Chapter 2

Novel Drug Delivery Systems of Resveratrol to Bioavailability and Therapeutic Effects

Poonam Devi, Pratibha Sharma, Charul Rathore and Poonam Negi

Additional information is available at the end of the chapter

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Abstract

Resveratrol is a naturally occurring product used in the prevention and treatment of various diseases by acting as a potent defensive antioxidant. Resveratrol can be used in various fields, but the use is limited due to its poor solubility and hence low bioavailability. For overcoming this limitation, various drug delivery systems of resveratrol were developed. The aim of the novel drug delivery system (NDDS) is to provide a therapeutic amount of drug to the target site to maintain the desired drug concentration. NDDS enhances the duration of therapeutic activity, increases plasma half-life, decreases the immunogenicity, increases the stability of biopharmaceuticals, improves the solubility of low molecular weight drugs so does the bioavailability, and has a potential of targeted drug delivery. However, they have their own advantages as well as limitations. This chapter focuses on: (1) general introduction to resveratrol and its various therapeutic uses, (2) pharmacokinetic- and bioavailability-related problems of resveratrol, and (3) general about various NDDS used in resveratrol formulations.

Keywords: microparticulate systems, cyclodextrin complex, solid lipid nanoparticles (SLNs), vesicular systems and polymeric micelles

1. Introduction

Natural products have been used in the prevention and treatment of diseases throughout history due to their wide acceptability. Among the various groups of natural products and plant metabolites that are available, resveratrol plays an important role in the treatment of various diseases by acting as a potent defensive antioxidant [1]. Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene) is

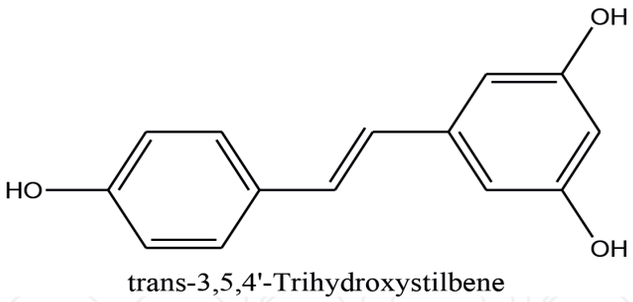

Figure 1. Chemical structure of resveratrol.

a natural phenol and a phytoalexin produced by several plants in response to injury by numerous plants in response to damage. The molecular formula is $C_{14}H_{12}O_3$ and molecular weight is MW 228.25 (**Figure 1**) [2]. Resveratrol is present in plants of families including Gnetaceae, Vitaceae, Cyperaceae, Dipterocarpaceae, and Leguminosae. A variety of food and food products such as grapes, wine, grape juice, cranberries, mulberries, cranberry juice, and peanuts contain resveratrol [3]. Resveratrol is a member of the stilbene family [4], characterized by two benzene rings linked through isopropyl moiety separated by a double bond [5]. Resveratrol plays a role in defense mechanism against various fungal, bacterial infections, viral, and damage from exposure to ultraviolet radiation (UV), which is very well depicted in **Table 1** [6]. Resveratrol also exhibits various therapeutic effects such as antiaging, neuroprotector, antioxidant, cardio protector, etc. The method of drug delivery has significant consequences over the efficacy of the constituent [7]. Drug delivery systems (DDSs) emerged as a new strategy based on interdisciplinary approach combining polymer science, bioconjugate chemistry, pharmaceutics, and molecular biology. DDS increases drug bioavailability and the fraction of

Sr. no	Role of resveratrol	Mechanism of action	Refs
1	Cardioprotective	Inhibition of transforming growth factor (TGF-β1) and atrial natriuretic peptide (ANP), increase in nuclear factor (NF-kB) activity	[13, 14]
2	Antioxidant	Neutralization and inhibition of reactive oxygen species (ROS), lipid peroxidation inhibition, and metal cations chelation	[10, 11]
3	Immunomodulatory	Increase in CD4/CD8 ratio, T lymphocytes proliferation, and B cell-mediated immune response, promotion of humoral immune response and improvement in the formation of antibody cells	[14]
4	Antihypertensive	Inhibition of vascular nicotinamide adenine dinucleotide phosphate (NADPH) oxidase induction and inhibition of COX-2	[20]
5	Anticancer	Suppression of protein kinase and suppression of NF-kB activation, suppression of protein kinase and suppression, induction of apoptosis, cell cycle arrest and suppression of growth factor receptor (GFR)-mediated pathway	[16]
6	Anti-inflammatory	Inhibition of NF-kB and nitric oxide synthases (NOS) expression and also reduction in proinflammatory IL-1β, cytokines, TNF-α, and COX-2	[20–22]

Table 1. Mechanism of action of resveratrol for different activities.

the drug accumulated in the required zone, and minimizes drug degradation, loss and harmful side effects. A variety of DDS are also available for resveratrol for modulating its delivery; for example, cyclodextrin complex; microparticulate systems; nanocarrier systems such as nanosuspension and solid lipid nanoparticles; and vesicular system such as niosomes, liposomes, transferosomes and ethosomes, and nanosponges.

2. Medicinal uses

Plants containing resveratrol have been widely used as a potent antioxidant [8] and also useful in the treatment of various disease [9] (**Figure 2**).

2.1. Antioxidant activity

Oxidative stress caused due to free radicals generated through endogenous and exogenous sources plays a significant role in the pathogenesis of a disease [10]. Resveratrol (RSV) also suppresses the action of the lipopolysaccharide, an inducible form of nitric oxide (NO) synthase, through the vascular endothelium, established by a reduction in nitric oxide production, also inhibiting the oxidation of the low-density lipoprotein (LDL) through the *in vivo* chelation of copper, therefore suggesting a potential role in the prevention of atherosclerosis and coronary heart disease [11]. The first antioxidant activity was reported by Frankel et al. of transresveratrol using different antioxidant assays including lipid peroxidation assay, 2,2-diphenylpicrylhydrazyl (DPPH) radical scavenging assay, total antioxidant activity, hydrogen peroxide scavenging activity assay, and reducing power assay. The results show that resveratrol has 2 μmol higher scavenging activity for diphenylpicrylhydrazyl (DPPH) radical as compared to the control group [12].

2.2. Cardioprotective activity

Various scientific studies reveal that utilization of plant extracts containing polyphenols, especially resveratrol, and red wine decreases mortality of coronary heart disease [13]. Due to its potent antioxidant, resveratrol, showing an overall good cardioprotective effect by inhibiting the oxidation of low-density lipoprotein (LDL), promotes vasodilation, reduces platelet aggregation, and enhances endothelial nitric oxide synthase activity [1].

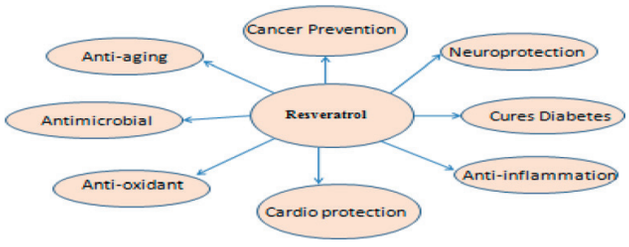

Figure 2. Medical benefits of resveratrol.

Resveratrol was also showing potential effect on protecting cardiac and vascular tissues by reducing the accumulation of reactive oxygen species (ROS) in renal hypertensive rats [14].

2.3. Immunomodulatory activity

Resveratrol was found to increase B cell-mediated immune response, and also increases CD4/CD8 ratio and T cell proliferation. Li et al. demonstrated immunomodulatory effect on mice with lymphocytic leukemia [15].

2.4. Anticancer activity

Cancer is a chronic disease with a high death rate. Carcinogenesis involves in accumulation of cancer-regulating genes [16]. Various studies suggested that fruit- and vegetable-rich diet leads to reduced incidence of cancer due to presence of polyphenolic compounds [17]. Subramanian et al. showed the antiproliferative, proapoptotic along with antiangiogenic activity of resveratrol by performing different *in vitro* studies on wide tumor cell lines [18]. Similarly, Hu et al. discussed treatment of hepatocellular carcinoma with different compounds such as curcumin, tanshinone II-A, quercetin, berberine, silibinin, resveratrol, and celastrol derived from Chinese herbal medicines [19].

2.5. Antihypertensive activity

Endothelium-dependent vasorelaxation improved using resveratrol. Researchers' findings show that early treatment with resveratrol preserves endothelial function, decreases oxidative stress and superoxide dismutase activity, and gradually lowers the incidence of hypertension with the reduction in hydrogen peroxide levels [20].

2.6. Anti-inflammatory and vasorelaxing activity

Oxidative and inflammatory responses attenuate by polyphenols in various cells [21]. Activatation of microglia causes secreation of neurotoxic and proinfammatory mediators after brain injury. Zhang et al. studied the effect of resveratrol in inhibiting microglia [22]. Resveratrol was also found to decrease the synthesis of prostaglandin (PGE_2) by inhibiting cyclooxygenase (COX-2) enzyme activity, thus useful in inflammation [23]. Anti-inflammatory activity of resveratrol in turbot (a fish species) in vertebrates carried out by Leiro et al. The results showed the drug-dependent inhibition of messenger ribonucleic acid (mRNA) production, and increased tumor necrosis factor (TNF-α) and interleukins (IL-1β) pre-mRNA levels, thus proving its anti-inflammatory activity in vertebrates [24]. A vasorelaxation effect was observed by the activity of nitrous oxide (NO) by Zenebe et al. in red wine polyphenols on rat femoral artery [25]. Resveratrol is a multipurpose compound found in wine polyphenol, that improves the endothelial function with NO and vasorelaxation effect [26].

2.7. Antimicrobial activity

Stilbenes have been studied broadly for their antimicrobial activities [27]. Paolillo et al. studied resveratrol using cells line (U937) and observed time and dose-dependent reduction in

NO level [28]. Another antibacterial study given by Paulo et al. has determined zone of inhibition and minimum inhibitory concentration (MIC) using different strains of gram-negative spiral-shaped bacillus of Helicobacter, *H. pylori*. Most of the strains show similar susceptibility patterns, and MIC was observed in range 25–100 μg/ml. The result shows that action of resveratrol in urease inhibition was found to be higher (90%), as compared to the positive control strains (<75%). Thus, the research confirmed that the antibacterial activity of resveratrol is due to urease inhibition [29].

2.8. Antidiabetic activity

Diabetes mellitus is a complex metabolic disease characterized by high concentration of blood glucose level and increased insulin resistance [30]. Su et al. carried out resveratrol treatment study on streptozotocin-induced diabetic rats, the results decrease in triglyceride concentration by 50.2 ± 3.2%, and plasma glucose level by 25.3 ± 4.2% was obtained on the fourteenth day after treatment. The drug also verifies a stimulatory effect on the glucose absorption by numerous cells including hepatocytes and adipocytes [31].

2.9. Radioprotective activity

Radiation exposure is a major problem of destruction of a living cell, which causes free radical generation and ROS activation. Different polyphenols have been studied for their radioprotective activities [32]. Aziz et al. studied that ultraviolet-B radiation causing skin damage of mouse was prevented using resveratrol. Topical use of 10 μmol solution of resveratrol in 200 μl acetone results in the inhibition of ornithine decarboxylase, increase in cellular proliferation, and protein levels of epidermal COX-2 were observed, thus confirming the radioprotective activity, which was mediated by programmed cell death and elimination of damaged cells [33].

2.10. Neurodegenerative diseases

2.10.1. Parkinson's disease

Neurodegeneration is associated with various factors such as gene alteration, inflammation, oxidative stress, and mitochondrial dysfunction [34]. Okawara et al. observed resveratrol in mid-brain segment culture that shows a protective role of Wistar rats on dopaminergic neurons. Cytotoxicity of 1-methyl-4-phenyl pyridinium (MPP^+) causes neurodegeneration, which was formed from the transformation of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Decrease in numbers of viable dopaminergic neurons was observed when segmented culture was applied with 30 μmol of MPP^+, but when applied with resveratrol, dose-dependent protection of neurons, which was due to antioxidative activity [35].

3. Bioavailability and pharmacokinetic studies of resveratrol

The absorption, distribution, metabolism, and excretion (ADME) and other pharmacokinetic parameters of resveratrol are well implicated. Instead of high oral absorption (~75%). The oral

bioavailability is less than 1% because of extensive and fast metabolism in intestine and liver leading into sulfate and glucuronide metabolites [36]. Almeida et al. determined the pharmacokinetic and safety contour of resveratrol. Four groups of five males and five females each were taken. Any two random subjects of each group were administered with placebo, while the remaining eight were administered with 25, 50, 100, and 150 mg of resveratrol, six times daily for 13 doses. Several pharmacokinetic parameters were determined out of which the peak plasma concentration (C_{max}) was found to be 0.8–1.5 h, whereas the mean C_{max} and mean area under the curve (AUC_{0-t}) were found to be dose dependent and found to be increasing with increase in dose from 25 to 150 mg [37].

4. Solubility and bioavailability enhancement of resveratrol

The reported aqueous solubility of resveratrol is <1 mg/ml, which is a key shortcoming of the drug [38]. The metabolic studies of resveratrol showed an increase in bioavailability when aglycone form of resveratrol was administered in solution of hydroxypropyl b-cyclodextrin [39]. Different approaches such as formulation of microparticles to reduce size to micron level [40], complexation with cyclodextrins [41], formulation of various vesicular systems such as liposomes [42], niosomes [43, 52], transfersomes and ethosomes [44], formulation of different nanocarrier systems for example nanostructured lipid carriers (NLCs), solid lipid nanoparticles (SLN) [45], nanosuspension [46], and nanocapsules [47] have been implied to improve different properties of resveratrol such as bioavailability, solubility, photo-sensitivity, and stability.

5. Drug delivery systems

The aim of novel drug delivery system (NDDS) is to provide a therapeutic amount of drug to the target site to maintain the desired drug concentration. NDDS enhances duration of therapeutic activity, increases plasma half-life, decreases the immunogenicity, increases the stability of biopharmaceuticals, improves the solubility of low molecular weight drugs so does the bioavailability, and has a potential of targeted drug delivery. Various NDDS given in **Table 2** can be explained as follows:

5.1. Microparticulate systems

These systems act as the carrier vehicle system for solid or liquid microparticles surrounded by polymeric layer ranging from 0.1 to 200 μm [48] in diameter (**Figure 3**), the type of polymer present in the layer improves bioavailability and controls the release of the drug [49]. Nam et al. improved the stability and antioxidant activity of the resveratrol possessing cyano-groups by formulating its porous polymeric microspheres by dispersion polymerization. Antioxidant property was characterized by DPPH radical scavenging activity [50]. Das et al. formulated microparticles of resveratrol and pectin utilizing glutaraldehyde as hardening agent and zinc ions as crosslinking agent, as resveratrol has potential therapeutic activity

Sr. no.	Drug delivery systems	Method of formulation	Model used	Observations	Refs
1	Microparticulate systems	Microparticles prepared by using resveratrol and pectin, containing glutaraldehyde as hardening agent and zinc ions as cross-linking agent for pectin	*In vitro* and *in vivo* drug release. Plasma appearance (C_p) of drug was delayed for 4–5 h in direct administration into stomach	Result shows enhancement of antioxidant activity and improved stability of resveratrol in microparticulate system as compared to that of pure resveratrol	[54, 56]
2	Microcapsules	Microparticles of resveratrol were prepared by microencapsulation using yeast cells	*In vitro*	Yeast-encapsulated resveratrol formulation shows increased stability, solubility, bioavailability and sustained-release profile	[6]
3	Cyclodextrin complex	Inclusion complexes prepared using combination of resveratrol with β-cyclodextrins and hydroxyl-β-cyclodextrins	*In vitro*	Enhanced solubility, antioxidant activity, and thermal stability	[59, 60]
4	Solid lipid nanoparticles	Lipid nanoparticles of resveratrol were prepared by using modified hot homogenization technique	*In vitro*	Results show increased oral bioavailability of poorly soluble compounds	[42]
5	Nanosuspension	Nanosuspension of resveratrol was prepared by using high-pressure homogenization technique	*In vitro*	High solubility and dissolution velocity, thus increasing the bioavailability	[43]
6	Vesicular systems liposomes	Liposomes was prepared by using Phosphatidylcholine (PC) and resveratrol were dissolved in mixture solvents such as chloroform and methanol using rota evaporator. The liposome suspension was then added dropwise to chitosan solution with stirring and then solution left overnight at 4°C. Finally, chitosan-coated liposomes were harvested using centrifugation	*In vitro*	Increased skin-permeation efficiency with effective transdermal delivery system	[66]
7	Niosomes	Resveratrol-loaded niosomes were prepared using two stage techniques that include mechanical agitation followed by sonication, where two different surfactants, span 80 and span 60, were used	*In vitro*	Results show increased stability and improved the bioavailability	[66]

Sr. no.	Drug delivery systems	Method of formulation	Model used	Observations	Refs
8	Transfersome and ethosomes	Transfersomes and ethanol-containing vesicles were prepared by thin lipid film hydration method (rota evaporator)	*In vitro* and permeation studies (porcine skin carried out on Franz diffusion cells)	Findings show that nanocarriers were found to possess an encapsulation efficiency of >70% with a mean diameter of 83–116 nm	[67]
9	Nanosponges	Nanosponges containing resveratrol were prepared by solubilizing the reagents in dimethyl sulfoxide (DMSO) at 100°C for 4 h	*In vitro* and permeation studies (pigskin)	Results increase the stability, cytotoxicity, and permeation of resveratrol. Decrease in crystallinity of resveratrol was observed after encapsulation	[65]
10	Microspheres	Microspheres of resveratrol (Res) using chitosan were prepared by emulsion chemical crosslinking method, and vanillin was used as the new crosslinker	Higuchi was the most suitable model for the controlled release profile	Microspheres of resveratrol were protected from light and heat as compared to free Res, and increase in stabilization of Res was achieved through crosslinking with vanillin	[67]

Table 2. Novel drug delivery systems for resveratrol (RSV) delivery.

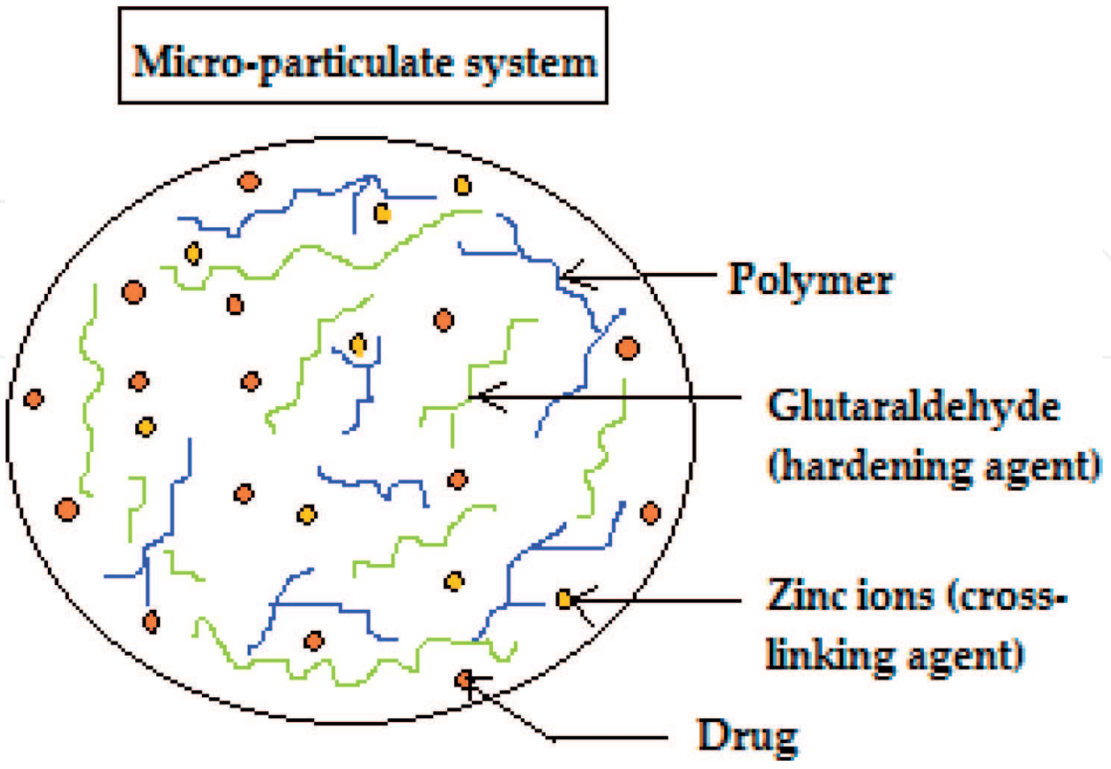

Figure 3. Microparticulate system.

on colitis and colon cancer, and was used as a model drug in the prepared formulation. By fluctuating the formulation variables, a variety of microparticles were prepared, which were investigated on different shape and size of the microparticles, weight loss during drying, moisture content, encapsulation efficiency, drug release pattern from the microparticles, and swelling-erosion ratio. The formed microparticles were spherical with less than 1 mm diameter and with greater than 94% encapsulation efficiencies. Colon-specific *in vivo* and *in vitro* drug release was shown by glutaraldehyde-modified microparticles (GMM) formulated at optimized conditions. GMM delayed the plasma appearance of the drug for 4–5 h after their administration straightaway into stomach, but the AUC was comparable to other control formulations of the experiment; this indicated the potential of the developed microparticle formulation of the resveratrol as a colon-specific drug delivery system [51].

5.2. Microcapsules

Microencapsulation is a technique in which tiny particles are enclosed by a coating to give small capsules (**Figure 4**). Microencapsulation can also be used to enclose solids, liquids, or gases surrounded by a hard or soft soluble film, in order to decrease dosing frequency and avoid the degradation of pharmaceuticals. Encapsulation of resveratrol was done by the yeast cell, which was characterized by FT-IR spectra, fluorescence and confocal micrographs of the microcapsules, yeast cells, and resveratrol. The release of the drug was characterized in simulated gastric fluid (SGF), and storage stability was determined by taking powder sample of the formed microcapsules at 25°C at 75% RH, 25°C at 90% RH, and 60°C under the dark or laboratory fluorescent lighting conditions. It was found that the encapsulated resveratrol possess high scavenging capacity on DPPH radical as compared to nonencapsulated resveratrol. The encapsulation does not cause any chemical change in the active moiety. Besides, the encapsulation enhances the DPPH radical-scavenging activity, stability, sustained-release and also solubility of resveratrol and so it's bioavailability [52].

5.3. Cyclodextrin complex

Cyclodextrins are cyclic oligosaccharides formed during bacterial digestion of cellulose. They are also known as cycloamyloses, cyclomaltoses, and Schrodinger dextrins. These complexes have a lipophilic core with hydrophilic outer surface and hence capable to form inclusion

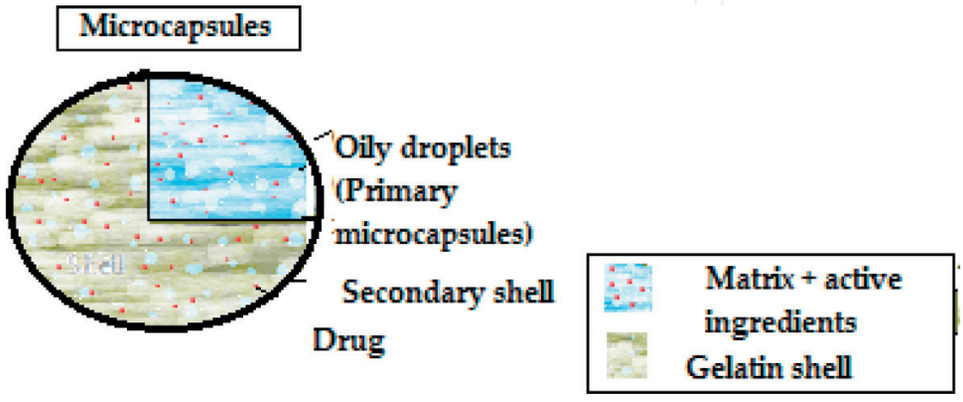

Figure 4. Microcapsules.

complexes and holding lipophilic drugs to their inner cavity (**Figure 5**). Thus, they improve solubility and so does the bioavailability of the poorly soluble drugs. These can be divided into α, β, and γ subtypes on the basis of presence of six, seven, or eight glucopyranose units, respectively. Cyclodextrins protect the drug from oxidation so act as a controlled dosage reservoir [53, 54]. Resveratrol is encapsulated in different native and modified cyclodextrins to form different inclusion complexes to enhance its poor aqueous solubility [55]. Lu et al. observed enhancement in aqueous solubility and antioxidant property of resveratrol by forming inclusion complex of resveratrol with β-cyclodextrins and hydroxyl-β-cyclodextrins. The drug and cyclodextrin interactions were evaluated in the solution for stoichiometry and stability constant by phase solubility analysis. Results proved the increased limited water solubility of resveratrol-cyclodextrins inclusion complexes. Resveratrol/hydroxy-β-cyclodextrin complex also exhibited superior antioxidant potential compared to β-cyclodextrin complex [56].

5.4. Nanocarrier systems

5.4.1. Solid lipid nanoparticles (SLNs)

SLNs are formed by a solid lipid matrix medium, which is stabilized by surfactants in the aqueous media, with potential to enhance drug bioavailability. The diameter ranges between 50 and 1000 nm. SLNs possess various advantages such as target-specific delivery, photo, and acid stability for sensitive drugs (**Figure 6**). SLNs elegantly control drug distribution at cellular, or even at subcellular level [57]. Teskac et al. prepared SLNs of resveratrol by melt-emulsification process and investigated cellular uptake, transport, and internalization of the drug in keratinocytes. Hydrodynamic diameter of loaded SLNs was calculated by photon correlation spectroscopy that was found to be 180 ± 8 nm. This confirmed the upgraded cellular uptake and cellular density of resveratrol by loaded SLNs. As SLNs were observed to concentrate around nuclei, it confirms sustained-release of drug, thus improving the bioavailability and stability [58]. A comparison is made between resveratrol nanostructured lipid carriers (NLCs) and SLNs

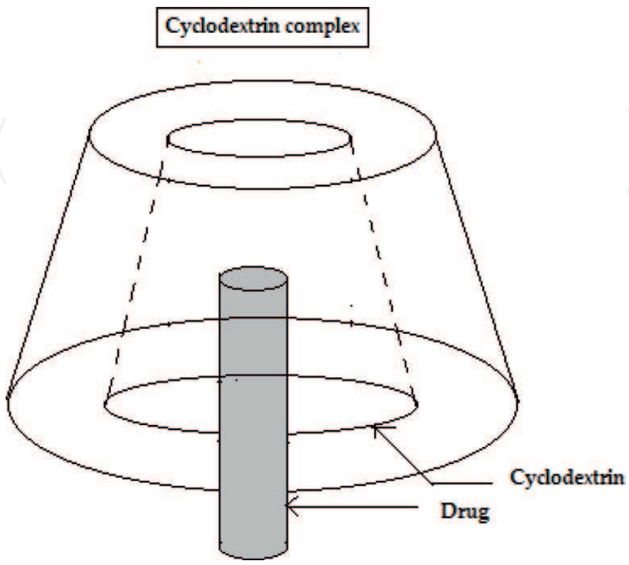

Figure 5. Structure of cyclodextrin complex.

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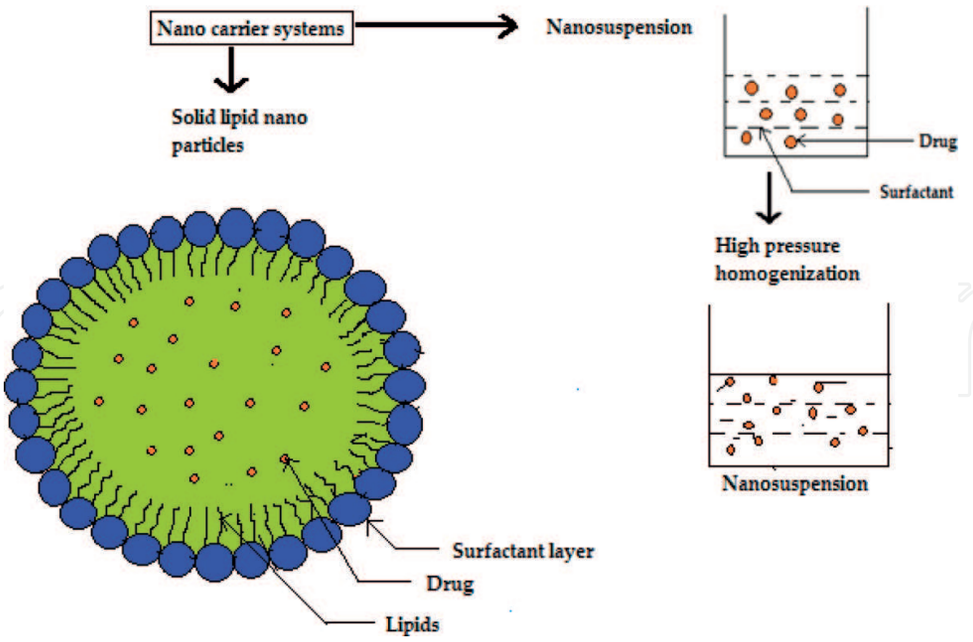

Figure 6. Structure of nanocarrier systems.

prepared by high shear homogenization using compritol 888ATO, myglyol, poloxamer 188, and tween 80. A potent antioxidant activity was observed for both formulations at a concentration of 50 μM, but resveratrol NLCs was observed to penetrate deeper into the skin [59].

Ana et al. developed lipid nanoparticles of resveratrol to increase the oral bioavailability. Modified hot homogenization technique was used to prepare resveratrol-loaded lipid nanoparticles (SLNs and NLCs). The encapsulation efficiency was found to be high for both SLNs and NLCs, with an average around 70%. The existence of solid state of SLNs and NLCs at both room (25°C) and body temperature (37°C) was confirmed by DSC studies. *In vitro* release studies performed in shelf storage conditions showed a negligible release of resveratrol over several hours for both systems, which concluded the high stability of both lipid nanoparticle systems [60].

5.4.2. Nanosuspension

These are the nanorange colloidal dispersions systems stabilized by surfactants, containing poorly water soluble drugs. These systems result in the improvement of bioavailability of the drug by improving its solubility. Kobierski et al. prepared nanosuspension of resveratrol in the range between 150 and 220 nm for dermal application using high-pressure homogenization technique. Nanosuspension showed high solubility and dissolution velocity for resveratrol and thus improved bioavailability [46].

5.5. Vesicular systems

Vesicular systems are the drug delivery systems composed of lipophilic polymeric core, and lipophobic tail or shell. These systems are capable of encapsulating both hydrophilic and

lipophilic drugs (**Figure 7**). They are shown to improve the bioavailability of the drug and thus enhancing duration of therapeutic activity. Examples of these systems are liposomes, niosomes, transfersome, phytosomes, ethosomes, etc. [61].

5.5.1. Liposomes

Liposomes are colloidal vesicular structures prepared from lipids capable of loading both lipophilic and hydrophilic drugs. The bioavailability of resveratrol was found to be improved by incorporating into liposomes [42]. Caddeo et al. formulated liposomes of resveratrol using phosphatidylcholine and oleic acid as penetration enhancers. Deep penetration of the drug into the skin was reported by these systems. The antioxidant potential of the resveratrol was also found to be unchanged by incorporating the drug into these systems [62]. Park et al. investigated chitosan-coated liposomes of resveratrol for improving transdermal delivery of the drug. The stability of the liposome was found to be increasing on chitosan coating, by preventing aggregation. Franz diffusion cells were used to investigate the transdermal delivery of uncoated and 0.1% chitosan-coated liposomes with 0.1% resveratrol. The proportions of resveratrol that permeated through the animal skin were found to be 40.42 and 30.84% for the coated and uncoated liposomes, respectively. This indicated the effective transdermal delivery of chitosan-coated liposomes for delaying skin aging using resveratrol [63].

5.5.2. Niosomes

Niosomes are nonionic surfactant vesicular systems comprised of aqueous inner core enclosed by nonionic surfactant membrane, thus forming a closed bilayer structure. These systems are capable of loading both hydrophilic and hydrophobic drugs. These are prepared by hydration of surfactants. Pando et al. formulated resveratrol encapsulated niosomes using two stage techniques, mechanical agitation followed by sonication by using two different surfactants, span 60 and span 80. The entrapment efficiency and particle size distribution of niosomes prepared from span 80 were found better as comparison to noisome prepared

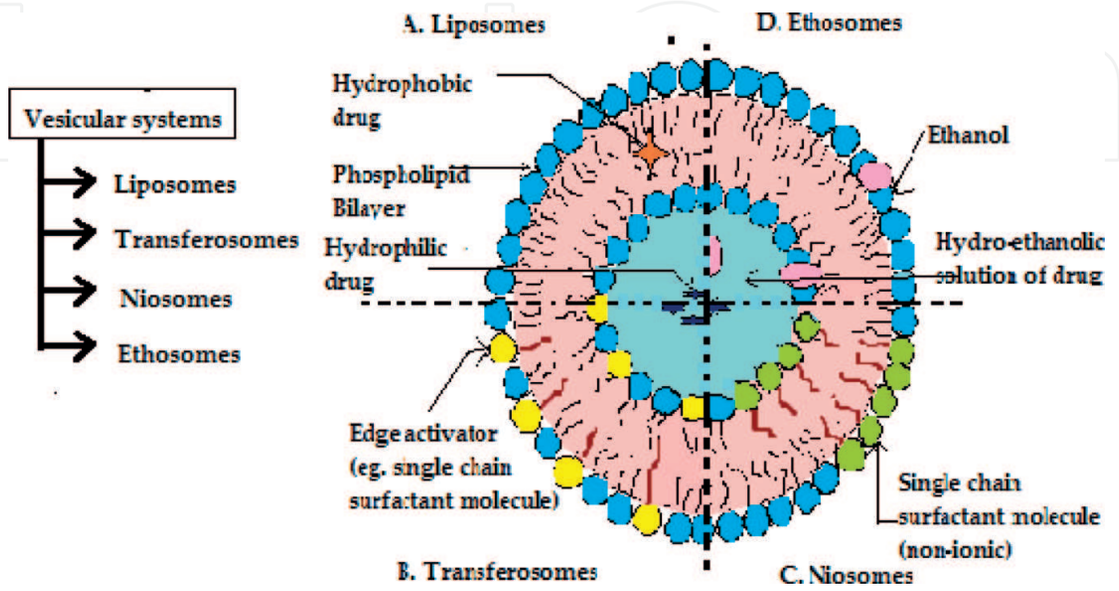

Figure 7. Vesicular systems.

from span 60, hence the bioavailability [43]. Poonam Negi et al. prepared niosome employing span 80 as surfactant by thin film hydration and ether injection methods at three different levels. Selection of best optimized formulation was done on the basis of entrapment efficiency (% EE), sedimentation volume, mean particle size, and microscopy. Optical microscopy and transmission electron microscope (TEM) confirmed the vesicular and spherical nature of the niosomes. Resveratrol entrapped niosomal gel was formulated by gelling in Carbopol 934. Ex vivo permeation studies confirmed better permeation and deposition of resveratrol in skin as compared to plain resveratrol [64].

5.5.3. Transfersomes and ethosomes

Transfersomes are ultraflexible lipid-based elastic vesicles, while ethosomes are vesicles containing phospholipids, ethanol, and water with the potential to penetrate into intact skin and delivering drug into systemic circulation through skin. Topical formulations of resveratrol as a potential drug were prepared as a vesicular system. The diameter of nanocarriers was found to possess a mean diameter of 83–116 nm with more than 70% encapsulation efficiency [44].

5.6. Nanosponges

Nanosponges are nanometric-range size particles with enclosed cavities, capable of encapsulating both lipophilic and hydrophilic drugs (**Figure 8**). These systems improve the solubility of poorly water soluble drugs and thus the bioavailability [65]. Ahmed et al. formulated

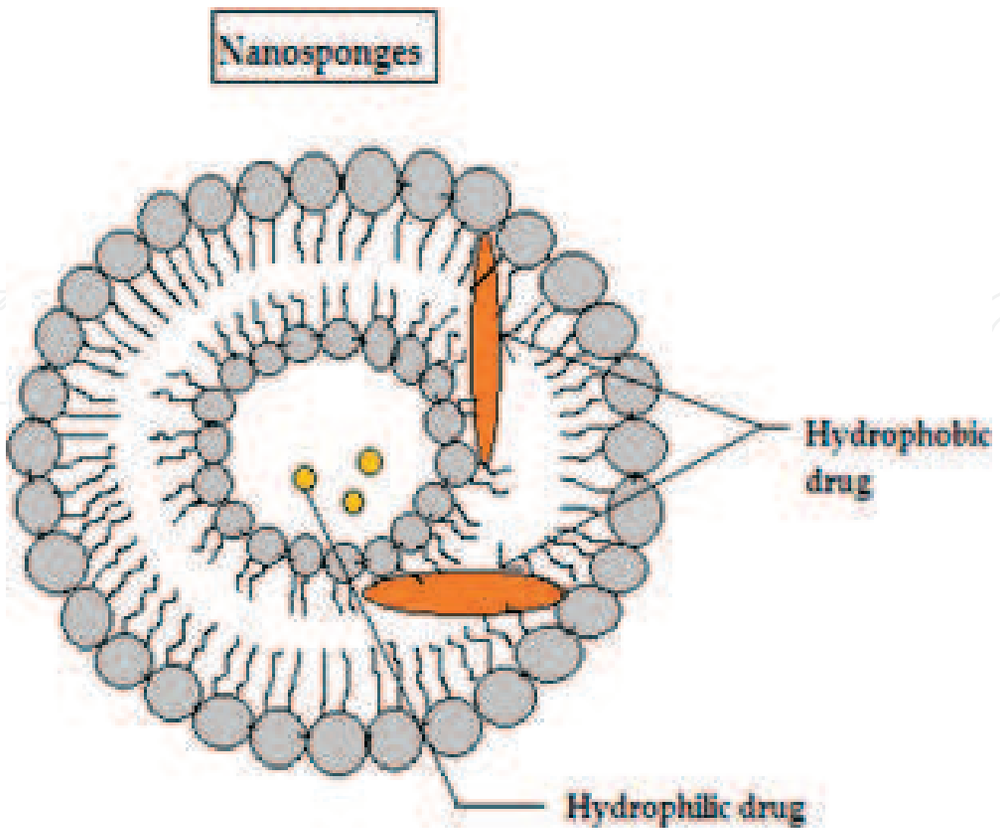

Figure 8. Nanosponges.

nanosponges of resveratrol by dissolving the reagents in dimethyl sulfoxide at 100°C for 4 h. Improvement of the stability and penetration of resveratrol was recorded by this system [66].

5.7. Microspheres

Microspheres are minute spheres comprising of porous/nonporous inner polymeric matrix with an outer, porous and regular to nonporous and irregular, polymeric surface (**Figure 9**). Diameter of these structures ranges from 1 to 500 μm. Peng et al. formulated microspheres by emulsion chemical crosslinking method using vanillin as a crosslinker. Stable chitosan-incorporated resveratrol microspheres were prepared. Encapsulation efficiency of resveratrol within microspheres was found to be 93.68%. Resveratrol encapsulated within microspheres was protected from light and heat compared to the free resveratrol [67].

5.8. Polymeric micelles

This system is made of amphipathic linear polymers formed spontaneously by self-assembly in water and a hydrophobic core in which the drug is encapsulated (**Figure 10**). The size of micelles varies from 20–100 nm, so that they do not cross the normal vessel walls, hence have a low volume of distribution and decrease the chances of side effects of the drugs. They carry various poorly soluble pharmaceutical agents due to their high *in vitro* and *in vivo* stability. They get accumulated in body areas with compromised vasculature and act as carrier systems for drug targeting as they can carry specific ligands on their surface. Katherine E. Washington formulated polymeric micelles of doxorubicin (DOX) and resveratrol (RSV), increasing loading of DOX. Co-loading of DOX and RSV in amphiphilic diblock copolymer micelles of poly(ethylene glycol)-*b*-poly(ε-caprolactone) (PEG-*b*-PCL) and poly(ethylene glycol)-*b*-poly(γ-benzyl-ε-caprolactone) (PEG-*b*-PBCL) results in improvement of loading efficiency and bioavailability [68].

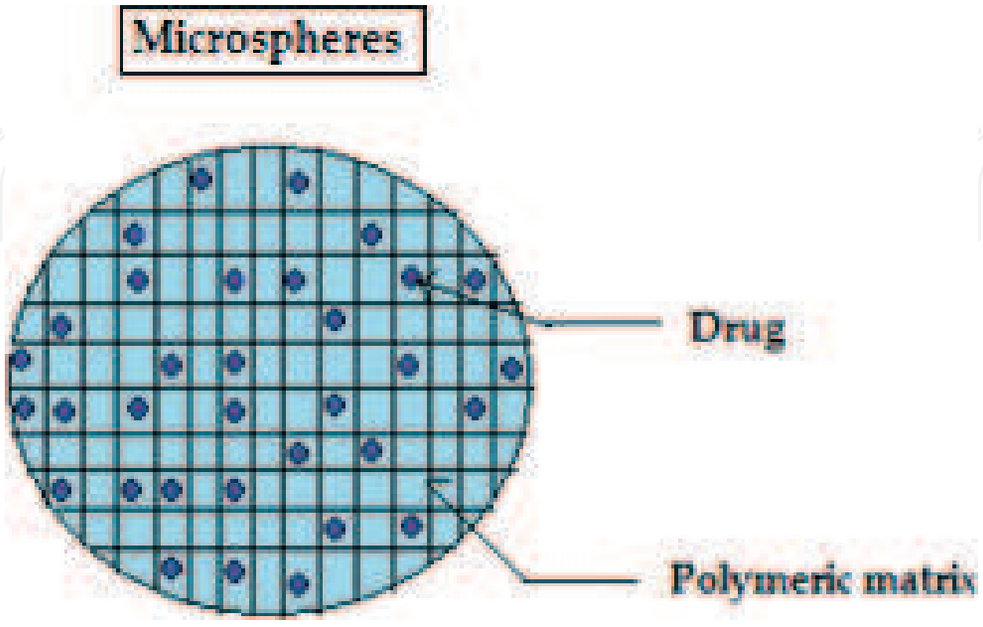

Figure 9. Microspheres.

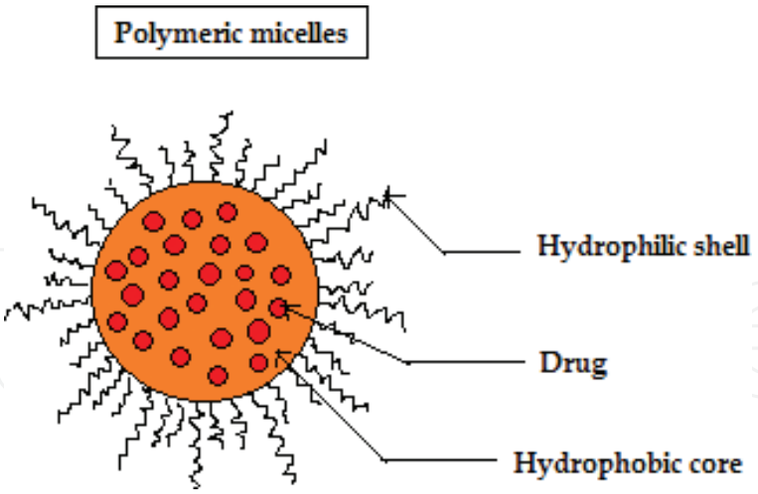

Figure 10. Polymeric micelles.

6. Conclusion

A wide variety of researches use resveratrol as a potential candidate for novel drug delivery. The present chapter provides detailed information about the novel drug delivery systems of resveratrol to bioavailability and therapeutic effects, issues related to drug delivery along with the different approaches utilized to improve the bioavailability of the drug. The novel drug delivery systems of resveratrol show immense benefits in therapeutic terms by various means, for example, by enhancing the solubility and thus the bioavailability, by increasing the half-life of the drug, by reducing the side effects and also focused on the target-specific delivery, etc. Various reports include microparticles formulation that shows colon-specific drug delivery; resveratrol is encapsulated in cyclodextrins to enhance its poor aqueous solubility, SLNs possess various advantages such as target-specific delivery, photo and acid stability, and nanosponges and nanosuspension systems results in the improvement of bioavailability of the drug by improving its solubility. The bioavailability of resveratrol was found to be improved by incorporating into liposomes and also improving transdermal delivery, vesicular systems such as transfersomes and ethosomes containing phospholipids, ethanol, and water with the potential to penetrate into intact skin and delivering drug into systemic circulation through skin; polymeric micelles has the capacity to hold drugs, which are poorly soluble in aqueous solution, results in enhanced bioavailability of resveratrol and also effective to target tumors, and stable chitosan incorporated resveratrol microspheres results controlled release and improved stabilization of resveratrol.

Author details

Poonam Devi, Pratibha Sharma, Charul Rathore and Poonam Negi*

*Address all correspondence to: poonamgarge@gmail.com

School of Pharmaceutical Sciences, Shoolini University, Solan, India

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