08 Ω for solution, 62 ± 1.05 Ω for RSV-LP, and 65 ± 1.00 Ω for RSV-P-LP. [18]

Table 13 Release and transport characteristics of nanoliposomal resveratrol [18]

Parameter	RSV solution	RSV-LP	RSV-P-LP	Ref.
Cumulative release at 24 h (%)	97.4	92.6	87.2	[18]
Transported RSV (%)	53.3	49.8	44.9	[18]
Papp, log k	0.079 ± 0.070	0.107 ± 0.058	0.105 ± 0.089	[18]
TEER (Ω)	72 ± 1.08	62 ± 1.05	65 ± 1.00	[18]

The same formulation was evaluated in glucose- and streptozotocin-induced diabetic β-TC cells. Following 24 h treatment, glucose concentrations decreased toward the normal range, while insulin secretion increased to above 93% of the control level in the treated diabetic-cell groups. The formulations also produced prolonged antioxidant activity through modulation of antioxidant enzymes. [18]

3.3.4 PEGylated dual-drug liposomes

A PEGylated liposomal system containing trans-resveratrol and doxorubicin hydrochloride was developed using egg phosphatidylcholine and DSPE-PEG. The optimised formulation used a Res: Dox ratio of 1:0.5 with EPC: DSPE-PEG at 38:2. Encapsulation efficiencies of approximately 80% for both drugs were obtained. [19]

The dual-loaded PEGylated liposomes had a mean size of 253.23 ± 38.8 nm, compared with 171.7 ± 12.8 nm for blank liposomes. The zeta potential was −30.53 ± 0.55 mV, and the formulation remained stable over 24 h in PBS at pH 7.4. [19]

Table 14. Characteristics of PEGylated Res/Dox dual-loaded liposomes [19]

Parameter	Dual drug-loaded liposomes	Ref.
Res: Dox ratio	1:0.5	[19]
EPC:DSPE-PEG ratio	38:2	[19]
Resveratrol EE	~80%	[19]
Doxorubicin EE	~80%	[19]
Particle size	253.23 ± 38.8 nm	[19]
Blank liposome size	171.7 ± 12.8 nm	[19]
Zeta potential	−30.53 ± 0.55 mV	[19]
Stability in PBS	24 h	[19]

Resveratrol exhibited slower release than doxorubicin from the dual-loaded system. In PBS at pH 7.4, the release of resveratrol followed a Higuchi diffusion pattern with Fickian behaviour. At pH 6.8, resveratrol release increased and followed Korsmeyer–Peppas non-Fickian kinetics. In simulated saliva containing 1% FBS, complete resveratrol release occurred within approximately 14 h, with first-order burst kinetics and a non-Fickian mechanism. [19]

Cell uptake studies in NT8e oral squamous cell carcinoma cells showed that liposomal uptake was predominantly clathrin-mediated during the first hour. At later time points, clathrin-mediated endocytosis, caveolae-mediated uptake, and micropinocytosis contributed to cellular entry. [19]

3.3.5 Deformable and ultradeformable liposomes

Tosato et al. compared conventional liposomes, deformable liposomes, ultradeformable liposomes, and ethosomes for transdermal resveratrol delivery. Conventional liposomes consisted of phosphatidylcholine, whereas deformable and ultradeformable systems incorporated Tween 80 and/or cholesterol. Ethosomes contained a high ethanol proportion. [20]

The formulations differed substantially in resveratrol encapsulation. LD-RSV showed the highest encapsulation efficiency (91.8%), followed by ethosomes (51.0%), conventional liposomes (23.0%), and ultradeformable liposomes (12.6%). The high encapsulation of LD-RSV was associated with Tween 80 and ethanol-mediated increases in lipid-bilayer fluidity. [20]

Table 15. Comparison of liposomal carriers for resveratrol [20]

Carrier	**Particle size with RSV (nm)**	**PDI**	**EE (%)**	**Application evaluated**	**Ref.**
Conventional liposome (L-RSV)	220.5 ± 2.2	0.22 ± 0.009	23.0	Transdermal	[20]
Deformable liposome (LD-RSV)	84.1 ± 1.0	0.28 ± 0.01	**91.8**	Transdermal	[20]
Ultradeformable liposome (LUD-RSV)	201.3 ± 0.8	0.21 ± 0.03	12.6	Transdermal	[20]
Ethosome (Etho-RSV)	289.6 ± 0.9	0.25 ± 0.005	51.0	Transdermal	[20]

The study identified LD-RSV as the most effective of the tested carriers for transdermal delivery, with 91.8% encapsulation efficiency and only a 10% increase in particle size after resveratrol incorporation. [20]

3.3.6 Relevance of liposomes to resveratrol delivery

The supplied papers demonstrate that liposomal systems can address several formulation barriers associated with resveratrol. The pH-driven approach increased the amount of resveratrol that could be incorporated into nanoliposomes but required strict control of alkaline exposure because of rapid degradation at high pH. Conventional and PEGylated nanoliposomes provided high encapsulation and slower release than free resveratrol, while deformable liposomes substantially increased encapsulation for transdermal delivery. [17,18,19,20]

3.4 Phytosomes

Phytosomes are phyto-phospholipid complexes formed by interaction between bioactive compounds and phospholipids. Phosphatidylcholine (PC) is the most commonly used phospholipid and contributes to interaction with biological membranes. For resveratrol, phytosome formation is relevant because low solubility, limited membrane permeability, and poor systemic bioavailability restrict its oral delivery. [23]

3.4.1 Phospholipid–Resveratrol Interaction

Computational analysis showed that hydrogen bonding and electrostatic interactions are major contributors to phytosome formation. For the resveratrol–phosphatidylcholine (Re–PC) complex, two intermolecular hydrogen bonds were identified, but their overall strength was lower than those of the other polyphenol–PC complexes studied. The Re–PC system also showed lower interaction strength and comparatively weaker hydrogen bonding, indicating that phytosome stability depends on the structure of the incorporated polyphenol. [23]

3.4.2 Resveratrol-Loaded Phytosome Nanoparticles

RES-PNPs were prepared using phosphatidylcholine and cholesterol by a modified thin-layer hydration method. The optimised formulation used a 1:2 molar ratio of resveratrol to phosphatidylcholine, with 5–10% w/w cholesterol relative to total lipids. TEM showed spherical nanoparticles of 80–135 nm, while DLS gave a mean hydrodynamic diameter of 190 nm, PDI 0.486, zeta potential −36 mV, and encapsulation efficiency of 84.03%. [22]

Table 16. Physicochemical characteristics of resveratrol-loaded phytosome nanoparticles

Parameter	RES-PNPs	Ref.
TEM particle size	80–135 nm	[22]
Hydrodynamic diameter	190 nm	[22]
PDI	0.486	[22]
Zeta potential	−36 mV	[22]
Encapsulation efficiency	84.03%	[22]

At 4 °C, the formulation remained relatively stable over 30 days, whereas storage at 25 °C increased particle size and PDI and reduced zeta-potential magnitude and encapsulation efficiency. [22]

3.4.3 Oral Pharmacokinetic Evidence

A commercial resveratrol Phytosome® was evaluated against coarse resveratrol in rats. The study reported approximately a three-fold increase in AUC for Phytosome® compared with free resveratrol. [21]

Table 17. Pharmacokinetic parameters of coarse resveratrol and resveratrol Phytosome®

Formulation	AUC (h/ng/mL)	Tmax (min)	Cmax (µg/mL)	MRT (h)	Ref.
Coarse resveratrol	250 ± 20	30 ± 1.4	0.21 ± 0.03	1.10 ± 0.02	[21]
Resveratrol Phytosome®	780 ± 26	15 ± 0.6	0.90 ± 0.05	1.10 ± 0.04	[21]

The study also compared lipid-coated resveratrol nanocrystals, which showed an AUC of 1570 ± 32 h/ng/mL. [21]

3.4.4 In Vivo Therapeutic Evidence of RES-PNPs

RES-PNPs were administered orally at **10 mg/kg/day for 20 days** in Ehrlich ascites carcinoma-bearing mice. Compared with free resveratrol, RES-PNPs produced greater reductions in ascitic fluid volume and viable tumor-cell count and increased mean survival time. [22]

Table 18. Antitumor effects of resveratrol-loaded phytosome nanoparticles in Ehrlich ascites carcinoma

Parameter	EAC	EAC + RES	EAC + RES-PNPs	Ref.
Mean survival time (days)	7.5	11	12	[22]
Ascitic fluid volume (mL)	8.76 ± 0.37	5.19 ± 0.22	3.37 ± 0.26	[22]
Viable EAC cells (10^6/mL)	33.27 ± 1.77	21.17 ± 1.03	12.43 ± 0.84	[22]

RES-PNPs also produced greater restoration of antioxidant status and reproductive parameters than free resveratrol. [22]

The supplied studies demonstrate that phytosomes can improve resveratrol incorporation and provide evidence of enhanced exposure and therapeutic activity after oral administration. The commercial Phytosome® increased AUC relative to free resveratrol, while RES-PNPs produced stronger antitumor and antioxidant-related effects than free resveratrol. However, the 2025 RES-PNP study did not include pharmacokinetic or biodistribution measurements; therefore, its therapeutic findings cannot by themselves establish an increase in systemic bioavailability. [21,22,23]

3.5 Self-Nanoemulsifying Drug Delivery Systems (SNEDDS)

SNEDDS are lipid-based systems composed of oil and surfactant/co-surfactant that spontaneously form fine oil-in-water nanoemulsions after dilution in gastrointestinal fluids. The supplied studies investigated SNEDDS to overcome the low aqueous solubility and dissolution-limited oral absorption of resveratrol. [24-28]

3.5.1 Resveratrol-SNEDDS Formulation and Optimization

Yen et al. developed a RES-SNEDDS using Capryol 90, Cremophor EL and Tween 20. Capryol 90 showed the highest RES solubility among the tested oils (23.58 mg/mL), while Cremophor EL and Tween 20 showed solubilities of 82.84 ± 1.94 and 107.75 ± 2.50 mg/mL, respectively. The optimised formulation (F7) contained Capryol 90/Cremophor EL/Tween 20 at 60:35:5% w/w/w, with a droplet size of 41.3 ± 4.1 nm and PDI of 0.38 ± 0.12. [24]

Table 19. Formulation characteristics of resveratrol-loaded SNEDDS

Study	SNEDDS composition	Droplet size	PDI	Ref.
Yen et al.	Capryol 90/Cremophor EL/Tween 20 = 60:35:5	41.3 ± 4.1 nm	0.38 ± 0.12	[24]
Singh and Pai	Lauroglycol FCC/Transcutol P	56.73 nm	—	[25]
Singh and Pai, S-SNEDDS	Lauroglycol FCC/Transcutol P + 5% HPMC	212.9 nm	0.468	[26]
Tripathi et al.	Capmul MCM EP/Cremophor RH40/Labrafil 1944CS = 30:45:25	149.56 nm*	0.203*	[27]
Jain et al.	Cremophor RH40/Labrafil 1944CS/Capmul	62.69 nm*	0.244	[28]

	MCM EP/α-tocopherol = 35:23:24:18			

*Predicted/optimized value reported by the respective study. The Singh and Pai studies used Lauroglycol FCC as lipid and Transcutol P as surfactant; the optimised formulation contained 100 mg resveratrol with 262 mg Lauroglycol FCC and 225 mg Transcutol P. The scanned study reports rapid emulsification and nanosized droplets. [25]

3.5.2 Improvement in Dissolution and Oral Bioavailability

The optimised Lauroglycol FCC–Transcutol P SNEDDS released approximately 80% of resveratrol within 30 min, compared with 66.56% for pure resveratrol. In rats, the formulation produced a 4.31-fold increase in AUC and a 3.29-fold increase in absorption rate constant (K_a) compared with pure resveratrol. In situ intestinal perfusion further showed approximately 2.94-fold and 3.79-fold increases in effective and wall permeability, respectively. [25]

Yen et al. reported a 3.2-fold increase in oral bioavailability for RES-SNEDDS compared with RES solution. The optimised formulation produced a Cmax of 869.2 ± 112.2 ng/mL and AUC_0–t of 77,055.4 ± 4857.7 ng·min/mL, compared with 386.2 ± 68.4 ng/mL and 23,950.5 ± 3691.3 ng·min/mL, respectively, for RES solution. [24]

Table 20. Pharmacokinetic comparison of resveratrol SNEDDS and resveratrol solution

Parameter	RES-SNEDDS	RES solution	Ref.
Cmax (ng/mL)	869.2 ± 112.2	386.2 ± 68.4	[24]
AUC_0–t (ng·min/mL)	77,055.4 ± 4857.7	23,950.5 ± 3691.3	[24]
Relative bioavailability	321.7%	100%	[24]

3.5.3 Supersaturable SNEDDS

To reduce precipitation after gastrointestinal dilution, Singh and Pai incorporated hydroxypropyl methylcellulose (HPMC) as a precipitation inhibitor into the previously optimised SNEDDS. The resulting S-SNEDDS maintained a higher apparent resveratrol concentration than the conventional formulation during the supersaturation study, and the precipitated resveratrol was predominantly amorphous. [26]

In rats, S-SNEDDS produced a mean Cmax of 0.382 μg/mL and an approximately 1.33-fold higher AUC_0–$_8$h than the conventional OPT-LCT-SNEDDS. In situ perfusion showed 3.92-fold and 5.24-fold increases in effective and wall permeability, while the absorption number and fraction absorbed increased 3.84-fold and 3.03-fold, respectively, compared with pure resveratrol. [26]

3.5.4 SNEDDS Containing Multiple Antioxidants

Tripathi et al. developed a SNEDDS containing quercetin, resveratrol and genistein using a QbD approach. The optimized formulation consisted of Capmul MCM EP/Cremophor RH40/Labrafil 1944CS at 30:45:25, with a predicted droplet size of 149.56 nm and PDI of 0.203. The optimised formulation showed a RES Cmax of 14,800.6 ± 270.2 ng/mL and AUC_0–∞ of 123,640.1 ± 5387.3 ng·min/mL, compared with 10,675.4 ± 783.2 ng/mL and 84,890.6 ± 3244.8 ng·min/mL for free RES, corresponding to approximately 1.45-fold higher AUC. [27]

3.5.5 α-Tocopherol-Containing SNEDDS

Jain et al. developed an α-tocopherol-containing SNEDDS co-loaded with resveratrol and CoQ10. The optimised formulation contained Cremophor RH40/Labrafil 1944CS/Capmul MCM EP/α-tocopherol at 35:23:24:18, with a reported droplet size of 62.69 nm and PDI of 0.244. The formulation remained stable after dilution in simulated gastric and intestinal fluids and showed no significant changes in droplet size, PDI or antioxidant content after 6 months of storage at 25 °C/55% RH. [28]

Oral administration produced approximately 2.3-fold higher RES AUC compared with free antioxidant, while the formulation also increased CoQ10 exposure. The α-tocopherol-containing SNEDDS produced lower tumor volume than the free antioxidant combination in the DMBA-induced breast cancer model. [28]

3.5.6 Overall Findings

The supplied studies demonstrate that SNEDDS improve the oral delivery of resveratrol primarily through improved solubilization, rapid nanoemulsification, enhanced dissolution, reduced precipitation, and increased intestinal absorption.

Across the supplied studies, oral exposure of resveratrol increased relative to free resveratrol or conventional SNEDDS, with reported improvements ranging from approximately 1.33-fold to 4.31-fold, depending on formulation and comparator. [24-28]

3.6 Nanoemulsions

Nanoemulsions have been investigated as oral delivery systems for resveratrol because of its poor aqueous solubility, instability and rapid intestinal metabolism. The supplied studies evaluated preformed oil-in-water nanoemulsions with different emulsifiers and investigated their effects on encapsulation, release, intestinal transport and oral pharmacokinetics. [29-32]

3.6.1 Labrasol-Containing Nanoemulsions

Zhou et al. developed resveratrol-loaded nanoemulsions using soybean oil, soy lecithin and either Labrasol or poloxamer 188 (F68). Lab-N contained 0.1% RES, 10% soybean oil, 2.2% soy lecithin and 1.51% Labrasol. The formulation showed a particle size of **132.2 ± 8.6 nm**, PDI of **0.181 ± 0.015**, zeta potential **−48.9 ± 4.5 mV**, and encapsulation efficiency of **92.5 ± 2.2%**. The corresponding F68-N showed a particle size of 140.4 ± 11.2 nm and EE of 91.2 ± 1.2%. [29]

Table 21. Physicochemical characteristics of Labrasol- and F68-containing resveratrol nanoemulsions

Formulation	Composition	Particle size (nm)	PDI	Zeta potential (mV)	EE (%)	Ref.
Lab-N	RES/soybean oil/soy lecithin/Labrasol	132.2 ± 8.6	0.181 ± 0.015	−48.9 ± 4.5	92.5 ± 2.2	[29]
Lab-F68-N	RES/soybean oil/soy lecithin/F68/Labrasol	135.3 ± 9.3	0.189 ± 0.012	−46.7 ± 3.7	93.4 ± 1.6	[29]
F68-N	RES/soybean oil/soy lecithin/F68	140.4 ± 11.2	0.176 ± 0.011	−44.5 ± 3.4	91.2 ± 1.2	[29]

Labrasol, unlike F68, inhibited resveratrol glucuronidation in the microsomal assay. In everted intestinal sacs, Labrasol-containing formulations increased RES transport and reduced formation of RES-3-glucuronide (RES-G). [29]

Following oral administration to rats, Lab-N produced an AUC of 5.345 ± 1.039 μg/mL·h and Cmax of 1.988 ± 0.617 μg/mL, compared with 0.954 ± 0.427 μg/mL·h and 0.181 ± 0.043 μg/mL for F68-N. The corresponding RES-G AUC decreased to 4.728 ± 0.765 μg/mL·h with Lab-N compared with 6.835 ± 1.314 μg/mL·h for F68-N. The authors attributed the enhanced RES exposure mainly to inhibition of intestinal glucuronidation by Labrasol. [29]

3.6.2 Lecithin-Based O/W Nanoemulsions

Sessa et al. developed peanut-oil-based O/W nanoemulsions containing 0.01% resveratrol using different lipophilic and hydrophilic emulsifiers. High-pressure homogenization was used to produce the nanoemulsions. The formulations ranged from approximately 128 to 235 nm. [31]

Table 22. Particle size and polydispersity of resveratrol-loaded O/W nanoemulsions

Formulation	Main composition	Droplet size (nm)	PDI	Ref.
R/LSL–DSL	Soy lecithin + defatted soy lecithin + peanut oil	211.8 ± 4.9	0.33 ± 0.09	[31]
R/LEC	Soy lecithin + peanut oil	235.4 ± 1.1	0.17 ± 0.02	[31]
R/LSL–SE	Soy lecithin + sugar ester + peanut oil	137.5 ± 0.4	0.22 ± 0.01	[31]
R/T20-GMO	Tween 20 + glycerol monooleate + peanut oil	128.2 ± 2.3	0.12 ± 0.01	[31]

Resveratrol showed a fluorescence shift from 400 nm in water to 386 nm in the nanoemulsion, indicating localisation within the hydrophobic core. The formulations did not damage Caco-2 monolayers, and smaller droplets generally showed greater transport through the cell layer. R/LSL-SE and R/T20-GMO, with mean droplet sizes of 138 and 128 nm, respectively, produced higher cumulative transport than the larger-droplet formulations. [31]

Nanoencapsulation also produced sustained release. Free resveratrol reached approximately 45% release within 3 h, whereas R/LSL-SE and R/LSL-DSL released approximately 80% after 24 h. The other nanoemulsions reached approximately 60% release after 24 h. [31]

3.6.3 Emulsified Resveratrol for Brain Delivery

Locatelli et al. prepared an emulsified resveratrol formulation (e-RESV) using orange oil, grape seed oil and Tween 80 by a low-energy emulsification method. Resveratrol was incorporated at 0.5 g/mL in the oil phase, followed by addition of Tween 80 and dispersion into phosphate buffer (5 mM, pH 7). TEM showed predominantly sub-100 nm droplets. [32]

In aged rats, oral e-RESV administered 24 h before surgery attenuated surgery-induced cognitive impairment and hippocampal neuroinflammation at 40 mg/kg or higher doses. The effect was associated with reduced hippocampal IL-1β and TNF-α and was attenuated by the SIRT1 inhibitor sirtinol. [32]

However, this study did not provide direct in-vivo pharmacokinetic measurements of e-RESV. The authors specifically identified the absence of pharmacokinetic data as a limitation; therefore, increased oral or brain bioavailability could not be quantitatively established from this study. [32]

3.7 Polymeric Nanoparticles: PLGA

PLGA nanoparticles provide a slowly degradable polymeric matrix capable of protecting resveratrol during gastrointestinal transit and supporting intestinal uptake. The supplied studies investigated galactosylated PLGA nanoparticles, PLGA-based Janus nanoparticles, and chitosan-oleate-coated PLGA nanoparticles. [33-35]

3.7.1 Galactosylated PLGA Nanoparticles

Siu et al. developed resveratrol-loaded galactosylated PLGA nanoparticles (RES-GNPs) using a solvent-diffusion method with PLGA, N-oleoyl-D-galactosamine and Tween 80. The optimised formulation contained 10 mg RES, 10 mg PLGA and 20 mg N-oleoyl-D-galactosamine with 125 µL Tween 80 in 2.5 mL water. RES-GNPs showed a particle size of 108.4 nm, PDI 0.217, zeta potential −46.3 mV, and entrapment efficiency 97.22 ± 2.31%. TEM showed spherical nanoparticles. [33]

Table 23. Physicochemical characteristics of galactosylated PLGA nanoparticles

Parameter	RES-GNPs	Ref.
Particle size	108.4 nm	[33]
PDI	0.217	[33]
Zeta potential	−46.3 mV	[33]
Entrapment efficiency	97.22 ± 2.31%	[33]
Formulation method	Solvent diffusion	[33]
Surface ligand	N-oleoyl-D-galactosamine	[33]

RES-GNPs showed slow resveratrol release in water. In situ intestinal perfusion demonstrated increased effective permeability, particularly in the duodenum and ileum, with greater enhancement for RES-GNPs than unmodified RES-NPs. Cellular uptake studies also showed enhanced transcellular transport. [33]

Oral administration produced a marked increase in systemic exposure. At a dose of 40 mg/kg, RES-NPs produced an AUC_0–t of 934.9 ± 112.4 ng/mL·h, whereas RES-GNPs produced 1894 ± 150.7 ng/mL·h. Cmax increased from 553 ± 54.1 ng/mL for RES suspension to 1311 ± 189 ng/mL for RES-NPs and 2393 ± 182 ng/mL for RES-GNPs. Relative bioavailability was 165.7 ± 19.92% for RES-NPs and 335.7 ± 26.72% for RES-GNPs. [33]

RES-GNPs also produced greater suppression of TNF-α, IL-6 and nitric oxide than free RES and RES-NPs in LPS-induced RAW 264.7 macrophages. [33]

3.7.2 PLGA-Based pH-Sensitive Janus Nanoparticles

Liu et al. developed a dual-drug PLGA-based Janus nanoparticle containing resveratrol and α-cobrotoxin (αCT). The particles were prepared by an improved double-emulsion solvent-evaporation method using PLGA, low-molecular-weight chitosan and sodium alginate. The nanoparticles exhibited a dumbbell-shaped, two-compartment structure, particle size of 283.2–350.8 nm, PDI 0.196–0.248, and zeta potential approximately +23.6 mV. Resveratrol EE and drug loading were 87.49 ± 3.43% and 59.28 ± 2.32%, respectively. [34]

Table 24. Physicochemical characteristics of αCT/Res-Janus nanoparticles

Parameter	αCT/Res-JNPs	Ref.
Particle size	283.2–350.8 nm	[34]
PDI	0.196–0.248	[34]
Zeta potential	+23.6 mV	[34]
Resveratrol EE	87.49 ± 3.43%	[34]
Resveratrol drug loading	59.28 ± 2.32%	[34]

The formulation showed pH-dependent release. Resveratrol release in simulated gastric fluid at pH 1.2 was markedly suppressed, whereas release increased in PBS at pH 7.4. Within 12 h, resveratrol release from αCT/Res-JNPs reached 94.57%. The nanoparticles also protected resveratrol against trypsin degradation. [34]

After intragastric administration, free resveratrol showed a Cmax of 92.06 ± 8.00 ng/mL and AUC_0–t of 84.64 ± 3.80 ng/mL·h, whereas αCT/Res-JNPs produced a Cmax of 204.52 ± 20.53 ng/mL and AUC_0–t of 677.96 ± 70.71 ng/mL·h. Tmax increased from 0.17 h to 0.75 h, indicating delayed absorption. [34]

The formulation showed intestinal epithelial uptake and transport, while lymphatic transport contributed only modestly to resveratrol absorption. [34]

3.7.3 Chitosan-Oleate-Coated PLGA Nanoparticles

Miele et al. compared resveratrol-loaded chitosan-oleate (CS-OA)-coated PLGA nanoparticles with CS-OA polymeric micelles. The PLGA nanoparticles contained a hydrophobic PLGA core surrounded by a CS-OA layer, providing a strongly positive surface charge. The PLGA core accommodated resveratrol within the polymer matrix. [35]

At a CS-OA concentration of 1.2 mg/mL, the RSV-loaded PLGA nanoparticles showed a particle size of 273 ± 3 nm, PDI 0.24 ± 0.02, and zeta potential +54.6 ± 1.2 mV. [35]

Table 25. Physicochemical characteristics of resveratrol-loaded CS-OA PLGA nanoparticles

Parameter	RSV-loaded CS-OA PLGA-NPs	Ref.
Particle size	273 ± 3 nm	[35]
PDI	0.24 ± 0.02	[35]
Zeta potential	+54.6 ± 1.2 mV	[35]
Drug location	PLGA hydrophobic core	[35]
Surface	Chitosan oleate	[35]

Resveratrol was efficiently incorporated into the PLGA nanoparticles, with an EE approximately two-fold higher than that of the CS-OA micelles. The final resveratrol concentration in the nanoparticle dispersion was approximately 10-fold higher than the resveratrol saturated solution, indicating improved incorporation of the poorly soluble drug. DSC and XRD analyses demonstrated amorphisation of resveratrol within the PLGA matrix. [35]

The release profile showed an initial faster phase followed by slower release. Resveratrol release from PLGA nanoparticles was slower than from the micelles, consistent with release from the PLGA matrix and its degradation. [35]

The system was evaluated in Caco-2 and HeLa cells. Unloaded nanoparticles maintained Caco-2 cell viability above 80% at the highest tested concentration, while resveratrol-loaded PLGA nanoparticles produced concentration-dependent effects at higher resveratrol concentrations. [35]

3.7.4 Comparative Summary

Table 26. Comparative summary of PLGA-based resveratrol nanoparticles

Study	PLGA system	Size	EE	Oral pharmacokinetic evidence	Ref.
Siu et al.	Galactosylated PLGA-NPs	108.4 nm	97.22%	Relative BA 335.7%	[33]
Liu et al.	PLGA-based αCT/Res-Janus NPs	283.2–350.8 nm	87.49% for RES	AUC 677.96 vs 84.64 ng/mL·h	[34]
Miele et al.	CS-OA-coated PLGA-NPs	273 ± 3 nm	~2× micelles	Not evaluated	[35]

3.8 Chitosan-Based Nanoparticles and Micelles

3.8.1 Chitosan-Based Nanoparticles

Low-molecular-weight chitosan was incorporated into a pH-sensitive Janus nanoparticle system containing resveratrol and α-cobrotoxin. The carrier combined chitosan/sodium alginate with PLGA and was prepared by an improved double-emulsion solvent-evaporation method. The resulting nanoparticles had a two-compartment dumbbell-shaped structure, with a particle size of 283.2–350.8 nm, PDI of 0.196–0.248, and zeta potential of approximately +23.6 mV. Resveratrol showed an entrapment efficiency of 87.49 ± 3.43% and drug loading of 59.28 ± 2.32%. [34]

The formulation showed pH-sensitive protection of resveratrol. In simulated gastric fluid at pH 1.2, free resveratrol showed 93.76% release within 1 h, whereas release from the Janus nanoparticles was minimal. In PBS at pH 7.4, resveratrol release was sustained, reaching 94.57% within 12 h. The nanoparticles also protected resveratrol from

trypsin degradation; after 1 h in the presence of trypsin, 76.96 ± 4.48% of encapsulated resveratrol remained compared with 47.23% for free resveratrol. [34]

Following intragastric administration in rats, free resveratrol showed a Cmax of 92.06 ± 8.00 ng/mL and AUCt of 84.64 ± 3.80 ng/mL·h. The αCT/Res-JNP formulation increased these values to 204.52 ± 20.53 ng/mL and 677.96 ± 70.71 ng/mL·h, respectively, while Tmax increased from 0.17 to 0.75 h. The formulation therefore prolonged exposure and increased systemic resveratrol exposure after oral administration. [34]

The intestinal studies showed that the nanoparticles could cross intestinal epithelial barriers through cellular uptake and endocytosis. Uptake was approximately 10–15% after 4 h in Caco-2 cells, decreasing to about 7% in Caco-2/HT29-MTX co-culture because of the mucus layer. Approximately 12–17% of nanoparticles were transported across the Caco-2/HT29-MTX/Raji model. Lymphatic transport represented only a limited fraction of systemic absorption. [34]

3.8.2 Chitosan Oleate Polymeric Micelles

Chitosan oleate (CS-OA) is an amphiphilic chitosan derivative that self-assembles in aqueous media into polymeric micelles with hydrophobic oleic-acid domains. In the supplied study, CS-OA micelles were used to incorporate poorly soluble resveratrol. Resveratrol was located within the hydrophobic domains formed by the self-assembled oleic acid chains. [35]

The resveratrol-loaded micelles had a particle size of 289 ± 13 nm, PDI of 0.33 ± 0.06, and zeta potential of +57.9 ± 1.1 mV. Resveratrol concentration in the micellar dispersion was approximately three-fold higher than that of the saturated resveratrol solution. [35]

DSC and X-ray analysis demonstrated disappearance of the crystalline resveratrol characteristics, indicating conversion to an amorphous state within the micellar system. Thermal analysis also showed that the PLGA nanoparticles in the same study were thermally more stable than the CS-OA micelles, although the micelles remained relatively stable. [35]

Resveratrol release from the micelles showed an initial rapid phase followed by slower release. Release was slightly higher from micelles than from CS-OA-coated PLGA nanoparticles, but the difference remained below 12% throughout the study. [35]

Cellular studies using Caco-2 and HeLa cells demonstrated internalisation of the CS-OA micelles. Confocal microscopy showed intracellular localisation of the labelled carrier in the cytosol and near the nuclei. Unloaded micelles maintained Caco-2 cell viability above 80% at the highest tested concentration, while resveratrol-loaded micelles generally maintained higher cell viability than free resveratrol. [35]

The supplied studies demonstrate that chitosan-based systems can protect resveratrol from gastrointestinal degradation, provide sustained release, facilitate intestinal and cellular uptake, and increase systemic exposure after oral administration. The Janus nanoparticle study provides direct oral pharmacokinetic evidence, whereas the CS-OA micelle study primarily demonstrates improved resveratrol incorporation, amorphisation, release behaviour, and cellular internalisation; it does not provide direct oral pharmacokinetic data. [34,35]

4. Comparative Analysis of Nanocarriers

4.1 Barrier-to-Carrier Matrix

Table 27. Barrier-to-carrier comparison of resveratrol nanocarriers

Barrier	Zein nanoparticles [36]	SNEDDS [37]	Galactosylated PLGA-NPs [38]	Labrasol nanoemulsion [39]	Ref.
Solubility	Nanoencapsulation; 87% EE.	Directly addressed by lipid/surfactant solubilization; Capryol 90, Cremophor EL and Tween 20 showed high RES solubility.	Addressed through encapsulation within PLGA nanoparticles; slow release reported.	Addressed through incorporation into oil droplets; Lab-N showed 92.5% EE.	[36–39]
Photoprotection	The paper identifies the need for protection from light, but direct photoprotection of NPZ-RSV was not evaluated.	The study focused on solubility and oral absorption; direct photostability testing was not reported.	Direct photoprotection was not evaluated in the supplied study.	Direct photoprotection comparison was not reported.	[36–39]
GI stability	Developed for oral delivery; the human study focused on systemic PK rather than direct GI stability testing.	Rapid self-emulsification under GI conditions and formulation stability were emphasized.	PLGA was described as slowly degradable, supporting structural integrity during GI transport.	Oral delivery benefit was mainly linked to reduced intestinal glucuronidation rather than direct gastric protection.	[36–39]
Permeability / intestinal transport	Human plasma exposure was demonstrated, but intestinal permeability was not directly measured.	Improved systemic exposure was demonstrated; the study discussed excipient effects on absorption and metabolism.	Strong direct evidence from in-situ intestinal perfusion and cellular uptake; Peff increased in all tested intestinal segments.	Everted intestinal sacs showed increased RES transport with Lab-N.	[36–39]
First-pass / presystemic metabolism	The study identified presystemic metabolism as a key RES limitation and measured RES plus RES-glucuronide in humans.	The study discussed effects of excipients on enzymes/transporters but did not establish a specific first-pass mechanism for RES.	The major demonstrated mechanism was enhanced intestinal transport rather than direct inhibition of metabolism.	Strong mechanistic evidence: Labrasol inhibited RES glucuronidation and reduced RES-3-glucuronide exposure.	[36–39]

Barrier	Zein nanoparticles [36]	SNEDDS [37]	Galactosylated PLGA-NPs [38]	Labrasol nanoemulsion [39]	Ref.
Efflux / transporter evidence	Not directly evaluated in the supplied human study.	Transporter/enzyme interactions were discussed, but a specific RES efflux mechanism was not established.	Cellular uptake and transcellular transport were demonstrated; galactose surface modification was linked to intestinal uptake.	Endocytosis and intestinal transport were evaluated; glucuronidation inhibition was the principal demonstrated mechanism.	[36–39]

4.2 Pharmacokinetic Comparison

Table 28. Pharmacokinetic comparison of resveratrol nanocarriers

Nanocarrier	Species	Dose	Comparator	Cmax	Cmax fold-change	AUC	AUC fold-change	Ref.
Zein nanoparticles [36]	Humans (n=16)	250 mg p.o.	No free-RES comparator	21.85 ± 2.29 ng/mL	Not calculable	AUC0–t: 82.68 ± 7.30 ng·h/mL	Not calculable	[36]
RES-SNEDDS [37]	Rats	50 mg/kg p.o.	RES solution	869.2 ± 112.2 vs 386.2 ± 68.4 ng/mL	2.25-fold	77,055.4 ± 4,857.7 vs 23,950.5 ± 3,691.3 ng·min/mL	3.22-fold	[37]
Galactosylated PLGA-NPs [38]	Rats (n=5)	40 mg/kg p.o.	RES suspension	2,393 ± 182 vs 553 ± 54.1 ng/mL	4.33-fold	1,894 ± 150.7 vs 564.1 ± 81.3 ng·mL^{-1}·h	3.36-fold	[38]
Labrasol nanoemulsion [39]	Rats	10 mg/kg p.o.	Free RES suspension	Reported increase	12.58-fold	AUC0–12h reported increase	6.12-fold	[39]

Zein nanoparticles. The human study reported Cmax of 21.85 ± 2.29 ng/mL and AUC0–t of 82.68 ± 7.30 ng·h/mL for resveratrol. Because no free-resveratrol control was included, a direct fold-change in Cmax or AUC cannot be calculated. The same study reported Cmax 986.29 ± 107.95 ng/mL and AUC0–t 3649.28 ± 280.25 ng·h/mL for resveratrol-glucuronide. [36]

SNEDDS. At 50 mg/kg orally in rats, the optimized RES-SNEDDS produced a Cmax of 869.2 ± 112.2 ng/mL versus 386.2 ± 68.4 ng/mL for RES solution and an AUC0–t of 77,055.4 ± 4,857.7 versus 23,950.5 ± 3,691.3 ng·min/mL, corresponding to approximately 2.25-fold higher Cmax and 3.22-fold higher AUC. [37]

Galactosylated PLGA nanoparticles. At 40 mg/kg orally in rats, Cmax increased from 553 ± 54.1 ng/mL for RES suspension to 2,393 ± 182 ng/mL, and AUC0–t increased from 564.1 ± 81.3 to 1,894 ± 150.7 ng·mL^{-1}·h. The reported relative bioavailability was 335.7 ± 26.72%. [38]

Labrasol nanoemulsion. At 10 mg/kg orally in rats, Lab-N increased RES Cmax by 12.58-fold and AUC0–12h by 6.12-fold relative to free RES. Compared with F68-N, the increases were 10.98-fold for Cmax and 5.60-fold for AUC. [39]

4.3 Strength of Evidence

Zein nanoparticles — human oral PK. This provides the strongest translational evidence among the four supplied studies because the formulation was administered orally to 16 healthy human volunteers at a single 250 mg dose, with plasma resveratrol and resveratrol-glucuronide measured. The limitation is the absence of a free-resveratrol comparator, preventing a direct comparative fold-change in bioavailability. [36]

Labrasol nanoemulsion — animal oral PK with mechanistic evidence. The study combined rat microsomal glucuronidation assays, everted intestinal sacs, Caco-2 experiments, lymphatic distribution and in-vivo pharmacokinetics. The increase in systemic exposure was specifically linked to inhibition of intestinal glucuronidation. [39]

Galactosylated PLGA nanoparticles — animal oral PK plus intestinal transport. The study combined oral pharmacokinetics with in-situ single-pass intestinal perfusion and cellular uptake. The formulation increased relative bioavailability to 335.7% and increased effective intestinal permeability. [38]

SNEDDS — animal oral PK with formulation and pharmacodynamic evidence. The study included solubility and self-emulsification optimization, oral pharmacokinetics and an anti-fatigue pharmacodynamic study. It demonstrated increased systemic exposure but did not establish a specific molecular mechanism for the PK improvement. [37]

Comparative evidence level. All supplied papers provide oral administration and pharmacokinetic evidence; none is an in-vitro-only study. The zein study is the only human oral PK study. The other three provide animal oral PK, with the Labrasol nanoemulsion and galactosylated PLGA studies providing particularly strong mechanistic intestinal evidence. [36–39]

5. Safety, Stability and Scale-Up

5.1 Toxicity of Surfactants

The supplied papers do not provide a direct toxicity evaluation of Cremophor EL or Tween 80 as individual surfactants. Therefore, their specific toxicity and safety profiles cannot be established from the supplied literature alone.

In the resveratrol liposome study, the formulation was evaluated by MTT assay in pancreatic beta-TC cells. Blank and resveratrol-loaded liposomes were not found to be toxic even at the highest tested formulation concentration, while the IC50 of free resveratrol was 50.69 microgram/mL. [18]

5.2 Chitosan Biocompatibility

The chitosan toxicity review showed that the toxicity of chitosan nanoparticles varies with concentration, exposure duration and pH, as well as with cell type, organ and animal model. Smaller nanoparticles generally showed greater cellular toxicity than larger nanoparticles. The review also reported differences between species and tissues, with toxicity observed in some zebrafish organs but not consistently reproduced in rats. The review further indicated that some chitosan nanoparticles produced minimal toxicity toward normal cells while showing greater cytotoxicity toward cancer cells. However, the available evidence was mainly derived from in-vitro and animal studies, and the review identified a lack of published clinical trials with available toxicity results. [40]

5.3 PLGA Biocompatibility

PLGA is described in the supplied systematic review as a biodegradable and biocompatible polymer and as an FDA- and European Medicines Agency-approved material for drug-delivery applications. However, the safety of PLGA nanoparticles depends on the characteristics of the complete nanoformulation and its loaded therapeutic agent. [41]

The systematic review evaluated 81 studies and found that cytotoxicity was related to nanoparticle characteristics. In particular, cytotoxicity potency was inversely related to particle size, with smaller nanoparticles generally showing lower IC50 values and greater cytotoxicity. The review therefore emphasized the need for comprehensive in-vitro, in-vivo, pharmacokinetic and toxicokinetic evaluation of PLGA nanocarriers. [41]

5.4 Shelf Life and Storage

The supplied resveratrol liposome study evaluated storage at 4 degrees C and 25 degrees C/60% relative humidity for 3 months. At 4 degrees C, no significant increase in particle size or decrease in zeta potential was observed during the study period. At 25 degrees C, particle size increased and zeta potential decreased significantly, indicating reduced physical stability at the higher temperature. [18]

Resveratrol degradation followed first-order kinetics. The calculated shelf life of conventional resveratrol liposomes was 25 days at 4 degrees C and 21 days at 25 degrees C, while PEGylated liposomes showed calculated shelf lives of 23 and 20 days, respectively. Thus, the approximately three-week shelf life reported for these formulations was mainly associated with chemical degradation of encapsulated resveratrol. [18]

The study also reported that liposomal resveratrol formulations could remain physically stable for up to three months at 4 degrees C, indicating a distinction between physical stability and the calculated chemical shelf life of the encapsulated drug. [18]

5.5 Solvent-Based and Solvent-Free Manufacturing

The supplied resveratrol liposome study used a solvent-based dry-film hydration method. DPPC and cholesterol were dissolved in chloroform, followed by evaporation under vacuum at approximately 44 degrees C to form a lipid film. The residual solvent was subsequently removed in a desiccator before hydration with resveratrol solution. [18]

The supplied papers do not provide a direct comparison between solvent-free and solvent-based manufacturing for resveratrol nanocarriers. Therefore, comparative conclusions concerning manufacturing efficiency, residual-solvent burden, scalability or process superiority cannot be established from these papers alone.

The supplied PLGA/resveratrol study also used a solvent-diffusion process in which resveratrol and PLGA were dissolved in acetone, rapidly injected into an aqueous phase, and the residual solvent was removed under reduced pressure. [38]

5.6 Regulatory Path for Nano-Formulations

The supplied papers provide limited regulatory information. The liposome study describes liposomes as an FDA-approved drug-delivery system and characterizes them as biocompatible and non-toxic. [18]

The PLGA systematic review states that PLGA is approved by the FDA and European Medicines Agency as a biodegradable and biocompatible material for drug-delivery applications. However, the supplied papers do not describe a complete regulatory pathway for resveratrol nanoformulations, including regulatory submission requirements, clinical-development stages or nanomedicine-specific approval procedures. [41]

6. Conclusion

Resveratrol's therapeutic promise is undermined by a pharmacokinetic problem, not a pharmacological one. Despite efficient intestinal absorption, extensive first-pass glucuronidation and sulfation in the gut and liver reduce its oral bioavailability to well under 1%, while poor aqueous solubility and susceptibility to light-induced isomerization compound the challenge before the compound ever reaches systemic circulation.

Across the nanocarrier strategies reviewed here, the common thread is that each platform addresses a distinct piece of this barrier. Solid lipid nanoparticles and nanostructured lipid carriers improve intestinal permeability and physical stability. Self-nanoemulsifying drug delivery systems increase dissolution rate and, in at least one case, directly inhibit the intestinal glucuronidation responsible for first-pass loss.

Polymeric nanoparticles, particularly PLGA-based systems, have produced some of the largest reported gains in oral bioavailability. Liposomes, phytosomes, and polymeric micelles offer further, if less extensively documented, improvements. Taken together, the comparative evidence indicates that no single carrier class is optimal for every barrier; rather, carrier selection should be matched to the specific limitation a formulation is intended to overcome.

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